Clinical trial results:
A randomized, double-blinded, regimen controlled, phase II, multicenter study to assess the efficacy and safety of two different vismodegib regimens in patients with multiple basal cell carcinomas

Summary

EudraCT number	2012-003305-10
Trial protocol	AT DE NL IT ES FR
Global end of trial date	

Results information

Result version number	v2
This version publication date	05 October 2016
First version publication date	13 July 2016
Version creation reason	• Correction of full data set Minor revisions to OM 1 and 3 in order to align with CTg posting.

Trial information

Trial identification

Sponsor protocol code	MO28295

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01815840
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 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, 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	Interim
Date of interim/final analysis	27 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, double-blind, regimen-controlled, phase II, multicenter study assessed the efficacy and safety of two different vismodegib regimens in subjects with multiple basal cell carcinoma. Subjects received vismodegib 150 mg orally once daily either in an intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo (Arm A) or as 24 weeks induction followed by an intermittent schedule of 8 weeks placebo followed by 8 weeks vismodegib (Arm B). Anticipated time on study treatment was 72 weeks.

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	30 April 2013
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	Netherlands: 10
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	229
EEA total number of subjects	149

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)	127
From 65 to 84 years	94
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

229 subjects were enrolled in 10 countries.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Vismodegib Intermittent Schedule

Arm description:

Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

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

Dosage and administration details:

Vismodegib 150 mg hard gelatin capsule orally once daily

Investigational medicinal product name	Vismodegib Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vismodegib placebo orally once daily

Arm title	Vismodegib Induction Followed by Intermittent Schedule

Arm description:

Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

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

Dosage and administration details:

Vismodegib 150 mg hard gelatin capsule orally once daily

Investigational medicinal product name	Vismodegib Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vismodegib placebo orally once daily

Number of subjects in period 1	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule
Started	116	113
Completed	0	0
Not completed	116	113
Still on study	73	64
Disease progression	1	-
Adverse event, non-fatal	8	14
Death	2	2
Refused treatment	3	1
Investigator decision	1	3
Lost to follow-up	1	2
Withdrew consent	26	26
Missing	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Vismodegib Intermittent Schedule
Reporting group description:	
Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up	
Reporting group title	Vismodegib Induction Followed by Intermittent Schedule
Reporting group description:	
Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up	

Reporting group values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule	Total
Number of subjects	116	113	229
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.1	59.9	
standard deviation	± 13.94	± 15.35	-
Gender categorical			
Units: Subjects			
Female	35	25	60
Male	81	88	169

End points

End points reporting groups

Reporting group title	Vismodegib Intermittent Schedule
Reporting group description:	
Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up	
Reporting group title	Vismodegib Induction Followed by Intermittent Schedule
Reporting group description:	
Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up	

Primary: Mean Percent Change From Baseline in the Number of Clinically Evident Basal Cell Carcinomas at Week 73 (After 72 Weeks of Treatment)

End point title	Mean Percent Change From Baseline in the Number of Clinically Evident Basal Cell Carcinomas at Week 73 (After 72 Weeks of Treatment)
End point description:	
The total number of clinically evident basal cell carcinomas = the total number of target and/or non-target lesions present in individual subjects. Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis. The last observation carried forward method was used.	
End point type	Primary
End point timeframe:	
Baseline; Week 73	

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	113		
Units: percent change				
arithmetic mean (standard deviation)	-62.7 (± 52.02)	-54 (± 55.68)		

Statistical analyses

Statistical analysis title	Difference in mean relative reduction
Statistical analysis description:	
The mean difference in the mean relative reduction between treatment arms, along with the corresponding 95% confidence interval, was estimated by fitting an ANCOVA model with treatment as main effect and the following covariates: number of basal cell carcinomas at baseline, geographical region, immunosuppression status, confirmed basal cell carcinoma nevus syndrome. Asymptotic confidence intervals are presented for the difference between treatment arms.	
Comparison groups	Vismodegib Intermittent Schedule v Vismodegib Induction Followed by Intermittent Schedule

Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23
upper limit	5.2

Secondary: Percentage of Subjects Who Discontinued Study Treatment Due to Tolerability Issues

End point title	Percentage of Subjects Who Discontinued Study Treatment Due to Tolerability Issues

End point description:

The percentage of subjects who discontinued study treatment (due either to adverse event, refusal of treatment, or withdrawal of consent) was summarized by treatment group.

Intent-to-Treat Analysis Population, defined as all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline to Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	113		
Units: percentage of subjects				
number (confidence interval 95%)				
Overall	37.1 (28.3 to 46.5)	40.7 (31.6 to 50.4)		
Adverse Events	19.8 (13 to 28.3)	26.5 (18.7 to 35.7)		
Refused Treatment	6 (2.5 to 12)	2.7 (0.6 to 7.6)		
Withdrew Consent	11.2 (6.1 to 18.4)	11.5 (6.3 to 18.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in Total Size of Three Target Basal Cell Carcinoma Lesions in Individual Subjects at Week 73

End point title	Mean Percent Change From Baseline in Total Size of Three Target Basal Cell Carcinoma Lesions in Individual Subjects at Week 73

End point description:

The three target basal cell carcinoma lesions = the three largest visible lesions, at least 5 mm in the longest diameter, in individual subjects.

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	85		
Units: percent change				
arithmetic mean (standard deviation)	-82.9 (± 27.01)	-68.8 (± 52.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With at Least 50% Reduction in the Number of Basal Cell Carcinomas at Week 73

End point title	Percentage of Subjects With at Least 50% Reduction in the Number of Basal Cell Carcinomas at Week 73

End point description:

Intent-to-Treat Analysis Population, defined as all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline; Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	113		
Units: percentage of subjects				
number (not applicable)	65.5	50.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With New Basal Cell Carcinomas at Week 73

End point title	Percentage of Subjects With New Basal Cell Carcinomas at Week 73

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	86		
Units: percentage of subjects				
number (not applicable)				
No new lesions	76.6	74.4		
1 new lesion	10.6	11.6		
2 new lesions	5.3	5.8		
3 new lesions	5.3	2.3		
>3 new lesions	2.1	5.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 85 (12 Weeks Following End of Treatment) (Recurrence Rate)

End point title	Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 85 (12 Weeks Following End of Treatment) (Recurrence Rate)

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 85

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	69		
Units: percent change				
arithmetic mean (standard deviation)	29.1 (± 34.47)	36.6 (± 37.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 97 (24 Weeks Following End of Treatment) (Recurrence Rate)

End point title	Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 97 (24 Weeks Following End of Treatment) (Recurrence Rate)

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 97

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	44		
Units: percent change				
arithmetic mean (standard deviation)	28.4 (± 29.58)	38.1 (± 36.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Total Number of Basal Cell Carcinomas Relative to

Baseline at Week 125 (52 Weeks Following End of Treatment) (Recurrence Rate)

End point title	Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 125 (52 Weeks Following End of Treatment) (Recurrence Rate)

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 125

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	26		
Units: percent change				
arithmetic mean (standard deviation)	35.5 (± 37.19)	46.2 (± 37.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Experiencing Any Adverse Event

End point title	Percentage of Subjects Experiencing Any Adverse Event

End point description:

Safety Analysis Population: Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 125 weeks

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	113		
Units: percentage of subjects				
number (not applicable)	99.1	97.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the Skindex-16 Symptom Domain Score at Week 73

End point title	Percent Change From Baseline in the Skindex-16 Symptom Domain Score at Week 73

End point description:

The Skindex-16 is a patient-reported outcome health questionnaire. Subjects were asked about their symptoms, and their answers were combined into a composite Symptom Domain Score. Scores range from 0 ("never bothered") to 100 ("always bothered").

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	77		
Units: percent change				
arithmetic mean (standard deviation)	-14.9 (± 25.75)	-12.7 (± 24.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the Skindex-16 Emotion Domain Score at Week 73

End point title	Percent Change From Baseline in the Skindex-16 Emotion Domain Score at Week 73

End point description:

The Skindex-16 is a patient-reported outcome health questionnaire. Subjects were asked about their emotional state, and their answers were combined into a composite Emotion Domain Score. Scores range from 0 ("never bothered") to 100 ("always bothered").

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	77		
Units: percent change				
arithmetic mean (standard deviation)	-27.4 (± 27.71)	-28.9 (± 28.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the Skindex-16 Function Domain Score at Week 73

End point title	Percent Change From Baseline in the Skindex-16 Function Domain Score at Week 73

End point description:

The Skindex-16 is a patient-reported outcome health questionnaire. Subjects were asked about their ability to function, and answers were combined into a composite Function Domain Score. Scores range from 0 ("never bothered") to 100 ("always bothered").

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 73

End point values	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	77		
Units: percent change				
arithmetic mean (standard deviation)	-9.5 (± 20.59)	-10.3 (± 26.32)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 125 weeks

Adverse event reporting additional description:

Safety Analysis Population: Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Vismodegib Intermittent Schedule

Reporting group description:

Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

Reporting group title	Vismodegib Induction Followed by Intermittent Schedule

Reporting group description:

Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

Serious adverse events	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 114 (19.30%)	19 / 113 (16.81%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 114 (0.88%)	2 / 113 (1.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spindle cell sarcoma			

subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (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	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Primary amyloidosis			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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			
Pulmonary embolism			
subjects affected / exposed	1 / 114 (0.88%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (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	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (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			
Ankle fracture			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (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	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital cerebral cyst			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 114 (0.88%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudolymphoma			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Xanthelasma			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (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			
Acute kidney injury			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			

subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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			
Arthralgia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 114 (2.63%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (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	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Kidney infection			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
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 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vismodegib Intermittent Schedule	Vismodegib Induction Followed by Intermittent Schedule	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 114 (93.86%)	108 / 113 (95.58%)	
Investigations			
Weight decreased			
subjects affected / exposed	24 / 114 (21.05%)	21 / 113 (18.58%)	
occurrences (all)	32	22	
Blood creatine phosphokinase increased			

subjects affected / exposed	11 / 114 (9.65%)	15 / 113 (13.27%)	
occurrences (all)	14	24	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 114 (6.14%)	5 / 113 (4.42%)	
occurrences (all)	8	5	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	75 / 114 (65.79%)	75 / 113 (66.37%)	
occurrences (all)	117	108	
Ageusia			
subjects affected / exposed	14 / 114 (12.28%)	13 / 113 (11.50%)	
occurrences (all)	17	17	
Headache			
subjects affected / exposed	11 / 114 (9.65%)	12 / 113 (10.62%)	
occurrences (all)	11	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	24 / 114 (21.05%)	26 / 113 (23.01%)	
occurrences (all)	30	31	
Asthenia			
subjects affected / exposed	15 / 114 (13.16%)	20 / 113 (17.70%)	
occurrences (all)	27	30	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 114 (17.54%)	18 / 113 (15.93%)	
occurrences (all)	33	22	
Nausea			
subjects affected / exposed	23 / 114 (20.18%)	14 / 113 (12.39%)	
occurrences (all)	31	25	
Abdominal pain			
subjects affected / exposed	8 / 114 (7.02%)	9 / 113 (7.96%)	
occurrences (all)	10	9	
Constipation			
subjects affected / exposed	9 / 114 (7.89%)	6 / 113 (5.31%)	
occurrences (all)	10	8	
Abdominal pain upper			

subjects affected / exposed	9 / 114 (7.89%)	5 / 113 (4.42%)	
occurrences (all)	12	6	
Vomiting			
subjects affected / exposed	7 / 114 (6.14%)	4 / 113 (3.54%)	
occurrences (all)	8	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	72 / 114 (63.16%)	73 / 113 (64.60%)	
occurrences (all)	98	93	
Pruritus			
subjects affected / exposed	8 / 114 (7.02%)	11 / 113 (9.73%)	
occurrences (all)	11	12	
Actinic keratosis			
subjects affected / exposed	10 / 114 (8.77%)	8 / 113 (7.08%)	
occurrences (all)	12	11	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	83 / 114 (72.81%)	93 / 113 (82.30%)	
occurrences (all)	187	190	
Arthralgia			
subjects affected / exposed	18 / 114 (15.79%)	16 / 113 (14.16%)	
occurrences (all)	23	24	
Myalgia			
subjects affected / exposed	18 / 114 (15.79%)	12 / 113 (10.62%)	
occurrences (all)	28	14	
Back pain			
subjects affected / exposed	7 / 114 (6.14%)	6 / 113 (5.31%)	
occurrences (all)	8	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 114 (5.26%)	12 / 113 (10.62%)	
occurrences (all)	9	15	
Folliculitis			
subjects affected / exposed	9 / 114 (7.89%)	7 / 113 (6.19%)	
occurrences (all)	12	9	
Bronchitis			

subjects affected / exposed	5 / 114 (4.39%)	7 / 113 (6.19%)	
occurrences (all)	5	9	
Upper respiratory tract infection			
subjects affected / exposed	7 / 114 (6.14%)	5 / 113 (4.42%)	
occurrences (all)	12	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 114 (18.42%)	17 / 113 (15.04%)	
occurrences (all)	32	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2013	Changes included: additional guidance on amenorrhea/irregular menses; additional laboratory testing to include creatine kinase to further investigate muscle spasm events; additional guidance on Vismodegib in seminal fluid to ensure male subjects did not donate sperm during treatment and for 2 months after treatment; updated eligibility criteria to exclude 1) subjects known or suspected to abuse alcohol and 2) with known rare hereditary disturbance of galactose metabolism; amended drug interaction language to reflect updated core documents regarding possible interactions with metabolize ethinyl estradiol contraceptive steroids; alteration to statistical analysis measure of precision.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported