Clinical trial results:
A multi-center, open-label, non-randomized, phase I dose escalation study of regorafenib (BAY73-4506) in pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy

Summary

EudraCT number	2013-003579-36
Trial protocol	IT GB FR ES
Global end of trial date	13 March 2024

Results information

Result version number	v1 (current)
This version publication date	13 September 2024
First version publication date	13 September 2024

Trial information

Trial identification

Sponsor protocol code	15906

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02085148
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30300139 003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30300139 003, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001178-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the dose escalation phase were: - To define the safety profile, maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of regorafenib administered orally as a single agent in a 3 weeks on/1 week off schedule in repeating cycles of 28 days in pediatric subjects with solid malignant tumors recurrent or refractory to standard therapy - To characterize the Pharmacokinetics (PK) of regorafenib The primary objective of the dose expansion phase was: - To define the safety profile, MTD and the RP2D of regorafenib administered orally in combination vincristine and irinotecan in pediatric subjects with RMS and other solid malignant tumors recurrent or refractory to standard therapy

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	62
EEA total number of subjects	35

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)	1
Children (2-11 years)	30
Adolescents (12-17 years)	31
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 15 study centers in 4 countries worldwide, between 11-Apr-2014 (first subject first visit) and 13-Mar-2024 (last subject last visit).

Pre-assignment

Screening details:

Dose escalation: 55 pediatric subjects were enrolled. Of these 12 premature discontinuations of screening and 43 subjects were assigned to treatment. 41 subjects received at least 1 dose of regorafenib and 2 subjects were never treated. Dose expansion: 28 pediatric subjects were screened and 21 subjects were assigned to treatment.

Period 1

Period 1 title	Dose escalation and expansion phase (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 60 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib 60 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: 60 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm title	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib 72 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: 72 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm title	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib 82 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: 82 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm title	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 93 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib 93 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: 93 mg/m^2 once daily in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Arm title	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 concomitantly administered with vincristine and irinotecan (VI) on a 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	cellcristin
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Pediatric subjects received Vincristine concomitantly 1.5 mg/m^2, maximum of 2 mg (0.05 mg/kg for subjects ≤ 10 kg), on Day 1 and Day 8 in 21 days cycles.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	irinotecan cell pharm
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pediatric subjects received irinotecan concomitantly over 1 hour, at a starting dose of 50 mg/m^2/day, on Day 1 to Day 5 in 21 days cycles.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib concomitantly administered with vincristine and irinotecan (VI), in the order of vincristine, irinotecan and regorafenib if 2 or 3 agents of the study treatment were scheduled to be administered in the same day. Regorafenib was orally taken at a starting dose of 72 mg/m^2 once daily from Day 1 to Day 14 in 21 days cycles.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: at a starting dose of 72 mg/m^2 once daily from Day 1 to Day 14 in 21 days cycles.

Arm title	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 sequentially followed by administration of VI on a 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	cellcristin
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Pediatric subjects received Vincristine sequentially 1.5 mg/m^2, maximum of 2 mg (0.05 mg/kg for subjects ≤ 10 kg), on Day 1 and Day 8 in 21 days cycles.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: at a starting dose of 72 mg/m^2 once daily from Day 8 to Day 21 in 21 days cycles.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib sequentially administered with vincristine and irinotecan (VI), in the order of vincristine, irinotecan and regorafenib if 2 or 3 agents of the study treatment were scheduled to be administered in the same day. Regorafenib was orally taken at a starting dose of 72 mg/m^2 once daily from Day 8 to Day 21 in 21 days cycles.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	irinotecan cell pharm
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pediatric subjects received irinotecan sequentially over 1 hour, at a starting dose of 50 mg/m^2/day, on Day 1 to Day 5 in 21 days cycles.

Arm title	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)

Arm description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m^2 sequentially administered with VI on a 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	cellcristin
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Pediatric subjects received Vincristine sequentially 1.5 mg/m^2, maximum of 2 mg (0.05 mg/kg for subjects ≤ 10 kg), on Day 1 and Day 8 in 21 days cycles.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	irinotecan cell pharm
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pediatric subjects received irinotecan sequentially over 1 hour, at a starting dose of 50 mg/m^2/day, on Day 1 to Day 5 in 21 days cycles.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects received regorafenib sequentially administered with vincristine and irinotecan (VI), in

the order of vincristine, irinotecan and regorafenib if 2 or 3 agents of the study treatment were scheduled to be administered in the same day. Regorafenib was orally taken at a starting dose of 82 mg/m^2 once daily from Day 8 to Day 21 in 21 days cycles.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Pediatric subjects who were unable to swallow tablets received regorafenib as granulate follow the same regime: at a starting dose of 82 mg/m^2 once daily from Day 8 to Day 21 in 21 days cycles.

Number of subjects in period 1	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)
Started	6	14	14
Completed	0	0	0
Not completed	6	14	14
Consent withdrawn by subject	-	-	1
Physician decision	-	-	-
Progressive disease - clinical progression	3	2	3
Completed	-	-	-
Adverse event, non-fatal	-	-	-
AE related with clinical disease progression	1	1	1
Unspecified	-	-	-
AE not related with clinical disease progression	-	2	-
Progressive disease	-	-	-
Progressive disease - radiological progression	2	9	9
Lack of efficacy	-	-	-

Number of subjects in period 1	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)
Started	7	2	6
Completed	0	0	0
Not completed	7	2	6
Consent withdrawn by subject	-	-	-
Physician decision	-	1	-
Progressive disease - clinical progression	1	-	-
Completed	-	-	1
Adverse event, non-fatal	-	-	1
AE related with clinical disease progression	-	-	-

Unspecified	-	-	-
AE not related with clinical disease progression	1	-	-
Progressive disease	-	1	3
Progressive disease - radiological progression	5	-	-
Lack of efficacy	-	-	1

Number of subjects in period 1	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)
Started	13
Completed	0
Not completed	13
Consent withdrawn by subject	1
Physician decision	3
Progressive disease - clinical progression	-
Completed	-
Adverse event, non-fatal	2
AE related with clinical disease progression	-
Unspecified	2
AE not related with clinical disease progression	-
Progressive disease	5
Progressive disease - radiological progression	-
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 60 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 93 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 concomitantly administered with vincristine and irinotecan (VI) on a 21-day cycle.	
Reporting group title	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 sequentially followed by administration of VI on a 21-day cycle.	
Reporting group title	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m^2 sequentially administered with VI on a 21-day cycle.	

Reporting group values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)
Number of subjects	6	14	14
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	12.5	13.2	10.2
standard deviation	± 2.3	± 3.2	± 4.7
Gender Categorical Units: Subjects			
Female	2	7	7
Male	4	7	7

Reporting group values	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)

Number of subjects	7	2	6
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	10.6	13.50	10.50
standard deviation	± 4.5	± 4.95	± 4.59
Gender Categorical Units: Subjects			
Female	5	0	2
Male	2	2	4

Reporting group values	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	Total	
Number of subjects	13	62	
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	8.73		
standard deviation	± 4.74	-	
Gender Categorical Units: Subjects			
Female	6	29	
Male	7	33	

End points

End points reporting groups

Reporting group title	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 60 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 93 mg/m^2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.	
Reporting group title	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 concomitantly administered with vincristine and irinotecan (VI) on a 21-day cycle.	
Reporting group title	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 sequentially followed by administration of VI on a 21-day cycle.	
Reporting group title	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)
Reporting group description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m^2 sequentially administered with VI on a 21-day cycle.	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of the study drug (regorafenib) will be included in the safety evaluation (Dose escalation phase: 41, dose expansion phase: 21).	
Subject analysis set title	MTD Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who completed Cycle 1 or discontinued during Cycle 1 due to an adverse event or dose-limiting toxicity (DLT) in the dose expansion phase will be included in the maximum tolerated dose (MTD) evaluation (Dose escalation phase: 23, dose expansion phase: 20).	
Subject analysis set title	Efficacy Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received at least 1 dose of regorafenib and either had at least one post-baseline efficacy evaluation or have clinical disease progression before the first post-baseline efficacy assessment (treatment failure) will be included in the efficacy evaluations (Dose escalation phase: 39, dose expansion phase: 21).	
Subject analysis set title	PK Analysis Set regorafenib
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects with valid evaluable PK data under regorafenib will be included in the evaluation of PK parameters (Dose escalation phase: 41, dose expansion phase: 20).	

Subject analysis set title	Regorafenib tablets
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pediatric subjects who taken regorafenib tablets	
Subject analysis set title	Regorafenib granulate
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pediatric subjects who taken regorafenib granulate	
Subject analysis set title	Regorafenib Seq + VI (dose expansion phase)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m^2 or 82 mg/m^2 sequentially followed by administration of VI on a 21-day cycle.	

Primary: Number of subjects with treatment emergent adverse events (TEAE)

End point title	Number of subjects with treatment emergent adverse events (TEAE)[1]
End point description:	
Adverse Events are considered treatment emergent if they have started or worsened after the first study treatment administration up to 30 days after the end of treatment with study treatment.	
End point type	Primary
End point timeframe:	
Up to 17 cycles for both dose escalation phase and dose expansion phase	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[2]	14[3]	14[4]	7[5]
Units: Subjects				
Any TEAE	6	14	14	7
Any Serious TEAE	3	10	9	1
Drug-related TEAE	6	14	14	6
Drug-related serious TEAE	0	5	1	1

Notes:

[2] - SAF

[3] - SAF

[4] - SAF

[5] - SAF

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[6]	6[7]	13[8]	

Units: Subjects				
Any TEAE	2	6	13	
Any Serious TEAE	2	5	9	
Drug-related TEAE	2	6	13	
Drug-related serious TEAE	2	2	3	

Notes:

[6] - SAF

[7] - SAF

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subject with DLT (MTD analysis set)

End point title	Number of subject with DLT (MTD analysis set)[9]

End point description:

For the assessment of the MTD, the incidence of DLTs occurring only during Cycle 1 per cohort (dose level) in the MTD analysis set was considered. In order to establish a recommended phase II dose (RP2D), the MTD cohort was expanded to have at least 12 evaluable subjects to confirm the RP2D.

End point type	Primary

End point timeframe:

Up to 17 cycles for both dose escalation phase and dose expansion phase

Notes:

[9] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[10]	6[11]	6[12]	5[13]
Units: Subjects	1	1	1	2

Notes:

[10] - MTD analysis set

[11] - MTD analysis set

[12] - MTD analysis set

[13] - MTD analysis set

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[14]	6[15]	12[16]	
Units: Subjects	2	1	1	

Notes:

[14] - MTD analysis set

[15] - MTD analysis set

[16] - MTD analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase II Dose (RP2D)

End point title	Recommended Phase II Dose (RP2D)[17]

End point description:

MTD cohort was expanded to have at least 12 evaluable subjects to confirm the RP2D. It was expected that at least 15 subjects evaluable for DLTs were necessary to establish the RP2D of the combination.

End point type	Primary

End point timeframe:

By cycle 1

Notes:

[17] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	MTD Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: mg/m^2	82			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose

End point title	Maximum Tolerated Dose[18]

End point description:

MTD was defined as the dose level at which ≤1 of 6 subjects experienced a DLT, when at least 2 of 3-6 subjects experienced a DLT at the next highest dose.

End point type	Primary

End point timeframe:

By cycle 1

Notes:

[18] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	MTD Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: mg/m^2	82			

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-24)md based on nominal dosing of regorafenib (dose escalation phase)

End point title	AUC(0-24)md based on nominal dosing of regorafenib (dose escalation phase)[19][20]

End point description:

Area under the concentration-time curve after multiple dose from time zero to 24 hours (AUC(0-24)md) based on nominal dosing. The PK parameters were calculated with a population pharmacokinetic (popPK) model using available data.

End point type	Primary

End point timeframe:

Dose escalation phase: Cycle 1 Day 1, Day 15 and Day 21

Notes:

[19] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[20] - 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: AUC(0-24)md based on nominal dosing of regorafenib in dose escalation phase and dose expansion phase were analyzed for primary endpoint and secondary endpoint respectively.

End point values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[21]	14[22]	14[23]	7[24]
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	34.1 (± 34.6)	47.3 (± 37.1)	54.4 (± 35.8)	49.6 (± 42.7)

Notes:

[21] - PK Analysis Set regorafenib

[22] - PK Analysis Set regorafenib

[23] - PK Analysis Set regorafenib

[24] - PK Analysis Set regorafenib

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-24)md based on nominal dosing of regorafenib (dose expansion Phase)

End point title	AUC(0-24)md based on nominal dosing of regorafenib (dose expansion Phase)[25]

End point description:

99999 indicates the value could not be evaluated due to the low number of subjects. The PK parameters were calculated with a PopPK model using available data.

End point type	Secondary

End point timeframe:

Expansion Phase: Cycle 1 Day1, Day 15 and Day 21

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only analyzed in dose expansion phase.

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	12	
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	64.4 (± 41.3)	55.6 (± 33.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax(0-24)md of regorafenib based on actual dosing

End point title	Cmax(0-24)md of regorafenib based on actual dosing

End point description:

The variability in Cmax(0-24)md could not be robustly estimated by the current model. Thus, no result is available for this endpoint.

End point type	Secondary

End point timeframe:

Dose escalation phase: Cycle 1 Day1, Day 15 and Day 21 Dose expansion phase: Cycle 1 Day1, Day 15 and Day 21

End point values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[26]	0[27]	0[28]	0[29]
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[26] - 99999 indicates the value is not available.

[27] - 99999 indicates the value is not available.

[28] - 99999 indicates the value is not available.

[29] - 99999 indicates the value is not available.

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[30]	0[31]	0[32]	
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[30] - 99999 indicates the value is not available.

[31] - 99999 indicates the value is not available.

[32] - 99999 indicates the value is not available.

Statistical analyses

No statistical analyses for this end point

Secondary: Cav(0-24)md of regorafenib based on actual dosing

End point title	Cav(0-24)md of regorafenib based on actual dosing

End point description:

Cav(0-24)md = Average plasma concentration over the 24 h dosing interval after multiple dosing. 99999 indicates the value could not be evaluated due to the low number of subjects. The PK parameters were calculated with a PopPK model using available data.

End point type	Secondary

End point timeframe:

Dose escalation phase: Cycle 1 Day1, Day 15 and Day 21 Dose expansion phase: Cycle 1 Day1, Day 15 and Day 21

End point values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	14	14	7
Units: mg/L				
geometric mean (geometric coefficient of variation)	1.42 (± 34.6)	1.97 (± 37.1)	2.27 (± 35.8)	2.06 (± 42.7)

End point values	Regorafenib (72 mg/m^2)	Regorafenib (72 mg/m^2)	Regorafenib (82 mg/m^2)	

	Conc + VI (dose expansion phase)	Seq + VI (dose expansion phase)	Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	12	
Units: mg/L				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	2.68 (± 41.3)	2.32 (± 33.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2eff,md of regorafenib based on actual dosing

End point title	t1/2eff,md of regorafenib based on actual dosing

End point description:

t1/2eff,md = effective half-life after multiple dosing. 99999 indicates the value could not be evaluated due to the low number of subjects. The PK parameters were calculated with a PopPK model using available data.

End point type	Secondary

End point timeframe:

Dose expansion phase: Cycle 1 Day1, Day 15 and Day 21 Dose escalation phase: Cycle 1 Day1, Day 15 and Day 21

End point values	Regorafenib Level 1 (60 mg/m^2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m^2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m^2) (dose escalation phase)	Regorafenib Level 4 (93 mg/m^2) (dose escalation phase)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	14	14	7
Units: hours				
geometric mean (geometric coefficient of variation)	33.2 (± 35.6)	36.1 (± 32.7)	32.9 (± 30.0)	26.1 (± 26.3)

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	12	
Units: hours				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	44.3 (± 32.3)	34.1 (± 37.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance of irinotecan and SN-38

End point title	Clearance of irinotecan and SN-38[33]

End point description:

The PK parameters were calculated with a PopPK model using available data.

End point type	Secondary

End point timeframe:

Expansion Phase: Cycle 1 Day1, Day 15 and Day 21

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only analyzed in dose expansion phase.

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib Seq + VI (dose expansion phase)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	2[34]	17		
Units: L/h				
geometric mean (geometric coefficient of variation)				
Clearance of irinotecan	99999 (± 99999)	22.3 (± 83.1)		
Clearance of SN-38	99999 (± 99999)	46.5 (± 74)		

Notes:

[34] - Could not be evaluated due to the low number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) under the study treatment (regorafenib in combination with vincristine and irinotecan)

End point title	Overall survival (OS) under the study treatment (regorafenib in combination with vincristine and irinotecan)[35]

End point description:

OS was defined as the time (days) from the date of first dose of study treatment to death due to any cause. 99999 indicates the value could not be evaluated due to the low number of subjects.

End point type	Secondary

End point timeframe:

60 months

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only analyzed in dose expansion phase.

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	13	
Units: Days				
median (inter-quartile range (Q1-Q3))				
25th percentile [95% CI]	477 (477 to 99999)	166 (121 to 222)	191 (42 to 391)	
Median [95% CI]	813 (477 to 99999)	207 (121 to 99999)	497 (102 to 99999)	
75th percentile [95% CI]	1149 (477 to 99999)	364 (166 to 99999)	99999 (391 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) under the study treatment (regorafenib in combination with vincristine and irinotecan)

End point title	Time to progression (TTP) under the study treatment (regorafenib in combination with vincristine and irinotecan)[36]

End point description:

TTP was defined as the time (days) from the date of the first dose of study treatment to the date of the first observed radiological disease progression. 99999 indicates the value could not be evaluated due to the low number of subjects or censored data.

End point type	Secondary

End point timeframe:

60 months

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only analyzed in dose expansion phase.

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	13	
Units: Days				

median (inter-quartile range (Q1-Q3))				
25th percentile [95% CI]	320 (320 to 99999)	88 (85 to 152)	89 (19 to 324)	
Median [95% CI]	437 (320 to 99999)	127 (85 to 99999)	324 (37 to 457)	
75th percentile [95% CI]	554 (320 to 99999)	198 (88 to 99999)	457 (214 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor response: Best overall response RECIST 1.1

End point title	Tumor response: Best overall response RECIST 1.1[37]

End point description:

Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as per investigator's and/or local radiologists assessment [complete response (CR), partial response (PR), stable disease, progressive disease (PD)] and semi-quantitative iodine-123 metaiodobenzylguanidine (mIBG) scintigraphy score for neuro-blastoma subjects [International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) score] in whom the disease is not evaluable per RECIST version 1.1.

End point type	Secondary

End point timeframe:

Up to 60 months

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only analyzed in dose expansion phase.

End point values	Regorafenib (72 mg/m^2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m^2) Seq + VI (dose expansion phase)	Regorafenib (82 mg/m^2) Seq + VI (dose expansion phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	13	
Units: Subjects				
Completed response (CR)	0	0	3	
Partial response (PR)	2	2	3	
Stable disease (SD)	0	3	4	
Non CR/Non PD	0	1	0	
Progressive disease (PD)	0	0	2	
Response rate (CR+PR)	2	2	6	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Taste and texture questionnaire of the regorafenib formulations

End point title	Taste and texture questionnaire of the regorafenib formulations

End point description:

The taste and texture questionnaire was used to determine children’s acceptance of the tablets and granulate formulation.

End point type	Other pre-specified

End point timeframe:

By cycle 1

End point values	Regorafenib tablets	Regorafenib granulate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	8		
Units: Subjects				
Bad	1	0		
Neutral	4	4		
Good	3	1		
Very good	3	2		
Not Assessable	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first study intervention up to 30 days after the end of study intervention. Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Regorafenib Level 1 (60 mg/m2) (dose escalation phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 60 mg/m2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Reporting group title	Regorafenib Level 2 (72 mg/m2) (dose escalation phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Reporting group title	Regorafenib Level 3 (82 mg/m2) (dose escalation phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Reporting group title	Regorafenib (82 mg/m2) Seq + VI (dose expansion phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 82 mg/m2 sequentially administered with VI on a 21-day cycle.

Reporting group title	Regorafenib (72 mg/m2) Conc + VI (dose expansion phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m2 concomitantly administered with vincristine and irinotecan (VI) on a 21-day cycle.

Reporting group title	Regorafenib (72 mg/m2) Seq + VI (dose expansion phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 72 mg/m2 sequentially followed by administration of VI on a 21-day cycle.

Reporting group title	Regorafenib Level 4 (93 mg/m2) (dose escalation phase)

Reporting group description:

Pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy received regorafenib 93 mg/m2 in a 3-weeks-on/1- week-off schedule in repeating cycles of 28 days.

Serious adverse events	Regorafenib Level 1 (60 mg/m2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m2) (dose escalation phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	10 / 14 (71.43%)	9 / 14 (64.29%)
number of deaths (all causes)	6	14	13
number of deaths resulting from adverse events	1	5	2

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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			
Death			
subjects affected / exposed	1 / 6 (16.67%)	4 / 14 (28.57%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 1
Facial pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 14 (28.57%)	3 / 14 (21.43%)
occurrences causally related to treatment / all	0 / 0	5 / 6	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Injury, poisoning and procedural complications			
Shunt occlusion			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (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			
Cardiac failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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 arrest			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (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
Hydrocephalus			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (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
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Haemolysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Abdominal pain lower			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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 pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Drug-induced liver injury			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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 and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Urinary tract obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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			
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Ear infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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
Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (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 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (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
Hypophagia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral salt-wasting syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Regorafenib (82 mg/m2) Seq + VI (dose expansion phase)	Regorafenib (72 mg/m2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m2) Seq + VI (dose expansion phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)	2 / 2 (100.00%)	5 / 6 (83.33%)
number of deaths (all causes)	8	2	6
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Tumour haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Hypotension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Facial pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Pyrexia			
subjects affected / exposed	4 / 13 (30.77%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 8	2 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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			
Shunt occlusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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 dehiscence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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			
Cardiac failure			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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			
Headache			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Hydrocephalus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Neuralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Lethargy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (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
Haemolysis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Febrile neutropenia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	2 / 2 (100.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (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
Abdominal pain lower			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic haematoma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Hepatic pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Urinary tract obstruction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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

Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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			
Bacteraemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (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
Ear infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tonsillitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (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
Hypophagia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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
Cerebral salt-wasting syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (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	Regorafenib Level 4 (93 mg/m2) (dose escalation phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Death				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Shunt occlusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac failure				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemolysis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic haematoma			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Urinary retention				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhinitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Clostridium difficile infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypophagia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral salt-wasting syndrome				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Regorafenib Level 1 (60 mg/m2) (dose escalation phase)	Regorafenib Level 2 (72 mg/m2) (dose escalation phase)	Regorafenib Level 3 (82 mg/m2) (dose escalation phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	14 / 14 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Tumour haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Tumour fistulisation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Peripheral coldness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Poor peripheral circulation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	1	3	3
General disorders and administration site conditions			
Feeling cold			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	5 / 6 (83.33%)	5 / 14 (35.71%)	4 / 14 (28.57%)
occurrences (all)	10	8	5
Facial pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	1 / 14 (7.14%)
occurrences (all)	0	5	3
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	1 / 14 (7.14%)
occurrences (all)	1	10	1
Application site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Generalised oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypothermia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	4 / 14 (28.57%)	6 / 14 (42.86%)
occurrences (all)	1	6	7
Malaise			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Vaccination site erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Vaccination site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Haemophagocytic lymphohistiocytosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Allergy to immunoglobulin therapy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Perineal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vaginal discharge			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Laryngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Choking			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 6 (16.67%)	4 / 14 (28.57%)	1 / 14 (7.14%)
occurrences (all)	1	4	1
Dysphonia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	1	5	2
Epistaxis			
subjects affected / exposed	2 / 6 (33.33%)	3 / 14 (21.43%)	2 / 14 (14.29%)
occurrences (all)	2	3	2
Nasal congestion			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nasal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pleuritic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	2
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	1	1	3
Confusional state			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Depressed mood			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1

Hallucination			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Sleep disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	5 / 14 (35.71%)	5 / 14 (35.71%)
occurrences (all)	2	7	6
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	5 / 14 (35.71%)	7 / 14 (50.00%)
occurrences (all)	3	8	10
Bilirubin conjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	4 / 14 (28.57%)	8 / 14 (57.14%)
occurrences (all)	2	12	17
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	5
Blood chloride increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood fibrinogen decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	4
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Blood urea increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	3	2	0
Haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			

subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	3	3	4
Lymphocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	4 / 14 (28.57%)	2 / 14 (14.29%)
occurrences (all)	0	8	8
Prothrombin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Prothrombin time ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Prothrombin time shortened			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Thyroxine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	4 / 14 (28.57%)
occurrences (all)	0	4	8
General physical condition abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Breath sounds abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			

subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Stoma site pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Skin laceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vascular access complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Radiation skin injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Skin wound			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Primary insulin like growth factor-1 deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Ataxia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	2	1	2
Burning sensation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Drooling			

subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Dysarthria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Aphasia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Haemorrhage intracranial			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Hemiparesis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Hydrocephalus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Hyperaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypersomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Lethargy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Monoplegia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	6 / 6 (100.00%)	5 / 14 (35.71%)	5 / 14 (35.71%)
occurrences (all)	14	13	8
Seizure			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Restless legs syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pyramidal tract syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Phantom limb syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	4
Somnolence			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	2
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	5 / 14 (35.71%)
occurrences (all)	0	3	7
Lymph node pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	6	2
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	5 / 14 (35.71%)
occurrences (all)	0	5	7
Monocytosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypofibrinogenaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	2 / 6 (33.33%)	4 / 14 (28.57%)	3 / 14 (21.43%)
occurrences (all)	9	7	3
Neutrophilia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	7 / 14 (50.00%)	3 / 14 (21.43%)
occurrences (all)	4	14	7

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Otorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Hypoacusis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Ear discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Ear pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Periorbital oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Miosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Eyelid ptosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Visual acuity reduced			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Orbital swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	5 / 14 (35.71%)
occurrences (all)	3	2	14
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	5 / 14 (35.71%)
occurrences (all)	1	4	7
Cheilitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Anal fissure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	0	2	4
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	1	1	0

Dysphagia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	5 / 14 (35.71%)
occurrences (all)	1	5	11
Gingival pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Glossitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Glossodynia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Odynophagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Lip pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	6 / 14 (42.86%)	4 / 14 (28.57%)
occurrences (all)	5	7	5

Proctalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Faeces soft			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lip exfoliation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Large intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Anal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	3 / 6 (50.00%)	8 / 14 (57.14%)	7 / 14 (50.00%)
occurrences (all)	7	13	12
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tongue ulceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Saliva altered			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Oral hyperaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Anal incontinence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Hyperaesthesia teeth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	2	1	2
Jaundice cholestatic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hepatic cytolysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gallbladder obstruction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hepatotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Acne			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	5 / 14 (35.71%)
occurrences (all)	0	1	5
Alopecia universalis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blister			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Petechiae			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	0	1	3
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	4 / 6 (66.67%)	3 / 14 (21.43%)	4 / 14 (28.57%)
occurrences (all)	10	3	4
Hair colour changes			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	3	1
Hair texture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Ingrowing nail			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Palmar erythema			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 6 (16.67%)	5 / 14 (35.71%)	4 / 14 (28.57%)
occurrences (all)	3	10	7
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	2 / 6 (33.33%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	3
Rash			
subjects affected / exposed	0 / 6 (0.00%)	4 / 14 (28.57%)	4 / 14 (28.57%)
occurrences (all)	0	4	11
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	5 / 14 (35.71%)	2 / 14 (14.29%)
occurrences (all)	1	9	3
Rash morbilliform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Skin depigmentation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Telangiectasia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Skin fissures			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

Skin hyperpigmentation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin hypopigmentation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Skin reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	2
Solar dermatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Skin disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin induration			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Pruritus allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Glycosuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			

subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Leukocyturia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Glucocorticoid deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	0	4	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	2 / 14 (14.29%)
occurrences (all)	0	4	6
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	4	3
Pain in jaw			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Musculoskeletal pain			

subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	2 / 14 (14.29%)
occurrences (all)	1	3	3
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Torticollis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Spinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Epstein-Barr virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Ear infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cytomegalovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	0	1	4
Lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Molluscum contagiosum			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Wound infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	0 / 14 (0.00%)
occurrences (all)	1	3	0

Pustule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Stoma site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Mucosal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Periorbital cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Viraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rhinovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	3 / 14 (21.43%)
occurrences (all)	1	8	4
Hypophosphataemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	4 / 14 (28.57%)
occurrences (all)	2	2	9
Hypoproteinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	6 / 14 (42.86%)	1 / 14 (7.14%)
occurrences (all)	1	6	6
Hypophagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hyperlipasaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Feeding intolerance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Regorafenib (82 mg/m2) Seq + VI (dose expansion phase)	Regorafenib (72 mg/m2) Conc + VI (dose expansion phase)	Regorafenib (72 mg/m2) Seq + VI (dose expansion phase)
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	13 / 13 (100.00%)	2 / 2 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tumour haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tumour fistulisation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Peripheral coldness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Poor peripheral circulation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	3	0	2
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			

subjects affected / exposed	2 / 13 (15.38%)	2 / 2 (100.00%)	2 / 6 (33.33%)
occurrences (all)	4	4	3
Facial pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	1
Application site rash			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	4 / 13 (30.77%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	5	0	1
Gait disturbance			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hypothermia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	8 / 13 (61.54%)	1 / 2 (50.00%)	3 / 6 (50.00%)
occurrences (all)	11	2	4
Malaise			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			

subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaccination site erythema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaccination site pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Allergy to immunoglobulin therapy			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Perineal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaginal discharge			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Laryngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Choking			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	3 / 13 (23.08%)	1 / 2 (50.00%)	2 / 6 (33.33%)
occurrences (all)	5	1	3
Dysphonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	3 / 13 (23.08%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	2
Nasal congestion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Nasal obstruction			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Sneezing			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Confusional state			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Sleep disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	18	0	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 13 (30.77%)	2 / 2 (100.00%)	3 / 6 (50.00%)
occurrences (all)	35	11	13
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 13 (30.77%)	2 / 2 (100.00%)	3 / 6 (50.00%)
occurrences (all)	41	12	15
Bilirubin conjugated increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	10	4	2
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood chloride increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	3 / 13 (23.08%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0

Blood fibrinogen decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	3	0	2
Blood urea increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 13 (23.08%)	2 / 2 (100.00%)	2 / 6 (33.33%)
occurrences (all)	18	4	3
Haemoglobin increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	3
Lymphocyte count decreased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	39	9	1
Lymphocyte count increased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	3 / 13 (23.08%)	1 / 2 (50.00%)	3 / 6 (50.00%)
occurrences (all)	25	11	8
Platelet count decreased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	32	0	8
Prothrombin time prolonged			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Prothrombin time ratio increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Prothrombin time shortened			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Thyroxine increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	5 / 13 (38.46%)	1 / 2 (50.00%)	2 / 6 (33.33%)
occurrences (all)	7	5	6
General physical condition abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Breath sounds abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	49	4	6
Injury, poisoning and procedural			

complications			
Sunburn			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stoma site pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular access complication			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Radiation skin injury			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin wound			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			

Primary insulin like growth factor-1 deficiency			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pericardial effusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	3 / 13 (23.08%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ataxia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Drooling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysarthria			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Aphasia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhage intracranial			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hemiparesis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hydrocephalus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypersomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	3
Monoplegia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	8	0
Neuropathy peripheral			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Paraesthesia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	2 / 6 (33.33%)
occurrences (all)	3	2	2
Seizure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyramidal tract syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Phantom limb syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Lymphopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymph node pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	87	0	11
Leukocytosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Febrile neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	9 / 13 (69.23%)	2 / 2 (100.00%)	4 / 6 (66.67%)
occurrences (all)	79	4	7
Monocytosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypofibrinogenaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	5
Thrombocytopenia			
subjects affected / exposed	5 / 13 (38.46%)	1 / 2 (50.00%)	3 / 6 (50.00%)
occurrences (all)	12	3	22
Neutrophilia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	5 / 13 (38.46%)	1 / 2 (50.00%)	4 / 6 (66.67%)
occurrences (all)	60	5	27
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Otorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear pruritus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Miosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eyelid ptosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Visual acuity reduced			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Orbital swelling			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 13 (61.54%)	2 / 2 (100.00%)	4 / 6 (66.67%)
occurrences (all)	17	5	7
Abdominal distension			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Constipation			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Cheilitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Anal fissure			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphagia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Diarrhoea			
subjects affected / exposed	13 / 13 (100.00%)	2 / 2 (100.00%)	5 / 6 (83.33%)
occurrences (all)	35	11	18
Gingival pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glossitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	5
Lip pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	6 / 13 (46.15%)	0 / 2 (0.00%)	3 / 6 (50.00%)
occurrences (all)	14	0	14
Proctalgia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Faeces soft			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lip exfoliation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Large intestinal obstruction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Anal inflammation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	8 / 13 (61.54%)	2 / 2 (100.00%)	3 / 6 (50.00%)
occurrences (all)	28	5	15
Toothache			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	3
Tongue ulceration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Saliva altered			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral hyperaesthesia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Anal incontinence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia teeth			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Jaundice cholestatic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatic cytolysis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gallbladder obstruction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatotoxicity			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	4 / 13 (30.77%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	6	0	2
Alopecia universalis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dermatitis diaper			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	6 / 13 (46.15%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	8	0	5
Eczema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Hair colour changes			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Palmar erythema			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	7
Dermatitis allergic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Rash			
subjects affected / exposed	4 / 13 (30.77%)	2 / 2 (100.00%)	3 / 6 (50.00%)
occurrences (all)	5	2	3
Rash macular			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	7	1	1
Rash morbilliform			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin depigmentation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Telangiectasia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Skin hyperpigmentation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Skin hypopigmentation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin reaction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Solar dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Skin induration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus allergic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Glycosuria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Proteinuria			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	2 / 6 (33.33%)
occurrences (all)	2	5	3
Urinary incontinence			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Leukocyturia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	3	0	2
Acute kidney injury			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glucocorticoid deficiency			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in jaw			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	2
Muscle spasms			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Musculoskeletal pain			

subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	5	0	2
Neck pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	5	0	3
Bone pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Torticollis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

Ear infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Cytomegalovirus infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Herpes virus infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0

Influenza			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Molluscum contagiosum			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Wound infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
Tonsillitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Pustule			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stoma site infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Periorbital cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viraemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rhinovirus infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Clostridium difficile infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	4
Candida infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Hypermagnesaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	5	0	3
Increased appetite			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			
subjects affected / exposed	5 / 13 (38.46%)	2 / 2 (100.00%)	1 / 6 (16.67%)
occurrences (all)	11	9	1
Hypomagnesaemia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			
subjects affected / exposed	2 / 13 (15.38%)	1 / 2 (50.00%)	1 / 6 (16.67%)
occurrences (all)	3	4	2
Hypophosphataemia			
subjects affected / exposed	3 / 13 (23.08%)	2 / 2 (100.00%)	2 / 6 (33.33%)
occurrences (all)	8	10	5
Hypoproteinaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Hypocalcaemia			
subjects affected / exposed	3 / 13 (23.08%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	8	4	0
Decreased appetite			
subjects affected / exposed	5 / 13 (38.46%)	2 / 2 (100.00%)	5 / 6 (83.33%)
occurrences (all)	10	6	8
Hypophagia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperlipasaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Feeding intolerance			
subjects affected / exposed	1 / 13 (7.69%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Regorafenib Level 4 (93 mg/m2) (dose escalation phase)		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	7 / 7 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tumour haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tumour fistulisation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Peripheral coldness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Poor peripheral circulation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fatigue			

subjects affected / exposed	3 / 7 (42.86%)			
occurrences (all)	3			
Facial pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Chills				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Chest pain				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Asthenia				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	3			
Application site rash				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Gait disturbance				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Generalised oedema				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hypothermia				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Pyrexia				
subjects affected / exposed	4 / 7 (57.14%)			
occurrences (all)	6			
Malaise				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Mucosal inflammation				

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vaccination site erythema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vaccination site pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Allergy to immunoglobulin therapy			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Perineal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vaginal discharge			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Laryngeal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Choking			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasal obstruction			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pleuritic pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Insomnia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 7 (57.14%)		
occurrences (all)	4		
Bilirubin conjugated increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood chloride increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Blood fibrinogen decreased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Blood lactate dehydrogenase increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Blood thyroid stimulating hormone increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Blood urea increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
C-reactive protein increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Fibrin D dimer increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	3			
Haemoglobin increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
International normalised ratio increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Lipase increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Lymphocyte count decreased				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	3			
Lymphocyte count increased				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Prothrombin time ratio increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Prothrombin time shortened			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Thyroxine increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General physical condition abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Breath sounds abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural			

complications			
Sunburn			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Stoma site pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vascular access complication			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Radiation skin injury			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin wound			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			

Primary insulin like growth factor-1 deficiency			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Bradycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Burning sensation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Drooling			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dysarthria			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Dysgeusia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Aphasia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Presyncope				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hemiparesis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hydrocephalus				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hyperaesthesia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hypersomnia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hypoaesthesia				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
IIIrd nerve paralysis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Lethargy				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Monoplegia				

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Seizure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Restless legs syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pyramidal tract syndrome			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Taste disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Phantom limb syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Lymphopenia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 3			
Lymph node pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Leukopenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Leukocytosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Febrile neutropenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Anaemia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3			
Monocytosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Hypofibrinogenaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 5			
Neutrophilia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Neutropenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0			
Ear and labyrinth disorders Ear pain				

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Otorrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoacusis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ear discomfort			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Ear pruritus			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Diplopia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Periorbital oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Miosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eyelid ptosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Orbital swelling			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Cheilitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dysphagia			

subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Diarrhoea				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	2			
Gingival pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Glossitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Glossodynia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Odynophagia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Oral pain				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Lip pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Haemorrhoids				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Haematochezia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	5 / 7 (71.43%)			
occurrences (all)	6			
Proctalgia				

subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Faeces soft				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Lip exfoliation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Large intestinal obstruction				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Anal inflammation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Vomiting				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	4			
Toothache				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Tongue ulceration				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Stomatitis				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Saliva altered				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Oral hyperaesthesia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Anal incontinence				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hyperaesthesia teeth				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Jaundice cholestatic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hepatic cytolysis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gallbladder obstruction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Acne			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Alopecia universalis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blister			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dermatitis acneiform			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Petechiae				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Dermatitis atopic				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Dermatitis diaper				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Dermatitis exfoliative generalised				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Dry skin				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	2			
Eczema				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hair colour changes				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Hair texture abnormal				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Ingrowing nail				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pain of skin				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Palmar erythema				

subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	3 / 7 (42.86%)			
occurrences (all)	3			
Dermatitis allergic				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Rash				
subjects affected / exposed	4 / 7 (57.14%)			
occurrences (all)	13			
Rash macular				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Rash maculo-papular				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Rash morbilliform				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Skin depigmentation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Telangiectasia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Skin exfoliation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Skin fissures				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			

Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin hypopigmentation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin reaction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Solar dermatitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin induration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pruritus allergic			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Glycosuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Urinary incontinence			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Leukocyturia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Glucocorticoid deficiency			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Torticollis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Spinal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Epstein-Barr virus infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Ear infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Cytomegalovirus infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Conjunctivitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Cellulitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Herpes virus infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Laryngitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			

Influenza				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Molluscum contagiosum				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Tooth infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Wound infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Varicella				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Urinary tract infection				
subjects affected / exposed	3 / 7 (42.86%)			
occurrences (all)	3			
Upper respiratory tract infection				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Skin infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			

Pustule				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Stoma site infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Device related infection				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Mucosal infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Periorbital cellulitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Viraemia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Rhinovirus infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Clostridium difficile infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Candida infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
COVID-19				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			

Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypermagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypoproteinaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Hypophagia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperlipasaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Feeding intolerance			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2014	- Addition of pediatric granulate formulation - Revised eligibility criteria - Updated storage conditions - Corrected study procedures (weight, temperature, hematology, urinalysis) - Updated regulatory status and clinical data - Addition of Active Follow-up period - Updated Study Medical Expert contact details - Updated language on re-screening of subjects - Removal of adverse events of special interest - Updated language on tumor assessments
25 March 2015	- Clarified guidance on the initial choice and later change of regorafenib formulation - Clarified guidance on drug interruption and cycle delay - Addition of body surface area (BSA) ranges for children 2-5 years old
29 May 2017	- Structural changes - Addition of the objectives of the dose expansion phase - Addition of backbone chemotherapy for the dose expansion phase - Updated introduction section - Addition of doses and dosing schedules for the dose expansion phase - Addition of duration of treatment for the dose expansion phase - Addition of indications for the dose expansion phase - Revised eligibility criteria for the dose expansion phase - Updated methodology - Addition of Pharmacokinetics (PK) sampling schedule for the dose expansion phase - Updated recommended phase 2 dose information for the dose expansion phase - Clarified the period for follow-up long-term effects - Clarified tumor response evaluation period for the dose expansion phase - Addition of number of subjects for the dose expansion phase - Addition of primary variable for the dose expansion phase - Updated language on safety follow-up visit/contact of the dose expansion phase - Clarified duration of each cycle for the dose escalation phase - Removal of optional retrospective independent review - Clarified that radiological progression were determined per local assessment - Updated plan for statistical analysis for the dose expansion phase - Updated data handling and quality assurance section - Updated list of CYP3A4 inhibitors and inducers - Updated regorafenib dosing based on BSA and dose level
13 June 2018	- PK sampling schedule for Irinotecan for the sequential dosing schedule changed - Updated language for use of Granulocyte colony-stimulating factor (G-CSF)
20 March 2019	- Removed the list of regorafenib Adverse drug reaction (ADR) information from the background and reference the Investigator’s Brochure (IB) - Clarified re-screening criteria - Clarified on dose delay requirement to up to 2 weeks instead of 1-2 weeks - Add the requirement for the tumor response assessment for patients that stay on treatment after Cycle 12 - Included lower BSA range for tablet dosing
13 July 2020	- Sentence added to clarify when subjects enter the active follow up phase - Clarification added that days 2-5 were not mandatory provided that a patient was no longer receiving irinotecan - Modified sentence to allow local control via surgery and/or radiotherapy and continued study treatment, provided response to treatment is significant enough for local therapy to be considered potentially curative.
01 March 2022	- Modified table to allow plasma sample for biomarker analysis and collection. Where appropriate the second sample may be collected during a routine visit prior to discontinuation of study treatment - Modified footnote to add language for height, weight, and BSA fields - Added language about Day 1 and Day 8 laboratory samples for patients receiving regorafenib alone

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.

Occurrence of "±" in relation with geometric CV is auto-generated and cannot be deleted.

Notes: