Clinical trial results:
A single arm, open-label, phase II, multicentre study, to assess the safety of vismodegib (GDC-0449) in patient 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	

Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	08 August 2015

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	Roche Trial Information Hotline , F. Hoffmann-La Roche AG , 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline , 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?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	06 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2013
Global end of trial reached?	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:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

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	Australia: 3
Country: Number of subjects enrolled	Austria: 60
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 179
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 75
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	501
EEA total number of subjects	456

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)	193
From 65 to 84 years	211
85 years and over	97

Subject disposition

Recruitment

Recruitment details:

Enrollment at interim analysis Secondary outcomes are not being assessed because it's an interim safety analysis.

Pre-assignment

Screening details:

Potential participants will undergo the following screening procedures no more than 28 days prior to Day 1, Cycle 1 (unless they have already been conducted during this time period as part of the patient’s routine clinical care)

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?	No
Arm title	Vismodegib - Locally Advanced

Arm description:

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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

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 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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

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	470	31
Completed	93	7
Not completed	377	24
Adverse event, serious fatal	9	1
Consent withdrawn by subject	60	2
Progression of Disease	55	15
Adverse event, non-fatal	173	5
Investigator Request	13	1
Other	62	-
Lost to follow-up	4	-
Not treated	1	-

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 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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

Reporting group title	Vismodegib - Metastatic

Reporting group description:

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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

Reporting group values	Vismodegib - Locally Advanced	Vismodegib - Metastatic	Total
Number of subjects	470	31	501
Age, Customized Units: years			
Adults (18-64 years)	176	17	193
From 65-84 years	199	12	211
85 years and over	95	2	97
Age continuous Units: years			
arithmetic mean	69	64.9	
standard deviation	± 17.07	± 12.86	-
Gender, Male/Female Units: participants			
Female	190	12	202
Male	280	19	299
Region of Enrollment			
The numbers of patients enrolled per country is referred to the Interim analysis, not the total number enrolled in the study.			
Units: Subjects			
Russian Federation	4	1	5
Sweden	16	1	17
Austria	57	3	60
Netherlands	5	0	5
Bulgaria	14	1	15
France	177	2	179
United Kingdom	10	2	12
Switzerland	7	0	7
Spain	32	2	34
New Zealand	1	0	1
Canada	22	3	25
Belgium	1	2	3
Denmark	1	0	1
Italy	69	6	75

Israel	4	0	4
Australia	2	1	3
Germany	48	7	55

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 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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

Reporting group title	Vismodegib - Metastatic

Reporting group description:

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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

Primary: Percentage of participants who experienced at least 1 adverse event

End point title	Percentage of participants who experienced at least 1 adverse event[1]

End point description:

End point type	Primary

End point timeframe:

Baseline to the data cut-off of 06 Nov 2013 (up to 2 years, 6 months)

Notes:

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

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461[2]	31[3]		
Units: percentage of participants				
number (not applicable)				
Any AEs	98.3	100		
Any TEAEs	98.1	100		
Any TEAEs with maximum severity of Grade 3	31.8	51.6		
Any TEAEs with maximum severity of Grade 4	4.9	3.2		
Any Serious TEAEs	20.5	35.5		
Any drug-related TEAEs	92.3	87.1		
Any serious drug-related TEAEs	6.6	6.5		
Any TEAEs leading to study drug interruption	35.4	45.2		
Any TEAEs leading to study drug discontinuation	38	16.1		
Any TEAEs leading to death	4.1	6.5		

Notes:

[2] - Safety population: All participants who received at least 1 dose of study medication.

[3] - Safety population: All participants who received at least 1 dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Symptoms in metastatic BCC patients: M.D. Anderson Symptom Inventory (MDASI)

End point title	Symptoms in metastatic BCC patients: M.D. Anderson Symptom Inventory (MDASI)

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: units				

Notes:

[4] - This is an interim safety analysis, efficacy is not reported at this time.

[5] - This is an interim safety analysis, efficacy is not reported at this time.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life: Skindex-16 questionnaire

End point title	Quality of life: Skindex-16 questionnaire

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: units				

Notes:

[6] - This is an interim safety analysis, efficacy is not reported at this time.

[7] - This is an interim safety analysis, efficacy is not reported at this time.

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor response rate according to Response Evaluation Criteria in Solid Tumors (RECIST)

End point title	Tumor response rate according to Response Evaluation Criteria in Solid Tumors (RECIST)

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: units				

Notes:

[8] - This is an interim safety analysis, efficacy is not reported at this time.

[9] - This is an interim safety analysis, efficacy is not reported at this time.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response

End point title	Time to response

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: units				

Notes:

[10] - This is an interim safety analysis, efficacy is not reported at this time.

[11] - This is an interim safety analysis, efficacy is not reported at this time.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: units				

Notes:

[12] - This is an interim safety analysis, efficacy is not reported at this time.

[13] - This is an interim safety analysis, efficacy is not reported at this time.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: units				

Notes:

[14] - This is an interim safety analysis, efficacy is not reported at this time.

[15] - This is an interim safety analysis, efficacy is not reported at this time.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Note: This is an interim safety analysis, efficacy is not reported at this time.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity (approximately 2 years)

End point values	Vismodegib - Locally Advanced	Vismodegib - Metastatic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: units				

Notes:

[16] - This is an interim safety analysis, efficacy is not reported at this time.

[17] - This is an interim safety analysis, efficacy is not reported at this time.

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 06 Nov 2013 (up to 2 years, 6 months)

Adverse event reporting additional description:

Safety population: First 500 patients who received at least 1 dose of study medication and had 1 year follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

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 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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

Reporting group title	Vismodegib - Metastatic

Reporting group description:

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.

vismodegib: 150 mg once daily until disease progression or unacceptable toxicity

Serious adverse events	Vismodegib - Locally Advanced	Vismodegib - Metastatic	
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 469 (20.47%)	11 / 31 (35.48%)	
number of deaths (all causes)	19	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER RECURRENT			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CANCER			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED NEOPLASM			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIP SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
METASTATIC SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON−SMALL CELL LUNG CANCER METASTATIC			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PLASMA CELL MYELOMA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL ADENOCARCINOMA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SQUAMOUS CELL CARCINOMA			

subjects affected / exposed	4 / 469 (0.85%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	3 / 469 (0.64%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
ARTERIAL HAEMORRHAGE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			

subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CHEST PAIN			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	7 / 469 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	4 / 8	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
MULTI−ORGAN FAILURE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
TERMINAL STATE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

DISORIENTATION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
EYEBALL AVULSION			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOREIGN BODY			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL INTESTINAL PERFORATION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC HAEMATOMA			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ATRIOVENTRICULAR BLOCK FIRST DEGREE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIO−RESPIRATORY ARREST			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
DILATATION VENTRICULAR			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	4 / 469 (0.85%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
SICK SINUS SYNDROME			

subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CONVULSION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	1 / 469 (0.21%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSGEUSIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL HERNIA OBSTRUCTIVE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS EROSIVE			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (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	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATITIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN ULCER			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL FAILURE CHRONIC			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETHRAL STENOSIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
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	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCESS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

BACTERIAL INFECTION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN ABSCESS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS BACTERIAL			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOCCAL SEPSIS			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			

subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS CLOSTRIDIAL			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN ABSCESS			
subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SKIN ULCER			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED INFECTION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			

subjects affected / exposed	8 / 469 (1.71%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SOFT TISSUE INFECTION			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	2 / 469 (0.43%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DECREASED APPETITE			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	4 / 469 (0.85%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			

subjects affected / exposed	0 / 469 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 469 (0.21%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vismodegib - Locally Advanced	Vismodegib - Metastatic	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	442 / 469 (94.24%)	29 / 31 (93.55%)	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	154 / 469 (32.84%)	8 / 31 (25.81%)	
occurrences (all)	281	11	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	18 / 469 (3.84%)	2 / 31 (6.45%)	
occurrences (all)	23	7	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	17 / 469 (3.62%)	3 / 31 (9.68%)	
occurrences (all)	21	7	
BLOOD CREATINE PHOSPHOKINASE INCREASED			

subjects affected / exposed	3 / 469 (0.64%)	3 / 31 (9.68%)	
occurrences (all)	3	6	
GAMMA−GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	16 / 469 (3.41%)	4 / 31 (12.90%)	
occurrences (all)	23	9	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	17 / 469 (3.62%)	5 / 31 (16.13%)	
occurrences (all)	32	5	
Nervous system disorders			
AGEUSIA			
subjects affected / exposed	106 / 469 (22.60%)	6 / 31 (19.35%)	
occurrences (all)	143	6	
DIZZINESS			
subjects affected / exposed	23 / 469 (4.90%)	2 / 31 (6.45%)	
occurrences (all)	25	3	
DYSGEUSIA			
subjects affected / exposed	252 / 469 (53.73%)	17 / 31 (54.84%)	
occurrences (all)	428	30	
HEADACHE			
subjects affected / exposed	32 / 469 (6.82%)	2 / 31 (6.45%)	
occurrences (all)	37	3	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	137 / 469 (29.21%)	3 / 31 (9.68%)	
occurrences (all)	219	3	
FATIGUE			
subjects affected / exposed	73 / 469 (15.57%)	6 / 31 (19.35%)	
occurrences (all)	106	13	
CHEST DISCOMFORT			
subjects affected / exposed	0 / 469 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
OEDEMA PERIPHERAL			
subjects affected / exposed	15 / 469 (3.20%)	2 / 31 (6.45%)	
occurrences (all)	16	3	
PAIN			

subjects affected / exposed	5 / 469 (1.07%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	24 / 469 (5.12%)	3 / 31 (9.68%)	
occurrences (all)	32	4	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	32 / 469 (6.82%)	2 / 31 (6.45%)	
occurrences (all)	40	4	
CONSTIPATION			
subjects affected / exposed	37 / 469 (7.89%)	6 / 31 (19.35%)	
occurrences (all)	52	7	
DIARRHOEA			
subjects affected / exposed	80 / 469 (17.06%)	6 / 31 (19.35%)	
occurrences (all)	99	16	
NAUSEA			
subjects affected / exposed	74 / 469 (15.78%)	5 / 31 (16.13%)	
occurrences (all)	96	10	
VOMITING			
subjects affected / exposed	38 / 469 (8.10%)	1 / 31 (3.23%)	
occurrences (all)	50	2	
DRY MOUTH			
subjects affected / exposed	12 / 469 (2.56%)	2 / 31 (6.45%)	
occurrences (all)	12	2	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	16 / 469 (3.41%)	3 / 31 (9.68%)	
occurrences (all)	16	3	
DYSPNOEA			
subjects affected / exposed	8 / 469 (1.71%)	4 / 31 (12.90%)	
occurrences (all)	9	4	
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 469 (0.21%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			

ALOPECIA			
subjects affected / exposed	288 / 469 (61.41%)	17 / 31 (54.84%)	
occurrences (all)	405	27	
PRURITUS			
subjects affected / exposed	31 / 469 (6.61%)	3 / 31 (9.68%)	
occurrences (all)	37	3	
ACTINIC KERATOSIS			
subjects affected / exposed	19 / 469 (4.05%)	3 / 31 (9.68%)	
occurrences (all)	22	3	
DERMATITIS ACNEIFORM			
subjects affected / exposed	6 / 469 (1.28%)	3 / 31 (9.68%)	
occurrences (all)	6	3	
HYPERKERATOSIS			
subjects affected / exposed	9 / 469 (1.92%)	2 / 31 (6.45%)	
occurrences (all)	11	5	
SKIN EROSION			
subjects affected / exposed	1 / 469 (0.21%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
SKIN ULCER			
subjects affected / exposed	4 / 469 (0.85%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	10 / 469 (2.13%)	3 / 31 (9.68%)	
occurrences (all)	12	3	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	43 / 469 (9.17%)	2 / 31 (6.45%)	
occurrences (all)	60	3	
BACK PAIN			
subjects affected / exposed	23 / 469 (4.90%)	4 / 31 (12.90%)	
occurrences (all)	26	4	
MUSCLE SPASMS			
subjects affected / exposed	299 / 469 (63.75%)	17 / 31 (54.84%)	
occurrences (all)	654	44	
MUSCULOSKELETAL PAIN			

subjects affected / exposed	8 / 469 (1.71%)	2 / 31 (6.45%)	
occurrences (all)	9	2	
SPINAL PAIN			
subjects affected / exposed	0 / 469 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	5	
MYALGIA			
subjects affected / exposed	34 / 469 (7.25%)	4 / 31 (12.90%)	
occurrences (all)	49	6	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	26 / 469 (5.54%)	4 / 31 (12.90%)	
occurrences (all)	36	5	
FOLLICULITIS			
subjects affected / exposed	17 / 469 (3.62%)	2 / 31 (6.45%)	
occurrences (all)	21	2	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	120 / 469 (25.59%)	6 / 31 (19.35%)	
occurrences (all)	170	6	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	3 / 469 (0.64%)	2 / 31 (6.45%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2009	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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported