Clinical trial results:
An open-label, multicenter, single-arm, Phase I dose-escalation with efficacy tail extension study of vemurafenib (RO5185426) in pediatric patients with surgically incurable and unresectable Stage IIIC or Stage IV melanoma harboring BRAFV600 mutations

Summary

EudraCT number	2011-000874-67
Trial protocol	DE GB IT SK ES PL
Global end of trial date	18 December 2015

Results information

Result version number	v2 (current)
This version publication date	10 September 2016
First version publication date	03 July 2016
Version creation reason	• Correction of full data set Record update for consistency with CTg record based on NIH comments.

Trial information

Trial identification

Sponsor protocol code	NO25390

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01519323
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000978-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the maximum tolerated dose (MTD) and to identify the recommended dose of vemurafenib in pediatric subjects aged 12 through 17 years with newly diagnosed or recurrent unresectable stage IIIc or stage IV BRAF mutation positive melanoma. This objective was to be accomplished in the dose escalation phase of the study.

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	24 January 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	Slovakia: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	6
EEA total number of subjects	4

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)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First investigational site was activated on 22 December 2011.

Pre-assignment

Screening details:

Subjects were enrolled in two separate cohorts with different starting doses based on greater than or equal to (>=)45 kilogram (kg) and other weighing less than (<)45 kg. Subjects >=45 kg were then enrolled in a dose escalation period. No subjects were enrolled in the <45 kg cohort.

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	Vemurafenib Dose Escalation Cohort Level 1

Arm description:

Subjects received 720 milligram (mg) of vemurafenib by mouth twice daily (BID).

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

Dosage and administration details:

Subjects with >=45 kg weight received vemurafenib (film-coated tablet) 720 mg by mouth BID on Day 1 of each cycle until disease progression, death or unacceptable toxicity.

Arm title	Vemurafenib Dose Escalation Cohort Level 2

Arm description:

Subjects received 960 mg of vemurafenib by mouth BID.

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

Dosage and administration details:

Subjects with >=45 kg weight received vemurafenib (film-coated tablet) 960 mg by mouth BID on Day 1 of each cycle until disease progression, death or unacceptable toxicity.

Number of subjects in period 1	Vemurafenib Dose Escalation Cohort Level 1	Vemurafenib Dose Escalation Cohort Level 2
Started	3	3
Completed	0	0
Not completed	3	3
Death	3	2
Study terminated by sponsor	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 15.8 ± 0.8	 -	
Gender categorical Units: Subjects			
Female	2	2	
Male	4	4	

Subject analysis sets

Subject analysis set title	Vemurafenib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received vemurafenib into two separate cohorts with different starting doses based on >=45 kg and other weighing <45 kg. The starting dose for subjects >=45 kg was 720 mg of vemurafenib by mouth BID and the next dose level for subjects in this cohort was 960 mg by mouth BID. The starting dose level for subjects weighing <45 kg was to be 480 mg of vemurafenib by mouth BID, but no subjects were enrolled into this cohort.

Reporting group values	Vemurafenib		
Number of subjects	6		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 15.8 ± 0.8	 	
Gender categorical Units: Subjects			
Female	2		
Male	4		

End points

End points reporting groups

Reporting group title	Vemurafenib Dose Escalation Cohort Level 1

Reporting group description:

Subjects received 720 milligram (mg) of vemurafenib by mouth twice daily (BID).

Reporting group title	Vemurafenib Dose Escalation Cohort Level 2

Reporting group description:

Subjects received 960 mg of vemurafenib by mouth BID.

Subject analysis set title	Vemurafenib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received vemurafenib into two separate cohorts with different starting doses based on >=45 kg and other weighing <45 kg. The starting dose for subjects >=45 kg was 720 mg of vemurafenib by mouth BID and the next dose level for subjects in this cohort was 960 mg by mouth BID. The starting dose level for subjects weighing <45 kg was to be 480 mg of vemurafenib by mouth BID, but no subjects were enrolled into this cohort.

Primary: Maximum Tolerated Dose (MTD)/Recommended Dose

End point title	Maximum Tolerated Dose (MTD)/Recommended Dose[1]

End point description:

The MTD was defined as the dose level at which six evaluable subjects had been treated and at most one subject experienced a dose limiting toxicity (DLT) and the next highest dose level was too toxic. Dose escalation occurred if 0 out of 3 or at most 1 out of 6 subject experienced DLT while being treated at a dose level; otherwise the dose was declared unsafe and thus above the MTD.

End point type	Primary

End point timeframe:

Up to 28 days of treatment

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: Only descriptive data was planned to be reported.

End point values	Vemurafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[2]			
Units: mg				
arithmetic mean (standard deviation)	()			

Notes:

[2] - A MTD could not be determined in this study because of the low number of subjects enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve for Vemurafenib

End point title	Area Under the Concentration-Time Curve for Vemurafenib

End point description:

Pharmacokinetic (PK) population included all enrolled subjects who received at least one dose or a partial dose of study treatment and provided at least one post-dose blood sample for PK analysis.

End point type	Secondary

End point timeframe:

Pre-dose, 2, 4, 8, 12 hours post dose on Cycle 1 Day 1 and Cycle 1 Day 22 (each cycle is of 28 days)

End point values	Vemurafenib Dose Escalation Cohort Level 1	Vemurafenib Dose Escalation Cohort Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: hour*nanogram per millilitre (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	16300 (± 80.5)	57000 (± 95.5)		
Cycle 1 Day 22	486000 (± 26.7)	963000 (± 23.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With an Adverse Event (AE)

End point title	Number of Subjects With an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with study treatment. Safety population included all subjects who received at least one dose or a partial dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 2 years 11 months

End point values	Vemurafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR)

End point title	Best Overall Response Rate (BORR)

End point description:

BORR was assessed by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. BORR was defined as the number of subjects who achieved a complete response (CR) or partial response (PR). CR was defined as complete disappearance of all target lesions and non-target disease. PR was defined as a >=30% decrease under baseline of the sum of diameters of all target lesions. BORR was summarized along with the associated exact 95% confidence interval (CI) using the method of Clopper–Pearson. Intent to treat population included all subjects enrolled.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Vemurafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 45.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR was defined as the number of subjects that achieved a CR, PR or stable disease (SD) (SD for at least 6 weeks) as assessed by investigators according to the RECIST v1.1. CR was defined as complete disappearance of all target lesions and non-target disease. PR was defined as a >=30% decrease under baseline of the sum of diameters of all target lesions. SD was defined as steady state of disease with neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). Intent to treat population included all subjects enrolled.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Vemurafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: percentage of subjects				
number (not applicable)	66.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time between the day of first treatment and the first documentation of progressive disease or death. Progression was defined as a 20% increase in the sum of the longest diameter of target lesions, the appearance of new lesions and increase of at least 5 mm in the sum of diameters of target lesions. Subjects who were withdrawn from the study without documented progression were to be censored at the date of the last known tumor assessment when the subject was known to be progression free. Median PFS was estimated using Kaplan-Meier method and 95% CI for median was computed using the Brookmeyer and Crowley method. Intent to treat population included all subjects enrolled.

End point type	Secondary

End point timeframe:

Randomisation date of first subject until disease progression or death or which ever occur first (2 years)

End point values	Vemurafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: days				
median (confidence interval 95%)	134.5 (83 to 157)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time 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 their last being known alive. Median overall survival was estimated using Kaplan-Meier method and 95% CI for median was computed using the Brookmeyer and Crowley method. Intent to treat population included all subjects enrolled.

End point type	Secondary

End point timeframe:

Randomisation date of first subject until death (2 years)

End point values	Vemurafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: days				
median (confidence interval 95%)	246.5 (156 to 364)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were reported for approximately 2 years 11 months. Related serious adverse events were required to be reported regardless of the time elapsed from the last study drug administration, even if the study had been closed.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a subject administered the investigational product which does not necessarily have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Vemurafenib

Reporting group description:

Subjects received vemurafenib into two separate cohorts with different starting doses based on >=45 kg and other weighing <45 kg. The starting dose for subjects >=45 kg was 720 mg of vemurafenib by BID and the next dose level for subjects in this cohort was 960 mg by mouth BID. The starting dose level for subjects weighing <45 kg was to be 480 mg of vemurafenib by mouth BID, but no subjects were enrolled into this cohort.

Serious adverse events	Vemurafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Squamous cell carcinoma			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Vemurafenib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Laryngeal inflammation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Platelet count decreased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
White blood cell count decreased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	3			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood cholesterol increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood phosphorus increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Carbon dioxide decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	2			
Lymphocyte count decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Neutrophil count decreased				

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Overdose subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all) Sinus bradycardia subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 2 1 / 6 (16.67%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 4 / 6 (66.67%) 7 1 / 6 (16.67%) 1 1 / 6 (16.67%) 2 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2		

Lymphopenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 8		
Nausea subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 4		
Vomiting subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Stomatitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders			

Photosensitivity reaction			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Alopecia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Dermatitis acneiform			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	4		
Skin mass			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Haemoglobinuria			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nephrolithiasis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Renal colic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			

Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Scrotal abscess			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Viral pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypokalaemia			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2013	1.The following text was added to Dose Escalation and Extension Phases for the Smaller Subject Cohort (Subjects Weighing <45 kg) "If the MTD can be determined for subjects weighing <45 kg, then these subjects may be enrolled in the extension phase at the recommended dose. If the MTD is the same for subjects weighing <45 kg as for those weighing >=45 kg, then subjects weighing <45 kg and enrolled in the extension phase will count as part of the 20 subjects required for extension phase accrual and analysis." 2.The squamous cell carcinoma (SCC) risk management plan to monitor for the occurrence of new primary melanoma and both cutaneous and non-cutaneous SCCs was updated. The appropriate sections of the protocol were revised to reflect this change. 3.The text was revised to state that an electrocardiogram (ECG) was required at the treatment completion visit. This had been inadvertently omitted in the original protocol and was changed to align with the Paediatric Investigation Plan (PIP). 4.The text was revised to state that tissue samples of any new primary melanoma or SCC (cutaneous and non cutaneous) were to be submitted to a central pathology laboratory to undergo molecular characterization. 5.The definitions of adverse event of special interest (AESIs) were revised to align with the vemurafenib program. The list of AESIs was changed to: a) Grade >=3 phototoxicity b) Grade >=3 QTc prolongation c) Grade >=4 elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin d) SCC (cutaneous and non-cutaneous including keratoacanthoma [KA]) e) New primary melanoma f) Non-SCC/KA suspicious skin lesions 6.Definition of Women of Childbearing Potential and Acceptable and Unacceptable Forms of Contraception was revised to shorten from 12 months to 6 months the period that women of childbearing potential were required to use 2 forms of acceptable contraception following discontinuation of vemurafenib.
13 September 2013	1.The definitions of AESIs were revised as follows: a) "A new primary invasive malignancy (other than cuSCC or new primary melanoma) or progression or recurrence of a prior invasive malignancy (other than the disease under study)" was added. b) "Grade >=3 phototoxicity" was deleted. c) "Non-SCC/KA suspicious skin lesions" was deleted. 2.Additional Assessments for SCC risk management plan [Treating Physician]) was clarified that chest CT scans that were required following study drug discontinuation needed to be obtained only up to 6 months after study drug discontinuation.
11 March 2014	1.The purpose of the amendment was to update the safety information in the Introduction section of the protocol, and to make other minor changes to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated on 18 December 2015 by the Sponsor due to recruitment challenges and therefore low enrollment.

Notes: