



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 | <ul style="list-style-type: none">• 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) | EMA-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 (\geq)45 kilogram (kg) and other weighing less than ($<$)45 kg. Subjects \geq 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 \geq 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 \geq 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 | 15.8 | | |
| standard deviation | ± 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 | 15.8 | | |
| standard deviation | ± 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 $\geq 30\%$ 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 $\geq 30\%$ 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 occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 6 (16.67%) 0 / 1 0 / 0 | | |
| Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 6 (16.67%) 0 / 1 0 / 0 | | |
| Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 6 (16.67%) 0 / 1 0 / 0 | | |
| Musculoskeletal and connective tissue disorders Spinal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 6 (16.67%) 0 / 1 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 occurrences (all) Hypertension subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 2 / 6 (33.33%) 3 1 / 6 (16.67%) 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 occurrences (all) | 3 / 6 (50.00%) 4 | | |
| Rash subjects affected / exposed occurrences (all) | 3 / 6 (50.00%) 4 | | |
| Alopecia subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 3 | | |
| Dry skin subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Pain of skin subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 4 | | |
| Skin mass subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 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 occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Oral candidiasis subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Oral herpes subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Scrotal abscess subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Skin infection subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Viral pharyngitis subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Hypokalaemia | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 12 April 2013 | <p>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."</p> <p>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.</p> <p>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).</p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none">a) Grade ≥3 phototoxicityb) Grade ≥3 QTc prolongationc) Grade ≥4 elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubind) SCC (cutaneous and non-cutaneous including keratoacanthoma [KA])e) New primary melanomaf) Non-SCC/KA suspicious skin lesions <p>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.</p> |
| 13 September 2013 | <p>1.The definitions of AESIs were revised as follows:</p> <ul style="list-style-type: none">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. <p>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.</p> |
| 11 March 2014 | <p>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.</p> |

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: