Clinical trial results:
An Open-Label, Multi-Center Phase II Study of the BRAF Inhibitor RO5185426 in Patients with Metastatic or Unresectable Papillary Thyroid Cancer (PTC) positive for the BRAF V600 Mutation and Resistant to Radioactive Iodine

Summary

EudraCT number	2010-024133-23
Trial protocol	NL IT
Global end of trial date	29 May 2015

Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016

Trial information

Trial identification

Sponsor protocol code	NO25530

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01286753
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	Final
Date of interim/final analysis	29 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This open-label, multi-center study evaluated the safety and efficacy of Vemurafenib (RO5185426) in subjects with metastatic or unresectable papillary thyroid cancer (PTC) positive for the BRAF V600 mutation and resistant to radioactive iodine therapy. Subjects received vemurafenib 960 milligrams (mg) orally twice daily until progressive disease or occurrence of 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	30 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	51
EEA total number of subjects	5

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)	24

From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TKI Naive

Arm description:

Vemurafenib 960 mg orally twice daily in subjects naive to any prior systemic tyrosine kinase inhibitor (TKI) therapy.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	Zelboraf®, RO5185426
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib 960 mg orally twice daily.

Arm title	TKI Experienced

Arm description:

Vemurafenib 960 mg orally twice daily in subjects previously treated with TKI therapy active against vascular endothelial growth factor receptor 2 (VEGFR).

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	Zelboraf®, RO5185426
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib 960 mg orally twice daily.

Number of subjects in period 1	TKI Naive	TKI Experienced
Started	26	25
Completed	0	0
Not completed	26	25
Adverse event, non-fatal	7	6

Progression	11	13
Refused treatment	1	-
Subject to receive radiotherapy	1	-
Withdrawal of consent	-	2
Discontinued to Join Extension Study	6	4

Baseline characteristics

Reporting groups	
Reporting group title	TKI Naive
Reporting group description:	
Vemurafenib 960 mg orally twice daily in subjects naive to any prior systemic tyrosine kinase inhibitor (TKI) therapy.	
Reporting group title	TKI Experienced
Reporting group description:	
Vemurafenib 960 mg orally twice daily in subjects previously treated with TKI therapy active against vascular endothelial growth factor receptor 2 (VEGFR).	

Reporting group values	TKI Naive	TKI Experienced	Total
Number of subjects	26	25	51
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 62.9 ± 13.5	 65.2 ± 9.1	 -
Gender categorical Units: Subjects			
Female	11	12	23
Male	15	13	28

End points

End points reporting groups

Reporting group title	TKI Naive
Reporting group description:	
Vemurafenib 960 mg orally twice daily in subjects naive to any prior systemic tyrosine kinase inhibitor (TKI) therapy.	
Reporting group title	TKI Experienced
Reporting group description:	
Vemurafenib 960 mg orally twice daily in subjects previously treated with TKI therapy active against vascular endothelial growth factor receptor 2 (VEGFR).	

Primary: Best Overall Response Rate in TKI-Naive Subjects

End point title	Best Overall Response Rate in TKI-Naive Subjects[1][2]
End point description:	
Best overall response rate was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Best overall response rate: the percentage of subjects with best objective response of complete response (CR) or partial response (PR) (calculated as the number of subjects with best response CR or PR divided by the total number of efficacy-evaluable subjects). CR: disappearance of all target lesions with reduction in target/non-target pathological lymph nodes to < 10 millimeters (mm). PR: ≥ 30% decrease in the sum of diameters of target lesions, compared to the baseline sum diameters. Efficacy population (TKI Naive group only), defined as all enrolled subjects who received at least one dose of study treatment and excluding 3 subjects in the TKI Experienced group who had previous BRAFi or MEKi treatment or withdrew consent.	
End point type	Primary
End point timeframe:	
Up to approximately 4 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 analysis was planned or performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point Best Overall Response Rate prespecified as primary for TKI Naive group.

End point values	TKI Naive			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percentage of subjects				
number (confidence interval 95%)	42.3 (23.35 to 63.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate in TKI-Experienced Subjects

End point title	Best Overall Response Rate in TKI-Experienced Subjects[3]

End point description:

Best overall response rate was assessed by the investigators according to RECIST v1.1. Best overall response rate: the percentage of subjects with best objective response of CR or PR (calculated as the number of subjects with best response CR or PR divided by the total number of efficacy-evaluable subjects subjects). CR: disappearance of all target lesions with reduction in target/non-target pathological lymph nodes to < 10 mm. PR: ≥ 30% decrease in the sum of diameters of target lesions, compared to the baseline sum diameters.

Efficacy population (TKI Experienced group only), defined as all enrolled subjects who received at least one dose of study treatment and excluding 3 subjects in the TKI Experienced group who had previous BRAFi or MEKi treatment or withdrew consent.

End point type	Secondary

End point timeframe:

Up to approximately 4 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: End point Best Overall Response Rate prespecified as secondary for TKI Experienced group.

End point values	TKI Experienced			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: percentage of subjects				
number (confidence interval 95%)	27.3 (10.73 to 50.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate

End point title	Clinical Benefit Rate

End point description:

Clinical benefit rate: the percentage of subjects with confirmed CR, PR, or stable disease (SD; maintained for at least 6 months) as assessed by investigators according to RECIST v1.1. CR: disappearance of all target lesions with reduction in target/non-target pathological lymph nodes to < 10 mm. PR: ≥ 30% decrease in the sum of diameters of target lesions, compared to the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, compared to the baseline sum diameters.

Efficacy population, defined as all enrolled subjects who received at least one dose of study treatment and excluding 3 subjects in the TKI Experienced group who had previous BRAFi or MEKi treatment or withdrew consent.

End point type	Secondary

End point timeframe:

Up to approximately 4 years

End point values	TKI Naive	TKI Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	22		
Units: percentage of subjects				
number (confidence interval 95%)	73.1 (52.21 to 88.43)	54.5 (32.21 to 75.61)		

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 (for subjects with confirmed best response CR or PR): the interval between earliest qualifying response and date of progression of disease (PD) or death for any cause, whichever occurred first; subjects with no documented progression after CR or PR were censored at the date of last known CR or PR, respectively. CR: disappearance of all target lesions with reduction in target/non-target pathological lymph nodes to < 10 mm. PR: ≥ 30% decrease in the sum of diameters of target lesions, compared to the baseline sum diameters. PD: ≥ 20% increase in the sum of diameters of target lesions, compared to the smallest sum on study.

Efficacy population, defined as all enrolled subjects who received at least one dose of study treatment and excluding 3 subjects in the TKI Experienced group who had previous BRAFi or MEKi treatment or withdrew consent.

999 = Not estimable due to an insufficient number of events.

End point type	Secondary

End point timeframe:

From the date of first qualifying response to the date of PD or death for any cause (up to approximately 4 years)

End point values	TKI Naive	TKI Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	22		
Units: months				
median (confidence interval 95%)	9.5 (5.7 to 999)	7.4 (3.7 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression-free survival: the interval between the day of first treatment and the first documentation of

PD or death; subjects who were withdrawn from the study without documented progression were censored at the date of the last tumor assessment when the subject was known to be progression-free; subjects without post baseline tumor assessments were censored at the time of enrollment. PD: ≥ 20% increase in the sum of diameters of target lesions, compared to the smallest sum on study.

Efficacy population, defined as all enrolled subjects who received at least one dose of study treatment and excluding 3 subjects in the TKI Experienced group who had previous BRAFi or MEKi treatment or withdrew consent.

End point type	Secondary

End point timeframe:

From the day of first treatment until the first documented PD or death (up to approximately 4 years)

End point values	TKI Naive	TKI Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	22		
Units: months				
median (confidence interval 95%)	18.2 (15.5 to 29.3)	8.9 (5.5 to 27.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival: the interval between the date of first treatment to the date of death, regardless of the cause of death; subjects who were alive at the time of the analysis were censored at the date of the last known alive; subjects with no post baseline information were censored at the time of enrollment.

Intent-to-Treat population, defined as all enrolled subjects.

999 = Not estimable due to an insufficient number of events.

End point type	Secondary

End point timeframe:

From the date of first treatment to the date of death for any cause (up to approximately 4 years)

End point values	TKI Naive	TKI Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: months				
median (confidence interval 95%)	999 (28.3 to 999)	14.4 (8.2 to 29.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events

End point description:

An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Safety population, defined as enrolled subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 4 years)

End point values	TKI Naive	TKI Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: percentage of subjects	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of Vemurafenib: Area Under the Concentration-Time Curve (AUC)

End point title	Pharmacokinetics of Vemurafenib: Area Under the Concentration-Time Curve (AUC)

End point description:

AUC is a measure of the drug or biologic concentration in the body following administration.

End point type	Secondary

End point timeframe:

Up to approximately 4 years

End point values	TKI Naive	TKI Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: h*ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - Data were not collected for this end point.

[5] - Data were not collected for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 4 years)

Adverse event reporting additional description:

Safety population, defined as enrolled 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	TKI Naive

Reporting group description:

Vemurafenib 960 mg orally twice daily in subjects naive to any prior systemic tyrosine kinase inhibitor (TKI) therapy.

Reporting group title	TKI Experienced

Reporting group description:

Vemurafenib 960 mg orally twice daily in subjects previously treated with TKI therapy active against vascular endothelial growth factor receptor 2 (VEGFR).

Serious adverse events	TKI Naive	TKI Experienced	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 26 (61.54%)	18 / 25 (72.00%)	
number of deaths (all causes)	8	16	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Keratoacanthoma			
subjects affected / exposed	2 / 26 (7.69%)	3 / 25 (12.00%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma in situ			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	7 / 26 (26.92%)	5 / 25 (20.00%)	
occurrences causally related to treatment / all	15 / 15	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multi-organ failure			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (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			
Aspiration			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
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			
Radiation necrosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 26 (3.85%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
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	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral lichen planus			

subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal vein thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
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 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral labyrinthitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
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	1 / 26 (3.85%)	0 / 25 (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	TKI Naive	TKI Experienced	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	24 / 25 (96.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	5 / 26 (19.23%)	1 / 25 (4.00%)	
occurrences (all)	6	1	
Dysplastic naevus			
subjects affected / exposed	3 / 26 (11.54%)	3 / 25 (12.00%)	
occurrences (all)	5	5	
Haemangioma			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	2	
Melanocytic naevus			
subjects affected / exposed	6 / 26 (23.08%)	3 / 25 (12.00%)	
occurrences (all)	8	5	
Seborrhoeic keratosis			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	3	
Skin papilloma			
subjects affected / exposed	13 / 26 (50.00%)	8 / 25 (32.00%)	
occurrences (all)	26	10	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 26 (23.08%)	3 / 25 (12.00%)	
occurrences (all)	7	3	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	5 / 26 (19.23%)	3 / 25 (12.00%)	
occurrences (all)	6	4	
Chills			
subjects affected / exposed	2 / 26 (7.69%)	4 / 25 (16.00%)	
occurrences (all)	2	5	
Cyst			
subjects affected / exposed	5 / 26 (19.23%)	0 / 25 (0.00%)	
occurrences (all)	11	0	
Fatigue			
subjects affected / exposed	18 / 26 (69.23%)	14 / 25 (56.00%)	
occurrences (all)	28	20	
Induration			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Localised oedema			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Nodule			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	
occurrences (all)	6	1	
Oedema peripheral			
subjects affected / exposed	4 / 26 (15.38%)	7 / 25 (28.00%)	
occurrences (all)	8	10	
Peripheral swelling			
subjects affected / exposed	0 / 26 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	6 / 25 (24.00%)	
occurrences (all)	1	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 26 (3.85%)	5 / 25 (20.00%)	
occurrences (all)	1	6	
Dysphonia			

subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 26 (3.85%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Productive cough			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Vocal cord thickening			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	
occurrences (all)	5	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 26 (15.38%)	5 / 25 (20.00%)	
occurrences (all)	5	5	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 26 (19.23%)	6 / 25 (24.00%)	
occurrences (all)	9	6	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 26 (26.92%)	6 / 25 (24.00%)	
occurrences (all)	12	8	
Blood bilirubin increased			

subjects affected / exposed	10 / 26 (38.46%)	10 / 25 (40.00%)		
occurrences (all)	22	13		
Blood creatinine increased				
subjects affected / exposed	13 / 26 (50.00%)	6 / 25 (24.00%)		
occurrences (all)	17	7		
Blood glucose increased				
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)		
occurrences (all)	3	0		
Blood pressure increased				
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)		
occurrences (all)	0	2		
Blood thyroid stimulating hormone increased				
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)		
occurrences (all)	2	1		
Blood uric acid increased				
subjects affected / exposed	4 / 26 (15.38%)	2 / 25 (8.00%)		
occurrences (all)	5	8		
Electrocardiogram QT prolonged				
subjects affected / exposed	4 / 26 (15.38%)	0 / 25 (0.00%)		
occurrences (all)	6	0		
Gamma-glutamyltransferase increased				
subjects affected / exposed	7 / 26 (26.92%)	7 / 25 (28.00%)		
occurrences (all)	7	11		
Haemoglobin decreased				
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)		
occurrences (all)	0	2		
Lymphocyte count decreased				
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)		
occurrences (all)	3	0		
Platelet count decreased				
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)		
occurrences (all)	0	2		
Weight decreased				

subjects affected / exposed	14 / 26 (53.85%)	14 / 25 (56.00%)	
occurrences (all)	15	19	
White blood cell count decreased			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Sunburn			
subjects affected / exposed	3 / 26 (11.54%)	4 / 25 (16.00%)	
occurrences (all)	4	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 26 (7.69%)	8 / 25 (32.00%)	
occurrences (all)	2	12	
Dysgeusia			
subjects affected / exposed	14 / 26 (53.85%)	6 / 25 (24.00%)	
occurrences (all)	16	6	
Headache			
subjects affected / exposed	7 / 26 (26.92%)	6 / 25 (24.00%)	
occurrences (all)	11	6	
Paraesthesia			
subjects affected / exposed	6 / 26 (23.08%)	1 / 25 (4.00%)	
occurrences (all)	8	2	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 26 (34.62%)	13 / 25 (52.00%)	
occurrences (all)	15	17	
Leukopenia			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	
occurrences (all)	6	2	
Lymphopenia			

subjects affected / exposed	5 / 26 (19.23%)	5 / 25 (20.00%)	
occurrences (all)	7	5	
Neutropenia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Photophobia			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Scleral discolouration			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Vision blurred			
subjects affected / exposed	2 / 26 (7.69%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	4 / 26 (15.38%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Diarrhoea			
subjects affected / exposed	12 / 26 (46.15%)	6 / 25 (24.00%)	
occurrences (all)	22	8	
Dry mouth			

subjects affected / exposed	3 / 26 (11.54%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	3	
Dysphagia			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	
occurrences (all)	4	4	
Gingival bleeding			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Leukoplakia oral			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	13 / 26 (50.00%)	7 / 25 (28.00%)	
occurrences (all)	26	9	
Oral disorder			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	2 / 26 (7.69%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	6 / 26 (23.08%)	6 / 25 (24.00%)	
occurrences (all)	12	10	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	7 / 26 (26.92%)	4 / 25 (16.00%)	
occurrences (all)	15	5	
Alopecia			

subjects affected / exposed	14 / 26 (53.85%)	7 / 25 (28.00%)	
occurrences (all)	16	7	
Dermal cyst			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	
occurrences (all)	8	3	
Dermatitis			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Dermatitis acneiform			
subjects affected / exposed	4 / 26 (15.38%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Dry skin			
subjects affected / exposed	6 / 26 (23.08%)	6 / 25 (24.00%)	
occurrences (all)	8	7	
Erythema			
subjects affected / exposed	2 / 26 (7.69%)	5 / 25 (20.00%)	
occurrences (all)	2	5	
Erythema nodosum			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Hyperkeratosis			
subjects affected / exposed	11 / 26 (42.31%)	6 / 25 (24.00%)	
occurrences (all)	16	19	
Keratosis pilaris			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	
occurrences (all)	4	3	
Macule			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Milia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Nail growth abnormal			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Palmar-plantar erythrodysaesthesia			

syndrome			
subjects affected / exposed	8 / 26 (30.77%)	6 / 25 (24.00%)	
occurrences (all)	8	7	
Panniculitis			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	4	3	
Papule			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	2	5	
Photosensitivity reaction			
subjects affected / exposed	8 / 26 (30.77%)	6 / 25 (24.00%)	
occurrences (all)	16	6	
Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	4 / 25 (16.00%)	
occurrences (all)	2	5	
Rash			
subjects affected / exposed	11 / 26 (42.31%)	7 / 25 (28.00%)	
occurrences (all)	14	11	
Rash macular			
subjects affected / exposed	1 / 26 (3.85%)	4 / 25 (16.00%)	
occurrences (all)	1	4	
Rash maculo-papular			
subjects affected / exposed	6 / 26 (23.08%)	4 / 25 (16.00%)	
occurrences (all)	6	5	
Rash papular			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	
occurrences (all)	3	2	
Seborrhoeic dermatitis			
subjects affected / exposed	2 / 26 (7.69%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Skin exfoliation			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Skin hyperpigmentation			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	

Skin induration			
subjects affected / exposed	5 / 26 (19.23%)	1 / 25 (4.00%)	
occurrences (all)	7	1	
Skin lesion			
subjects affected / exposed	5 / 26 (19.23%)	4 / 25 (16.00%)	
occurrences (all)	5	8	
Skin mass			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Micturition urgency			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Pollakiuria			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Proteinuria			
subjects affected / exposed	6 / 26 (23.08%)	4 / 25 (16.00%)	
occurrences (all)	9	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 26 (46.15%)	9 / 25 (36.00%)	
occurrences (all)	24	10	
Back pain			
subjects affected / exposed	3 / 26 (11.54%)	4 / 25 (16.00%)	
occurrences (all)	3	4	
Bursitis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Muscular weakness			

subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Musculoseletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Musculoskeletal pain			
subjects affected / exposed	3 / 26 (11.54%)	5 / 25 (20.00%)	
occurrences (all)	3	5	
Myalgia			
subjects affected / exposed	9 / 26 (34.62%)	5 / 25 (20.00%)	
occurrences (all)	16	7	
Neck pain			
subjects affected / exposed	4 / 26 (15.38%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Pain in extremity			
subjects affected / exposed	4 / 26 (15.38%)	7 / 25 (28.00%)	
occurrences (all)	7	12	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 26 (11.54%)	2 / 25 (8.00%)	
occurrences (all)	3	3	
Conjunctivitis			
subjects affected / exposed	4 / 26 (15.38%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Folliculitis			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Hordeolum			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	3 / 26 (11.54%)	2 / 25 (8.00%)	
occurrences (all)	5	2	
Nasopharyngitis			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	2	3	

Oral candidiasis			
subjects affected / exposed	3 / 26 (11.54%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Rhinitis			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Skin infection			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	3 / 26 (11.54%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	3 / 26 (11.54%)	4 / 25 (16.00%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 26 (50.00%)	11 / 25 (44.00%)	
occurrences (all)	16	11	
Dehydration			
subjects affected / exposed	1 / 26 (3.85%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Hypercholesterolaemia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Hyperglycaemia			
subjects affected / exposed	4 / 26 (15.38%)	5 / 25 (20.00%)	
occurrences (all)	9	8	
Hyperkalaemia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Hypoalbuminaemia			

subjects affected / exposed	2 / 26 (7.69%)	5 / 25 (20.00%)	
occurrences (all)	3	7	
Hypocalcaemia			
subjects affected / exposed	5 / 26 (19.23%)	4 / 25 (16.00%)	
occurrences (all)	10	8	
Hypoglycaemia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	3 / 26 (11.54%)	6 / 25 (24.00%)	
occurrences (all)	4	10	
Hypomagnesaemia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Hyponatraemia			
subjects affected / exposed	4 / 26 (15.38%)	7 / 25 (28.00%)	
occurrences (all)	6	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2011	Revised secondary and exploratory objectives; revised eligibility criteria; allowed dose adjustments for medications predominantly metabolized by CYP1A2 and CYP3A4, as well as warfarin or other narrow therapeutic index drugs metabolized by CYP2C9; revised dosing instructions to state that co-administration of vemurafenib with drugs that cause QTc prolongation or cardiac arrhythmia should be avoided; added that dosing was to be interrupted if subject QT interval was > 500 ms or if there was a change of > 60 ms from baseline, and that other cardiac risk factors (e.g., hypertension, CHF, bradyarrhythmias, diabetes, etc.) were to be corrected per standard of care; added that all squamous cell carcinoma (SCC) and keratoacanthoma (KA) adverse events be reported as serious adverse events; revised secondary variables; revised to state that a DSMB would be utilized to ensure subject safety; reduced length of time that subjects were to use contraception after discontinuation of vemurafenib was reduced from 12 months to 6 months.
22 December 2011	Lengthened follow-up time for development of secondary malignancies to 12 months; allowed subjects with prior treatment with multi-targeted TKIs with activity against VEGFR2 to be eligible if the therapies did not specifically or selectively target BRAF or MEK pathway, without requiring the subject to have also failed sorafenib; revised primary and secondary objectives; papillary thyroid carcinoma (PTC) histologies that were eligible for enrollment were clarified and specified in more detail; clarified language regarding concomitant medications metabolized via CYP1A2 and CYP3A4; identified additional adverse events of special interest; content was added to specify that cuSCC events were to be reported to the sponsor as SAEs.
04 May 2012	Clarified that the RMP exists to evaluate subjects for the development of SCC or of any new primary malignancy that occurred during the treatment period and up to 12 months post-last dose; added mandatory laryngoscopy after 9 months of treatment and every 6 months thereafter during vemurafenib treatment to evaluate for new primary malignancies/neoplasms.
29 October 2012	Clarified the schedule of assessments for laryngoscopy, dermatology evaluation, and the head and neck examination ass part of the safety evaluation for SCC.
30 April 2014	Allow subjects still on active therapy to rollover to extension study GO28399; every-3-month PK sampling and central ECG review were removed from the schedule of assessments because these data were already well characterized and further collection of this data was no longer warranted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported