Clinical trial results:
A single arm, open-label, phase II, multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma (BCC).

Summary

EudraCT number	2011-000195-34
Trial protocol	SE AT DE BG GB BE IT ES NL SI DK HU CZ GR SK IE PT PL NO LT FI EE
Global end of trial date	14 June 2017

Results information

Result version number	v2 (current)
This version publication date	24 June 2018
First version publication date	08 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO25616

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01367665
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This single-arm, open-label, multi-center study will evaluate the safety and efficacy of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma. Patients will receive oral doses of vismodegib 150 mg once daily until disease progression or unacceptable toxicity.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 302
Country: Number of subjects enrolled	Italy: 182
Country: Number of subjects enrolled	Germany: 111
Country: Number of subjects enrolled	Spain: 94
Country: Number of subjects enrolled	Austria: 76
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Switzerland: 23
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Turkey: 10

Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Slovenia: 6
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Norway: 2
Worldwide total number of subjects	1215
EEA total number of subjects	1018

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	425
From 65 to 84 years	553
85 years and over	237

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1232 participants were enrolled in the study, but only 1215 participants received at least one dose of any study treatment. Results include only the treated 1215 participants.

Period 1

Period 1 title	Overall Study (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	Vismodegib - Locally Advanced

Arm description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received vismodegib 150 mg orally once a day until one of the following occurs: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Arm title	Vismodegib - Metastatic

Arm description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received vismodegib 150 mg orally once a day until one of the following occurs: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Number of subjects in period 1	Vismodegib - Locally Advanced	Vismodegib - Metastatic
Started	1119	96
Completed	677	41
Not completed	442	55
Adverse event, serious fatal	102	19
Not Done	118	14
Lost to follow-up	222	22

Baseline characteristics

Reporting groups	
Reporting group title	Vismodegib - Locally Advanced
Reporting group description:	
Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.	
Reporting group title	Vismodegib - Metastatic
Reporting group description:	
Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.	

Reporting group values	Vismodegib - Locally Advanced	Vismodegib - Metastatic	Total
Number of subjects	1119	96	1215
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	382	43	425
From 65-84 years	511	42	553
85 years and over	226	11	237
Age Continuous Units: years			
arithmetic mean	69.7	66.6	
standard deviation	± 16.1	± 13.0	-
Sex: Female, Male Units: Subjects			
Female	485	36	521
Male	634	60	694
Race/Ethnicity, Customized Units: Subjects			
Race: Asian	1	0	1
Race: Black or African American	1	1	2
Race: White	787	92	879
Race: Other	15	0	15
Race: Not Applicable/Missing	315	3	318

End points

End points reporting groups

Reporting group title	Vismodegib - Locally Advanced

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Reporting group title	Vismodegib - Metastatic

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Primary: Percentage of Participants who Experienced any Adverse Events (AEs), AEs Grade 3 or 4, AEs Leading to Drug Interruptions or Discontinuations and any Serious Adverse Events (SAEs)

End point title	Percentage of Participants who Experienced any Adverse Events (AEs), AEs Grade 3 or 4, AEs Leading to Drug Interruptions or Discontinuations and any Serious Adverse Events (SAEs)[1]

End point description:

Adverse events were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival.

End point type	Primary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

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

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1119	96		
Units: percentage of participants				
number (not applicable)				
Any AEs	98.4	99.0		
Any AEs with maximum severity of Grade 3 or 4	43.4	52.1		
Any Serious AEs	24.3	32.3		
Any AEs leading to study drug interruption	40.5	35.4		
Any AEs leading to study drug discontinuation	33.8	17.7		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants who Died due to Adverse Events, Disease Progression or Other reasons

End point title	Percentage of Participants who Died due to Adverse Events, Disease Progression or Other reasons[2]

End point description:

Reasons for "other" included "unknown," "natural causes," "cardiac decompensation," "general state alteration," "deterioration of general state," "clinical deterioration taking into consideration patient's age," "old age," and "disease progression of mediastinal squamous cell carcinoma (SCC)."

End point type	Primary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

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

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1119	96		
Units: percentage of participants				
number (not applicable)				
Adverse Event	6.1	6.3		
Disease Progression	1.9	13.5		
Other	1.3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants who Report a Shift in NCI CTCAE Grades to 3/4 in Hematology and Biochemistry Laboratory Parameters

End point title	Percentage of Participants who Report a Shift in NCI CTCAE Grades to 3/4 in Hematology and Biochemistry Laboratory Parameters[3]

End point description:

End point type	Primary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

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

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1119	96		
Units: percentage of participants				
number (not applicable)				
Hemoglobin (High)	0.1	0		
Hemoglobin (Low)	1.3	2.1		
Neutrophils, Total, Abs (Low)	0.5	0		
Platelet (Low)	0.2	0		
White Blood Cell Count (High)	0.2	1.0		
White Blood Cell Count (Low)	0.2	0		
Alkaline Phosphatase (High)	0.6	0		
SGPT/ALT (alanine aminotransferase) - High	2.2	4.2		
SGOT/AST (aspartate aminotransferase) - High	1.5	3.1		
Creatine Kinase (High)	0.1	0		
Creatinine (High)	1.3	2.1		
Glucose (Low)	0.4	0		
Potassium (High)	1.1	4.2		
Potassium (Low)	0.8	1.0		
Sodium (High)	0.2	0		
Sodium (Low)	2.6	4.2		
Total Bilirubin (High)	0.5	0		

Statistical analyses

No statistical analyses for this end point

Primary: Exposure to Study Treatment: Duration on Treatment

End point title	Exposure to Study Treatment: Duration on Treatment[4]

End point description:

Duration on treatment was the number of days between first and last dose of study treatment.

End point type	Primary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

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

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1119	96		
Units: days				
median (full range (min-max))	256.0 (2 to 1904)	337.0 (2 to 1932)		

Statistical analyses

No statistical analyses for this end point

Primary: Exposure to Study Treatment - Dose Intensity

End point title	Exposure to Study Treatment - Dose Intensity[5]

End point description:

Dose intensity was defined as the percentage of actual number of doses received versus planned.

End point type	Primary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

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

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1119	96		
Units: percentage				
median (full range (min-max))	97.62 (44.9 to 100.0)	98.51 (67.8 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR)

End point title	Best Overall Response Rate (BORR)

End point description:

BORR was defined as the percentage of participants achieving either a complete response (CR) or a partial response (PR) as assessed by the Investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. CR was defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) required a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1103	89		
Units: percentage of participants				
number (not applicable)				
CR	33.9	4.8		
PR	35.3	32.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as the time interval between the date of the earliest qualifying response (CR or PR) and the date of disease progression or death for any cause. Median duration of response was estimated using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	745	31		
Units: months				
median (confidence interval 95%)	18.89 (17.64 to 22.57)	13.93 (9.23 to 18.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occur first). 99999 represented data that was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1076	83		
Units: months				
median (confidence interval 95%)	3.65 (2.92 to 3.71)	99999 (5.49 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time interval between the date of the first therapy and the date of progression or death for any causes, whichever occurs first. Disease progression was assessed by the investigator.

End point type	Secondary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1103	89		
Units: months				
median (confidence interval 95%)	20.30 (19.38 to 21.82)	12.85 (11.30 to 17.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of first treatment to the date of death, regardless of the cause

of death. 99999 represented data that was not estimable. The median OS was not reached in both the metastatic BCC and locally advanced BCC cohorts.

End point type	Secondary

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1103	89		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Scores of Skindex-16 Questionnaire Domains of Emotion, Function and Symptom

End point title	Change from Baseline Scores of Skindex-16 Questionnaire Domains of Emotion, Function and Symptom

End point description:

The Skindex-16 questionnaire includes three domains for the assessment of the effects of skin disease on participants' quality of life: symptoms, emotions and function. Responses from the questionnaire were transformed to a linear scale of 100 varying from 0 (never bothered, i.e., best) to 100 (always bothers, i.e., worst).

End point type	Secondary

End point timeframe:

Baseline to the data cut-off date of 14 June 2017 (up to 6 years).

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1111	89		
Units: Skindex-16 Composite Domain Scores				
arithmetic mean (standard deviation)				
Emotion: C2D1 (Cycle 2 Day 1)	-18.02 (± 26.12)	-8.68 (± 23.50)		
Emotion: C7D1	-26.04 (± 30.80)	-13.14 (± 33.25)		
Emotion: End of Study	-24.66 (± 33.13)	7.76 (± 27.61)		
Function: C2D1	-7.43 (± 22.18)	-1.71 (± 16.31)		

Function: C7D1	-11.09 (± 26.49)	-10.00 (± 24.74)		
Function: End of Study	-9.84 (± 28.03)	4.81 (± 29.80)		
Symptom: C2D1	-9.92 (± 22.02)	-5.06 (± 23.10)		
Symptom: C7D1	-12.03 (± 24.95)	-6.73 (± 28.92)		
Symptom: End of Study	-11.85 (± 27.05)	1.85 (± 22.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a ≥ 30% Reduction in Disease-Related Symptoms According to MDASI Scale

End point title	Percentage of Participants with a ≥ 30% Reduction in Disease-Related Symptoms According to MDASI Scale[6]

End point description:

M.D. Anderson Symptom Inventory (MDASI) scale. The MDASI core instrument is a 19-item patient self-report questionnaire whose items comprise two scales, symptom severity and symptom interference. For 13 items (i.e., pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling), participants were asked to rate how severe the symptoms were when "at their worst" in the last 24 hours. For the remaining 6 items, participants were asked to rate how much the symptoms have interfered with 6 areas of functioning (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours.

End point type	Secondary

End point timeframe:

08-May-2013 (Protocol Version ≥ 4) to the data cut-off date of 14 June 2017 (approximately 4 years and 1 month).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, the MDASI measurements were measured in Metastatic patients only.

End point values	Vismodegib - Metastatic			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Percentage of participants				
number (not applicable)	60.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a ≥ 30% Reduction in Composite Symptom Severity Score According to MDASI Scale

End point title	Percentage of participants with a ≥ 30% Reduction in Composite Symptom Severity Score According to MDASI Scale[7]

End point description:

M.D. Anderson Symptom Inventory (MDASI) scale. The MDASI core instrument is a 19-item patient self-report questionnaire whose items comprise two scales, symptom severity and symptom interference. For 13 items (i.e., pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling), participants were asked to rate how severe the symptoms were when "at their worst" in the last 24 hours. For the remaining 6 items, participants were asked to rate how much the symptoms have interfered with 6 areas of functioning (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours.

End point type	Secondary

End point timeframe:

08-May-2013 (Protocol Version ≥ 4) to the data cut-off date of 14 June 2017 (approximately 4 years and 1 month).

Notes:

[7] - 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: Per protocol, the MDASI measurements were measured in Metastatic patients only.

End point values	Vismodegib - Metastatic			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Percentage of participants				
number (not applicable)	33.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Vismodegib - Metastatic

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Reporting group title	Vismodegib - Locally Advanced

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

Serious adverse events	Vismodegib - Metastatic	Vismodegib - Locally Advanced	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 96 (32.29%)	272 / 1119 (24.31%)	
number of deaths (all causes)	19	103	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER RECURRENT			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CANCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED NEOPLASM			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

LIP SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
METASTATIC SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON−SMALL CELL LUNG CANCER METASTATIC			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RECTAL ADENOCARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	1 / 96 (1.04%)	10 / 1119 (0.89%)	
occurrences causally related to treatment / all	0 / 1	5 / 10	
deaths causally related to treatment / all	0 / 1	0 / 2	

ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT NEOPLASM OF EYELID			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN NEOPLASM OF ADRENAL GLAND			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLON CANCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC CANCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL ADENOCARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVASIVE LOBULAR BREAST			

CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MARGINAL ZONE LYMPHOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO BONE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL CAVITY CANCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAPILLARY RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARATHYROID TUMOUR BENIGN			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL CANCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RECTAL CANCER STAGE III			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN NEOPLASM BLEEDING			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL BREAST CARCINOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ARTERIAL HAEMORRHAGE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	1 / 96 (1.04%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
AORTIC ANEURYSM			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CIRCULATORY COLLAPSE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HAEMORRHAGE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK HAEMORRHAGIC			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
EYELID OPERATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 96 (0.00%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
CHEST PAIN			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 96 (1.04%)	11 / 1119 (0.98%)	
occurrences causally related to treatment / all	0 / 1	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 4	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SUDDEN DEATH			
subjects affected / exposed	1 / 96 (1.04%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
TERMINAL STATE			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ILL-DEFINED DISORDER			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYST			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
GAIT DISTURBANCE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERNIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERFORMANCE STATUS DECREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 96 (0.00%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
PNEUMONITIS			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
DYSPNOEA			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS POLYP			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYPNOEA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISORIENTATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
DEVICE DISLOCATION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	5 / 1119 (0.45%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD TEST ABNORMAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST INCREASED			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
EYEBALL AVULSION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	0 / 96 (0.00%)	8 / 1119 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOREIGN BODY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	6 / 1119 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL INTESTINAL PERFORATION			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC HAEMATOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL WOUND DEHISCENCE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE CONTUSION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARTILAGE INJURY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST INJURY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONCUSSION			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LACERATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIMB INJURY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND SECRETION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WRIST FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK FIRST DEGREE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC FAILURE CONGESTIVE			

subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
LEFT VENTRICULAR DILATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 96 (1.04%)	8 / 1119 (0.71%)	
occurrences causally related to treatment / all	0 / 1	3 / 8	
deaths causally related to treatment / all	0 / 0	2 / 6	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS NODE DYSFUNCTION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
ACUTE LEFT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			

subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
DIZZINESS			
subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSGEUSIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	1 / 96 (1.04%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 96 (0.00%)	6 / 1119 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN OEDEMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROSPINAL FISTULA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR DISORDER			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DEMENTIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARALYSIS			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARESIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOCAL DYSCOGNITIVE SEIZURES			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED TONIC-CLONIC SEIZURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LETHARGY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			

subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRIGEMINAL NEURALGIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	1 / 96 (1.04%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

NORMOCHROMATIC NORMOCYTIC ANAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOMPENIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTIGO POSITIONAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
DIPLOPIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LAGOPHTHALMOS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL ARTERY OCCLUSION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS EROSIVE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOLVULUS			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGO−OESOPHAGEAL DIVERTICULUM			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			

subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL INCARCERATED HERNIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC PERFORATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL ISCHAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 96 (0.00%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
BILE DUCT OBSTRUCTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY COLIC			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY CYST			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGITIS ACUTE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC MASS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS TOXIC			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOCELLULAR INJURY			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN ULCER			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DECUBITUS ULCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMAL CYST			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LICHEN SCLEROSUS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL FAILURE			
subjects affected / exposed	2 / 96 (2.08%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
URETHRAL STENOSIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE KIDNEY INJURY			

subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE PRERENAL FAILURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE URINARY TRACT			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL DISORDER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRALGIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE SPASMS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROTIC FRACTURE			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROTATOR CUFF SYNDROME			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE MASS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCESS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN ABSCESS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM COLITIS			

subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS BACTERIAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOCCAL SEPSIS			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 96 (1.04%)	5 / 1119 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS CLOSTRIDIAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN ABSCESS			

subjects affected / exposed	1 / 96 (1.04%)	0 / 1119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SKIN ULCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 96 (1.04%)	17 / 1119 (1.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 18	
deaths causally related to treatment / all	0 / 0	0 / 2	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
SOFT TISSUE INFECTION			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 96 (0.00%)	5 / 1119 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	0 / 96 (0.00%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
UROSEPSIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS LIMB			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACTINOMYCOSIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE SINUSITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOPHTHALMITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GANGRENE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS BACTERIAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MORGANELLA INFECTION			

subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORBITAL INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIORBITAL CELLULITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
DECREASED APPETITE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	1 / 96 (1.04%)	4 / 1119 (0.36%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			

subjects affected / exposed	1 / 96 (1.04%)	1 / 1119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	2 / 1119 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	3 / 1119 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vismodegib - Metastatic	Vismodegib - Locally Advanced	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 96 (93.75%)	1065 / 1119 (95.17%)	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	38 / 96 (39.58%)	471 / 1119 (42.09%)	
occurrences (all)	63	774	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 96 (6.25%)	54 / 1119 (4.83%)	
occurrences (all)	15	69	
ASPARTATE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	7 / 96 (7.29%)	52 / 1119 (4.65%)	
occurrences (all)	15	66	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	10 / 96 (10.42%)	59 / 1119 (5.27%)	
occurrences (all)	23	129	
GAMMA−GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	5 / 96 (5.21%)	55 / 1119 (4.92%)	
occurrences (all)	11	85	
BLOOD CREATININE INCREASED			
subjects affected / exposed	6 / 96 (6.25%)	31 / 1119 (2.77%)	
occurrences (all)	8	43	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	6 / 96 (6.25%)	58 / 1119 (5.18%)	
occurrences (all)	6	86	
Nervous system disorders			
AGEUSIA			
subjects affected / exposed	12 / 96 (12.50%)	201 / 1119 (17.96%)	
occurrences (all)	13	264	
DIZZINESS			
subjects affected / exposed	9 / 96 (9.38%)	66 / 1119 (5.90%)	
occurrences (all)	17	71	
DYSGEUSIA			
subjects affected / exposed	47 / 96 (48.96%)	620 / 1119 (55.41%)	
occurrences (all)	80	1007	
HEADACHE			
subjects affected / exposed	9 / 96 (9.38%)	87 / 1119 (7.77%)	
occurrences (all)	12	109	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	19 / 96 (19.79%)	276 / 1119 (24.66%)	
occurrences (all)	29	411	
FATIGUE			

subjects affected / exposed	16 / 96 (16.67%)	185 / 1119 (16.53%)	
occurrences (all)	27	287	
OEDEMA PERIPHERAL			
subjects affected / exposed	5 / 96 (5.21%)	34 / 1119 (3.04%)	
occurrences (all)	7	36	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	14 / 96 (14.58%)	81 / 1119 (7.24%)	
occurrences (all)	23	112	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	8 / 96 (8.33%)	78 / 1119 (6.97%)	
occurrences (all)	10	101	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	6 / 96 (6.25%)	64 / 1119 (5.72%)	
occurrences (all)	8	79	
DIARRHOEA			
subjects affected / exposed	18 / 96 (18.75%)	183 / 1119 (16.35%)	
occurrences (all)	37	301	
CONSTIPATION			
subjects affected / exposed	14 / 96 (14.58%)	107 / 1119 (9.56%)	
occurrences (all)	18	152	
NAUSEA			
subjects affected / exposed	24 / 96 (25.00%)	197 / 1119 (17.61%)	
occurrences (all)	38	290	
VOMITING			
subjects affected / exposed	6 / 96 (6.25%)	96 / 1119 (8.58%)	
occurrences (all)	10	138	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	12 / 96 (12.50%)	64 / 1119 (5.72%)	
occurrences (all)	19	71	
DYSPNOEA			

subjects affected / exposed	12 / 96 (12.50%)	26 / 1119 (2.32%)	
occurrences (all)	16	29	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	50 / 96 (52.08%)	700 / 1119 (62.56%)	
occurrences (all)	78	972	
PRURITUS			
subjects affected / exposed	9 / 96 (9.38%)	61 / 1119 (5.45%)	
occurrences (all)	13	73	
ACTINIC KERATOSIS			
subjects affected / exposed	5 / 96 (5.21%)	46 / 1119 (4.11%)	
occurrences (all)	6	60	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	9 / 96 (9.38%)	117 / 1119 (10.46%)	
occurrences (all)	13	160	
BACK PAIN			
subjects affected / exposed	7 / 96 (7.29%)	53 / 1119 (4.74%)	
occurrences (all)	9	60	
MUSCLE SPASMS			
subjects affected / exposed	62 / 96 (64.58%)	754 / 1119 (67.38%)	
occurrences (all)	147	1801	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	8 / 96 (8.33%)	31 / 1119 (2.77%)	
occurrences (all)	8	35	
PAIN IN EXTREMITY			
subjects affected / exposed	9 / 96 (9.38%)	49 / 1119 (4.38%)	
occurrences (all)	9	66	
MYALGIA			
subjects affected / exposed	7 / 96 (7.29%)	78 / 1119 (6.97%)	
occurrences (all)	10	111	
Infections and infestations			
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	6 / 96 (6.25%)	55 / 1119 (4.92%)	
occurrences (all)	8	77	

Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	23 / 96 (23.96%) 27	283 / 1119 (25.29%) 415	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2012	Key changes to the protocol included increasing the number of patients to be enrolled from 150 to 550 patients. The length of study was amended to include an end of treatment phase visit when a patient received their last dose of vismodegib and thereafter discontinued vismodegib (regardless of when it occurred), and one Safety Follow-Up Visit 30 days after the last dose of vismodegib.
08 November 2012	Key changes to the protocol included increasing the number of patients to be enrolled from 550 to 800 patients. The length of study was amended to include five safety follow-up visits 1 month, 3 months, 6 months, 9 months and 12 months after the last dose of vismodegib (+/-5 days). Clarification was added regarding use of contraceptive methods during the study. Further details on the frequency of interim analyses and Data Safety Monitoring Board (DSMB) Committee reviews were also added to this version of the protocol.
08 May 2013	Key changes to the protocol included increasing the number of patients to be enrolled from 800 to approximately 1200 patients. In addition, this amendment included increased number of interim analyses and increased stringency of contraception requirements. Following a request by the EMA, disease symptoms and tumor tissue of patients with metastatic disease were to be assessed following approval of this version of the protocol.
03 October 2013	(EU) Key changes to the protocol included extension of enrollment to accrue additional patients with metastatic BCC to allow for an extension of enrollment above the 1200 patients previously planned in order to ensure that 10 − 15 patients with metastatic BCC were evaluated according to Protocol Amendment version 4 (dated 8 May 2013), which included additional assessments for metastatic BCC patients. In addition, post-treatment PK testing in a sub cohort of patients for a period of 12 months to further characterize the PK profile of vismodegib up to 12 months after dosing cessation, and PK testing for patients with persistent vismodegib related AEs (6 months after discontinution of vismodegib) to further assess vismodegib exposure in these patients, were added during this amendment.
20 November 2013	(Rest of the world) Key changes to the protocol included extension of enrollment to accrue additional patients with metastatic BCC to allow for an extension of enrollment above the 1200 patients previously planned in order to ensure that 10 − 15 patients with metastatic BCC were evaluated according to Protocol Amendment version 4 (dated 8 May 2013), which included additional assessments for metastatic BCC patients. In addition, post-treatment PK testing in a sub cohort of patients for a period of 12 months to further characterize the PK profile of vismodegib up to 12 months after dosing cessation, and PK testing for patients with persistent vismodegib related AEs (6 months after discontinution of vismodegib) to further assess vismodegib exposure in these patients, were added during this amendment.
04 April 2016	Key changes to the protocol included revised pregnancy prevention duration and the waiting time for blood donations after vismodegib discontinuation from 7 to 9 months after the last dose of vismodegib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported