Clinical trial results:
BRIM 3: A Randomized, Open-Label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients with Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving Vemurafenib (RO5185426) or Dacarbazine

Summary

EudraCT number	2009-012293-12
Trial protocol	NL DE FR SE IT GB
Global end of trial date	08 July 2015

Results information

Result version number	v2 (current)
This version publication date	22 July 2016
First version publication date	15 March 2015
Version creation reason	
Summary attachment (see zip file)	NO25026 CTg Receipt (NO25026 Receipt.pdf)

Trial information

Trial identification

Sponsor protocol code	NO25026

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01006980
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, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 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	08 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, open-label study evaluated the efficacy, safety and tolerability of vemurafenib (RO5185426) as compared to dacarbazine in previously untreated subjects with metastatic melanoma. Subjects were randomized to receive either vemurafenib 960 mg orally twice daily or dacarbazine 1000 mg/m2 intravenously every 3 weeks. Anticipated time on study treatment was until occurrence of disease progression or unacceptable toxicity. Subjects in the dacarbazine arm were permitted to cross over to vemurafenib treatment.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 57
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	France: 103
Country: Number of subjects enrolled	Germany: 93
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Italy: 70
Country: Number of subjects enrolled	Netherlands: 40
Country: Number of subjects enrolled	New Zealand: 20
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Switzerland: 22
Country: Number of subjects enrolled	United Kingdom: 74
Country: Number of subjects enrolled	United States: 139
Worldwide total number of subjects	675
EEA total number of subjects	386

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)	1
Adults (18-64 years)	513
From 65 to 84 years	157
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

675 participants were randomized. One participant randomized to dacarbazine was treated in error with vemurafenib throughout the study and is included in the Vemurafenib arm in the table below and for exposure and safety analyses and is included in the dacarbazine arm for efficacy analyses.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vemurafenib

Arm description:

Participants received continuous oral doses of vemurafenib (RO5185426) 960 mg twice a day. Participants took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).

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

Dosage and administration details:

960 mg (4 x 240 mg tablets) twice daily

Arm title	Dacarbazine

Arm description:

Dacarbazine was administered intravenously 1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks

Number of subjects in period 1	Vemurafenib	Dacarbazine
Started	337	338
Treated	336	293
Completed	0	0
Not completed	337	338
Withdrawal of Consent	4	6
Protocol violation	2	3
Randomized but not treated	1	45
Adverse event, non-fatal	25	5
Refuse Treatment	9	6
Death	13	12
Reason Not Specified	26	43
Progression	257	218

Baseline characteristics

Reporting groups	
Reporting group title	Vemurafenib
Reporting group description:	
Participants received continuous oral doses of vemurafenib (RO5185426) 960 mg twice a day. Participants took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).	
Reporting group title	Dacarbazine
Reporting group description:	
Dacarbazine was administered intravenously 1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).	

Reporting group values	Vemurafenib	Dacarbazine	Total
Number of subjects	337	338	675
Age categorical Units: Subjects			
< 65 years	244	270	514
>=65 years	93	68	161
Gender, Male/Female Units: participants			
Female	137	157	294
Male	200	181	381

End points

End points reporting groups

Reporting group title	Vemurafenib

Reporting group description:

Participants received continuous oral doses of vemurafenib (RO5185426) 960 mg twice a day. Participants took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).

Reporting group title	Dacarbazine

Reporting group description:

Dacarbazine was administered intravenously 1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Primary: Overall Survival

End point title	Overall Survival

End point description:

An Overall survival event was defined as death due to any cause. The number of participants with overall survival events is reported.

The intent-to-treat (ITT) population was defined as all randomized participants, whether or not study treatment was received. The ITT population was analyzed according to the treatment assigned at randomization. Overall survival was assessed on participants randomized at least 15 days prior to the clinical cutoff date of December 30, 2010.

End point type	Primary

End point timeframe:

From randomization (initiated January 2010) to December 30 2010. Median follow-up time in the vemurafenib group was 3.75 months (range 0.3 to 10.8) and in the dacarbazine group was 2.33 months (range <0.1 to 10.3).

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336	336		
Units: participants				
number (not applicable)				
Participants with events	43	75		
Participants without events	293	261		

Statistical analyses

Statistical analysis title	Statistical analysis - Overall Survival

Statistical analysis description:

The trial had a power of 80% to detect a hazard ratio of 0.65 for overall survival with an alpha level of 0.045 (an increase in median survival from 8 months for dacarbazine to 12.3 months for vemurafenib), one interim analysis for overall survival at 50% information.

The hazard ratio for death for vemurafenib relative to dacarbazine and the associated 95% confidence interval were computed using an unstratified Cox regression model.

Comparison groups	Vemurafenib v Dacarbazine
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.55

Primary: Progression-free Survival

End point title	Progression-free Survival

End point description:

A progression-free survival (PFS) event was defined as disease progression or death due to any cause. Tumor response (progression) was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria using computed tomography (CT) scans or magnetic resonance imaging (MRI).

The analysis population for PFS consisted of all ITT participants randomized by October 27, 2010 (at least 9 weeks prior to the clinical cutoff date of December 30, 2010). The 9-week interval was chosen to allow time for participants to have had their first scheduled post baseline tumor assessment CT scan.

End point type	Primary

End point timeframe:

From randomization (initiated January 2010) to December 30 2010.

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	275	274		
Units: participants				
number (not applicable)				
Participants with events	104	182		
Participants without events	171	92		

Statistical analyses

Statistical analysis title	Statistical analysis - PFS

Statistical analysis description:

The trial had a power of 90% to detect a hazard ratio of 0.55 for progression-free survival with an alpha level of 0.005 (an increase in median survival from 2.5 months for dacarbazine to 4.5 months for vemurafenib).

Hazard ratios for treatment with vemurafenib, as compared with dacarbazine, were estimated with the

use of unstratified Cox regression.

Comparison groups	Vemurafenib v Dacarbazine
Number of subjects included in analysis	549
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.33

Secondary: Participants with a Best Overall Response (BOR) of complete response or partial response

End point title	Participants with a Best Overall Response (BOR) of complete response or partial response

End point description:

BOR was defined as a complete response (CR) or partial response (PR) confirmed per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Participants who never received study treatment and treated participants without any post-baseline tumor assessments were considered as non-responders. CR: Disappearance of all target lesions, all non-target lesions and no new lesion. Any pathological lymph nodes must have had reduction in the short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion and no new lesion.

The analysis population consisted of all ITT participants randomized by September 22, 2010 (at least 14 weeks prior to the clinical cutoff date of December 30, 2010). The 14-week interval was chosen as it was the minimum time needed to observe a confirmed overall response according to protocol-specified schedule for the first two tumor assessments.

End point type	Secondary

End point timeframe:

From randomization (initiated January 2010) until December 30, 2010

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: participants				
number (not applicable)				
Responders	106	12		
Non-responders	113	208		

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 was defined as the time between the date of the earliest qualifying response and the date of disease progression or death due to any cause. Duration of response was calculated only for participants who had a best overall response of Complete Response or Partial Response and was estimated using the Kaplan–Meier method.

The analysis population included all participants randomized by September 22, 2010 and with a best overall confirmed response of complete response or partial response.

999 = Median duration of response was not reached as only 2 of the 12 participants with a qualifying response had subsequent disease progression or death due to any cause at the time of the analysis.

End point type	Secondary

End point timeframe:

From randomization (initiated in January 2010) until December 30, 2010.

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	12		
Units: months				
median (confidence interval 95%)	5.49 (3.98 to 5.72)	999 (4.6 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to confirmed response

End point title	Time to confirmed response

End point description:

Time to response was defined as the time from randomization to confirmed response (complete response or partial response).

The analysis population included all participants randomized by September 22, 2010 and with a best overall confirmed response of complete response or partial response.

End point type	Secondary

End point timeframe:

From randomization (initiated January 2010) until December 30, 2010.

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	12		
Units: months				
median (full range (min-max))	1.45 (1 to 5.5)	2.72 (1.6 to 5.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Treatment failure was defined as a secondary endpoint in the protocol, defined as death, disease progression or premature withdrawal of study treatment. This endpoint was not included in the Statistical analysis plan; therefore no analyses of time to treatment failure were performed.

End point type	Secondary

End point timeframe:

approximately 3 years

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[1] - Data not analyzed; no subjects achieved clinical remission during the study.

[2] - Data not analyzed; no subjects achieved clinical remission during the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs)

End point title	Number of participants with adverse events (AEs)

End point description:

The intensity of AEs was graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (Grade 1 to 5: Mild, Moderate, Severe, Life-threatening and Death). A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution, for example is life-threatening, requires hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or requires intervention to prevent one or other of the outcomes listed above.

The safety population was defined as all treated participants who had at least one on-study assessment. The safety population was analyzed according to the treatment received.

End point type	Secondary

End point timeframe:

From randomization (initiated January 2010) until December 30, 2010.

End point values	Vemurafenib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336	282		
Units: participants				
number (not applicable)				
Any adverse event	326	253		
Serious adverse event	110	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Pre and Post-dose Plasma vemurafenib Concentration by Study Day

End point title	Pre and Post-dose Plasma vemurafenib Concentration by Study Day[3]

End point description:

The pharmacokinetics of vemurafenib were assessed at the beginning of each 21-day cycle using predose and 2-4 hours post-dose sampling.

The pharmacokinetic (PK) analysis population included all participants who received vemurafenib and provided valid PK assessments. The PK population at specific time points varied depending on the availability of confirmed dosing and PK assessment times. "n" indicates the number of participants with available PK data at each time point.

End point type	Secondary

End point timeframe:

Plasma samples were collected before the morning dose (troughs) and 2-4 hours after the morning dose at the beginning of each cycle (Days 1, 22, 43, 64, 106, 148 and 190).

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: Descriptive analysis was performed.

End point values	Vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	260			
Units: µg/mL				
arithmetic mean (standard deviation)				
Pre-Dose Day 1 (n = 260)	0 (± 0)			
Post-Dose Day 1 (n = 255)	4.3 (± 4.35)			
Pre-Dose Day 22 (n = 204)	53 (± 26.66)			
Post-Dose Day 22 (n = 221)	54 (± 25.67)			
Pre-Dose Day 43 (n = 166)	54.4 (± 24.13)			
Post-Dose Day 43 (n = 170)	54.4 (± 23.28)			
Pre-Dose Day 64 (n = 141)	57.4 (± 23.79)			
Post-Dose Day 64 (n = 138)	57.7 (± 22.29)			

Pre-Dose Day 106 (n = 77)	55 (± 17.62)			
Post-Dose Day 106 (n = 75)	56.3 (± 20.36)			
Pre-Dose Day 148 (n = 38)	51.8 (± 24.13)			
Post-Dose Day 148 (n = 39)	53.3 (± 21.55)			
Pre-Dose Day 190 (n = 9)	53.6 (± 12.6)			
Post-Dose Day 190 (n = 9)	50.5 (± 20.16)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through the end of study (maximum exposure: 57.07 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Vemurafenib

Reporting group description:

Adverse events reported for this group include those occurring in participants receiving vemurafenib starting at their baseline visit.

Participants received continuous oral doses of vemurafenib (RO5185426) 960 mg twice a day. Participants took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).

Reporting group title	Dacarbazine

Reporting group description:

Adverse events reported for this group include those occurring in participants receiving dacarbazine starting at their baseline visit until study discontinuation or treatment switch.

Dacarbazine was administered intravenously 1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Reporting group title	Vemurafenib After Crossover

Reporting group description:

Adverse events reported for this group include those occurring following switch to vemurafenib in those participants who switched from dacarbazine to vemurafenib during the study.

Serious adverse events	Vemurafenib	Dacarbazine	Vemurafenib After Crossover
Total subjects affected by serious adverse events			
subjects affected / exposed	165 / 336 (49.11%)	52 / 293 (17.75%)	44 / 84 (52.38%)
number of deaths (all causes)	271	170	71
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	10 / 336 (2.98%)	2 / 293 (0.68%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	16 / 18	0 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	3 / 336 (0.89%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	36 / 336 (10.71%)	3 / 293 (1.02%)	6 / 84 (7.14%)
occurrences causally related to treatment / all	47 / 47	1 / 3	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	7 / 336 (2.08%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	6 / 8	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin papilloma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	66 / 336 (19.64%)	2 / 293 (0.68%)	12 / 84 (14.29%)
occurrences causally related to treatment / all	129 / 129	0 / 2	15 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 336 (0.00%)	2 / 293 (0.68%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	3 / 336 (0.89%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 336 (0.60%)	1 / 293 (0.34%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 336 (1.49%)	4 / 293 (1.37%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	2 / 5	3 / 6	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 336 (0.89%)	2 / 293 (0.68%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Epistaxis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	3 / 336 (0.89%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	4 / 336 (1.19%)	2 / 293 (0.68%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood bilirubin increased			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio decreased			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			

subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 336 (0.89%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensorimotor disorder			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orbital oedema			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	3 / 336 (0.89%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 336 (0.60%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhagee			

subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 336 (0.60%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	3 / 336 (0.89%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 336 (0.89%)	1 / 293 (0.34%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage urinary tract			

subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 336 (0.89%)	2 / 293 (0.68%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatinaemia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			

subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 336 (1.49%)	2 / 293 (0.68%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 5	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 336 (0.60%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	1 / 336 (0.30%)	0 / 293 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 336 (0.00%)	0 / 293 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 336 (0.30%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vemurafenib	Dacarbazine	Vemurafenib After Crossover
Total subjects affected by non-serious adverse events			
subjects affected / exposed	333 / 336 (99.11%)	247 / 293 (84.30%)	83 / 84 (98.81%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	39 / 336 (11.61%)	3 / 293 (1.02%)	9 / 84 (10.71%)
occurrences (all)	56	3	11
Seborrhoeic keratosis			
subjects affected / exposed	46 / 336 (13.69%)	2 / 293 (0.68%)	8 / 84 (9.52%)
occurrences (all)	61	2	11
Skin papilloma			
subjects affected / exposed	96 / 336 (28.57%)	1 / 293 (0.34%)	17 / 84 (20.24%)
occurrences (all)	162	1	24
Vascular disorders			
Flushing			

subjects affected / exposed	17 / 336 (5.06%)	6 / 293 (2.05%)	2 / 84 (2.38%)
occurrences (all)	19	11	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	50 / 336 (14.88%)	29 / 293 (9.90%)	7 / 84 (8.33%)
occurrences (all)	70	47	13
Chest pain			
subjects affected / exposed	26 / 336 (7.74%)	5 / 293 (1.71%)	4 / 84 (4.76%)
occurrences (all)	30	5	4
Chills			
subjects affected / exposed	23 / 336 (6.85%)	3 / 293 (1.02%)	2 / 84 (2.38%)
occurrences (all)	30	5	3
Fatigue			
subjects affected / exposed	158 / 336 (47.02%)	101 / 293 (34.47%)	32 / 84 (38.10%)
occurrences (all)	245	128	54
Influenza like illness			
subjects affected / exposed	29 / 336 (8.63%)	5 / 293 (1.71%)	3 / 84 (3.57%)
occurrences (all)	33	5	7
Oedema peripheral			
subjects affected / exposed	49 / 336 (14.58%)	15 / 293 (5.12%)	8 / 84 (9.52%)
occurrences (all)	73	17	10
Pain			
subjects affected / exposed	30 / 336 (8.93%)	14 / 293 (4.78%)	2 / 84 (2.38%)
occurrences (all)	48	22	2
Peripheral swelling			
subjects affected / exposed	26 / 336 (7.74%)	0 / 293 (0.00%)	5 / 84 (5.95%)
occurrences (all)	42	0	5
Pyrexia			
subjects affected / exposed	71 / 336 (21.13%)	26 / 293 (8.87%)	18 / 84 (21.43%)
occurrences (all)	110	31	24
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	52 / 336 (15.48%)	24 / 293 (8.19%)	6 / 84 (7.14%)
occurrences (all)	63	28	10
Dyspnoea			

subjects affected / exposed	33 / 336 (9.82%)	24 / 293 (8.19%)	8 / 84 (9.52%)
occurrences (all)	40	27	9
Oropharyngeal pain			
subjects affected / exposed	27 / 336 (8.04%)	5 / 293 (1.71%)	3 / 84 (3.57%)
occurrences (all)	36	5	4
Psychiatric disorders			
Depression			
subjects affected / exposed	21 / 336 (6.25%)	7 / 293 (2.39%)	3 / 84 (3.57%)
occurrences (all)	24	7	3
Insomnia			
subjects affected / exposed	37 / 336 (11.01%)	16 / 293 (5.46%)	7 / 84 (8.33%)
occurrences (all)	40	18	7
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	28 / 336 (8.33%)	4 / 293 (1.37%)	6 / 84 (7.14%)
occurrences (all)	35	6	8
Aspartate aminotransferase increased			
subjects affected / exposed	25 / 336 (7.44%)	3 / 293 (1.02%)	8 / 84 (9.52%)
occurrences (all)	32	3	9
Blood alkaline phosphatase increased			
subjects affected / exposed	33 / 336 (9.82%)	0 / 293 (0.00%)	9 / 84 (10.71%)
occurrences (all)	57	0	14
Blood bilirubin increased			
subjects affected / exposed	31 / 336 (9.23%)	1 / 293 (0.34%)	2 / 84 (2.38%)
occurrences (all)	65	2	3
Blood creatine increased			
subjects affected / exposed	28 / 336 (8.33%)	1 / 293 (0.34%)	7 / 84 (8.33%)
occurrences (all)	42	1	13
Gamma-glutamyltransferase increased			
subjects affected / exposed	24 / 336 (7.14%)	4 / 293 (1.37%)	7 / 84 (8.33%)
occurrences (all)	42	5	15
Weight decreased			
subjects affected / exposed	32 / 336 (9.52%)	8 / 293 (2.73%)	4 / 84 (4.76%)
occurrences (all)	39	10	5
Injury, poisoning and procedural complications			

Sunburn			
subjects affected / exposed	57 / 336 (16.96%)	0 / 293 (0.00%)	15 / 84 (17.86%)
occurrences (all)	117	0	24
Nervous system disorders			
Dizziness			
subjects affected / exposed	41 / 336 (12.20%)	14 / 293 (4.78%)	3 / 84 (3.57%)
occurrences (all)	51	15	3
Dysgeusia			
subjects affected / exposed	55 / 336 (16.37%)	10 / 293 (3.41%)	9 / 84 (10.71%)
occurrences (all)	63	11	12
Headache			
subjects affected / exposed	113 / 336 (33.63%)	29 / 293 (9.90%)	23 / 84 (27.38%)
occurrences (all)	165	57	37
Hyperaesthesia			
subjects affected / exposed	17 / 336 (5.06%)	1 / 293 (0.34%)	0 / 84 (0.00%)
occurrences (all)	18	1	0
Paraesthesia			
subjects affected / exposed	30 / 336 (8.93%)	16 / 293 (5.46%)	6 / 84 (7.14%)
occurrences (all)	40	28	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 336 (9.52%)	22 / 293 (7.51%)	13 / 84 (15.48%)
occurrences (all)	41	46	21
Neutropenia			
subjects affected / exposed	1 / 336 (0.30%)	34 / 293 (11.60%)	0 / 84 (0.00%)
occurrences (all)	1	64	0
Thrombocytopenia			
subjects affected / exposed	5 / 336 (1.49%)	20 / 293 (6.83%)	1 / 84 (1.19%)
occurrences (all)	7	56	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	18 / 336 (5.36%)	5 / 293 (1.71%)	2 / 84 (2.38%)
occurrences (all)	21	5	2
Abdominal pain			
subjects affected / exposed	35 / 336 (10.42%)	12 / 293 (4.10%)	3 / 84 (3.57%)
occurrences (all)	49	22	3
Abdominal pain upper			

subjects affected / exposed	37 / 336 (11.01%)	8 / 293 (2.73%)	5 / 84 (5.95%)
occurrences (all)	52	12	6
Constipation			
subjects affected / exposed	52 / 336 (15.48%)	72 / 293 (24.57%)	8 / 84 (9.52%)
occurrences (all)	67	94	11
Diarrhoea			
subjects affected / exposed	124 / 336 (36.90%)	36 / 293 (12.29%)	24 / 84 (28.57%)
occurrences (all)	226	70	47
Dyspepsia			
subjects affected / exposed	20 / 336 (5.95%)	2 / 293 (0.68%)	2 / 84 (2.38%)
occurrences (all)	36	3	2
Nausea			
subjects affected / exposed	132 / 336 (39.29%)	128 / 293 (43.69%)	33 / 84 (39.29%)
occurrences (all)	229	258	41
Vomiting			
subjects affected / exposed	73 / 336 (21.73%)	77 / 293 (26.28%)	20 / 84 (23.81%)
occurrences (all)	123	109	22
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	15 / 336 (4.46%)	0 / 293 (0.00%)	5 / 84 (5.95%)
occurrences (all)	23	0	5
Actinic keratosis			
subjects affected / exposed	44 / 336 (13.10%)	12 / 293 (4.10%)	13 / 84 (15.48%)
occurrences (all)	71	14	16
Alopecia			
subjects affected / exposed	162 / 336 (48.21%)	7 / 293 (2.39%)	25 / 84 (29.76%)
occurrences (all)	199	8	27
Dermal cyst			
subjects affected / exposed	26 / 336 (7.74%)	1 / 293 (0.34%)	3 / 84 (3.57%)
occurrences (all)	29	2	3
Dermatitis acneiform			
subjects affected / exposed	18 / 336 (5.36%)	1 / 293 (0.34%)	4 / 84 (4.76%)
occurrences (all)	22	1	6
Dry skin			
subjects affected / exposed	80 / 336 (23.81%)	2 / 293 (0.68%)	16 / 84 (19.05%)
occurrences (all)	98	2	16

Erythema			
subjects affected / exposed	61 / 336 (18.15%)	4 / 293 (1.37%)	12 / 84 (14.29%)
occurrences (all)	137	6	18
Hyperkeratosis			
subjects affected / exposed	99 / 336 (29.46%)	1 / 293 (0.34%)	15 / 84 (17.86%)
occurrences (all)	175	1	21
Keratosis pilaris			
subjects affected / exposed	32 / 336 (9.52%)	1 / 293 (0.34%)	7 / 84 (8.33%)
occurrences (all)	37	1	9
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	34 / 336 (10.12%)	2 / 293 (0.68%)	11 / 84 (13.10%)
occurrences (all)	49	2	19
Photosensitivity reaction			
subjects affected / exposed	136 / 336 (40.48%)	13 / 293 (4.44%)	26 / 84 (30.95%)
occurrences (all)	204	14	31
Pruritus			
subjects affected / exposed	86 / 336 (25.60%)	5 / 293 (1.71%)	14 / 84 (16.67%)
occurrences (all)	125	5	15
Rash			
subjects affected / exposed	143 / 336 (42.56%)	6 / 293 (2.05%)	28 / 84 (33.33%)
occurrences (all)	270	6	44
Rash erythematous			
subjects affected / exposed	9 / 336 (2.68%)	0 / 293 (0.00%)	5 / 84 (5.95%)
occurrences (all)	12	0	7
Rash maculo-papular			
subjects affected / exposed	34 / 336 (10.12%)	1 / 293 (0.34%)	10 / 84 (11.90%)
occurrences (all)	51	1	13
Skin exfoliation			
subjects affected / exposed	18 / 336 (5.36%)	0 / 293 (0.00%)	2 / 84 (2.38%)
occurrences (all)	20	0	3
Skin lesion			
subjects affected / exposed	40 / 336 (11.90%)	4 / 293 (1.37%)	4 / 84 (4.76%)
occurrences (all)	59	4	4
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	189 / 336 (56.25%)	9 / 293 (3.07%)	48 / 84 (57.14%)
occurrences (all)	452	11	120
Back pain			
subjects affected / exposed	53 / 336 (15.77%)	20 / 293 (6.83%)	11 / 84 (13.10%)
occurrences (all)	72	27	17
Musculoskeletal pain			
subjects affected / exposed	44 / 336 (13.10%)	11 / 293 (3.75%)	12 / 84 (14.29%)
occurrences (all)	56	15	16
Myalgia			
subjects affected / exposed	50 / 336 (14.88%)	5 / 293 (1.71%)	15 / 84 (17.86%)
occurrences (all)	82	7	17
Pain in extremity			
subjects affected / exposed	76 / 336 (22.62%)	18 / 293 (6.14%)	14 / 84 (16.67%)
occurrences (all)	116	19	20
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	20 / 336 (5.95%)	1 / 293 (0.34%)	2 / 84 (2.38%)
occurrences (all)	24	2	2
Folliculitis			
subjects affected / exposed	28 / 336 (8.33%)	3 / 293 (1.02%)	2 / 84 (2.38%)
occurrences (all)	37	3	2
Influenza			
subjects affected / exposed	18 / 336 (5.36%)	4 / 293 (1.37%)	3 / 84 (3.57%)
occurrences (all)	22	5	3
Lower respiratory tract infection			
subjects affected / exposed	8 / 336 (2.38%)	2 / 293 (0.68%)	6 / 84 (7.14%)
occurrences (all)	11	2	9
Nasopharyngitis			
subjects affected / exposed	36 / 336 (10.71%)	10 / 293 (3.41%)	4 / 84 (4.76%)
occurrences (all)	57	14	6
Upper respiratory tract infection			
subjects affected / exposed	19 / 336 (5.65%)	5 / 293 (1.71%)	4 / 84 (4.76%)
occurrences (all)	23	5	7
Urinary tract infection			

subjects affected / exposed occurrences (all)	9 / 336 (2.68%) 10	9 / 293 (3.07%) 11	5 / 84 (5.95%) 7
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	76 / 336 (22.62%) 112	24 / 293 (8.19%) 31	20 / 84 (23.81%) 30

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2010	• Clarified information on the BRAF analysis and the process for the BRAF mutation analysis. • Clarified the timing of clinical assessments and procedures and reorganized them to match the new schedule of assessments. • For patients for whom a computerized tomography (CT) scan was contraindicated, a clarification was added that a magnetic resonance imaging (MRI) scan could be used for assessment of non-cutaneous squamous cell carcinoma (SCC) surveillance. • Added information about the length of acceptable delay/interruption in vemurafenib dosing to clarify when interruptions/delays occur depending on the grade of adverse events (AEs). • Clarified that all SCC events should be reported as SAEs.
01 November 2010	• Changed the estimated treatment effect of vemurafenib as measured by the hazard ratio for death from 0.75 to 0.65 due to emerging results from Phase 1 and 2 studies; with the change in the type 1 error rate, this resulted in a reduction in the number of deaths required for final analysis from 468 to approximately 196. • Changed the number of interim analyses for OS from two (at 50% and 75%) to one (at 50% information). • Added PFS as a co-primary endpoint and as part of the study's primary objective. • Changed the type 1 error rate for the study from 0.025 (two-sided) to 0.05 (two-sided). • Added allowance for crossover from the dacarbazine arm to the vemurafenib arm if recommended by the DSMB based on their review of efficacy data at the time of the interim analysis of OS.
16 February 2011	• Added allowance for crossover from the dacarbazine group to the vemurafenib group for all patients on dacarbazine with a wash-out period of 14 days. Crossover from the vemurafenib group to the dacarbazine group was disallowed. • Added cautions for concomitant medications: for potential drug-drug interactions with any concomitant medications that are primarily metabolized by the CYP450 1A2, 3A4 and 2C9, those that strongly inhibit or induce CYP3A4, and for medications and supplements that may affect QT interval prolongation. • Increased monitoring of ECG and electrolytes before initiating treatment with vemurafenib and during treatment, as well as recommendations to manage potential QTc prolongation. • Added evaluation and assessment of molecular characteristics of suspicious lesions in addition to the evaluation of cuSCC.
19 June 2012	• Risk Management Plan was revised with new timelines for SCC (both cutaneous and noncutaneous) follow-up, which was to occur during the treatment period and up to a maximum of 6 months after last dose during follow-up. • Tissue samples of any new primary neoplasm or SCC (cutaneous or noncutaneous) were to be submitted a central pathology laboratory for molecular characterization. • Serious AEs (SAEs) section was updated as follows: Keratoacanthoma, basal cell carcinoma, and any occurrence of a new primary malignancy were added as reportable SAEs. SAE reporting requirements were changed from reporting them within 1 working day to reporting them within 24 hours of knowledge of the event. • Gamma-glutamyltransferase (GGT) was added to Laboratory Assessments. The assessment had been ongoing in the study but was not documented in previous versions of the protocol. • Safety monitoring intervals for the DSMB changed and were outlined in the DSMB Charter.

01 December 2012	• Timing of PK sampling was clarified (patients receiving vemurafenib in Arm A only). Plasma and serum biomarker samples were to be obtained at disease progression or on the same day as the final dose of study treatment, whichever occurred first. • Timing of the optional biopsy at disease progression was clarified. • Dermatological evaluation was updated to include secondary primary melanoma consistently throughout the protocol.
21 April 2014	• The Sponsor was permitted to end the current study and permit eligible patients still receiving vemurafenib treatment to be offered enrollment in the extension study (Study GO28399). • Safety information was updated for cutaneous SCC (cuSCC), liver function abnormalities and liver-related AEs, and neutropenia in patients treated with vemurafenib. • Safety information was included for cases of adenomatous colonic polyps, NRAS-mutated chronic myelomonocyte leukemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms syndrome. • Information on the effects of vemurafenib on QT interval from Study NP22657 was included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported