Clinical trial results:
A Phase II (BRF113710) single-arm, open-label study of dabrafenib (GSK2118436) in previously treated BRAF mutant metastatic melanoma

Summary

EudraCT number	2009-015297-36
Trial protocol	FR DE IT
Global end of trial date	17 June 2016

Results information

Result version number	v2 (current)
This version publication date	21 October 2017
First version publication date	02 July 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	113710

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 866 435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 866 435-7343,

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	10 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the overall response rate (ORR), defined as the proportion of participants with investigator-assessed complete responses or partial responses, in participants with metastatic melanoma treated with the oral agent GSK2118436 in subjects.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 August 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	92
EEA total number of subjects	55

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants received Dabrafenib (GSK2118436) 150 milligram (mg) twice daily and continued on treatment until disease progression, death, unacceptable adverse event (AE), or early termination of the study. The total duration of the study including a long-term follow-up phase was 5 years.

Pre-assignment

Screening details:

A total of 211 participants with histologically confirmed BRAF mutation positive metastatic melanoma (Stage IV) were screened for eligibility. 152 participants had a BRAF V600E or V600K mutation and 92 participants with positive mutation were included in the study.

Period 1

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

Arms

Arm title	GSK2118436 150 mg

Arm description:

Participants received GSK2118436 (gelatin capsules) 150 mg orally twice a day and continued on treatment until disease progression, death, or unacceptable AEs . Participants who are benefiting from GSK2118436 at the time of study completion will have the option to enter Study BRF114144 (NCT01231594), which is a rollover study for GSK2118436.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib (GSK2118436)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Debrafenib 150 milligram (mg) was administered twice daily under fasting conditions, either 1 hour before or 2 hours after a meal with approximately 200 milliliter (mL) of water.

Number of subjects in period 1	GSK2118436 150 mg
Started	92
Completed	71
Not completed	21
Study closed	16
Physician decision	2
Consent withdrawn by subject	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	GSK2118436 150 mg

Reporting group description:

Participants received GSK2118436 (gelatin capsules) 150 mg orally twice a day and continued on treatment until disease progression, death, or unacceptable AEs . Participants who are benefiting from GSK2118436 at the time of study completion will have the option to enter Study BRF114144 (NCT01231594), which is a rollover study for GSK2118436.

Reporting group values	GSK2118436 150 mg	Total	
Number of subjects	92	92	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54.8 ± 14.44	 -	
Gender categorical Units: Subjects			
Female	43	43	
Male	49	49	
Race/Ethnicity, Customized Units: Subjects			
White	91	91	
American Indian or Alaska Native	1	1	

End points

End points reporting groups

Reporting group title	GSK2118436 150 mg

Reporting group description:

Participants received GSK2118436 (gelatin capsules) 150 mg orally twice a day and continued on treatment until disease progression, death, or unacceptable AEs . Participants who are benefiting from GSK2118436 at the time of study completion will have the option to enter Study BRF114144 (NCT01231594), which is a rollover study for GSK2118436.

Primary: Number of participants with a best overall response of confirmed complete response (CR) or partial response (PR) as assessed by the investigator for participants who had a BRAF V600E mutation

End point title	Number of participants with a best overall response of confirmed complete response (CR) or partial response (PR) as assessed by the investigator for participants who had a BRAF V600E mutation[1]

End point description:

A participant was defined as a responder if he/she achieved either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 millimeter (mm) in the short axis.) or PR (at least a 30 percent decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]). To be assigned a status of PR or CR, a confirmatory disease assessment was required at Week 12 if an initial response was seen at the Week 6 scan. Initial responses (CR/PR) that occured at Week 12 or later were required to be confirmed not less than 4 weeks and not more than 6 weeks after the criteria for response were first met. The analysis was performed on Primary efficacy Population which comprised of all participants who received at least one dose of GSK2118436 (All Treated Participants Population) and had a BRAF V600E mutation. The estimated value for the percentage of participants was 59 with 95% CI as 48.2-70.3.

End point type	Primary

End point timeframe:

Up to 60 months

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: The estimated value for the percentage of participants and 95% CI was presented in End Point Details Description as it is a single arm study.

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	76[2]			
Units: Participants				
CR	5			
PR	40			

Notes:

[2] - Primary efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a best overall response of CR or PR as assessed by the investigator and an independent reviewer for participants who had a BRAF V600K mutation

End point title	Number of participants with a best overall response of CR or PR as assessed by the investigator and an independent reviewer for participants who had a BRAF V600K mutation

End point description:

A participant was defined as a responder if he/she achieved either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30 percent decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]). To be assigned a status of PR or CR, a confirmatory disease assessment had to have been performed at Week 12 if an initial response was seen at the Week 6 scan. Initial responses (CR/PR) that occured at Week 12 or later should have been confirmed not less than 4 weeks and not more than 6 weeks after the criteria for response were first met. The analysis was performed on Secondary efficacy analysis Population which comprised of all participants who received at least one dose of GSK2118436 (All Treated Participants Population) and had a BRAF V600K mutation.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	16[3]			
Units: Participants				
Investigator-assessed CR	0			
Investigator-assessed PR	2			

Notes:

[3] - Secondary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) as assessed by the investigator and an independent reviewer for participants who had a BRAF V600E mutation

End point title	Progression-free Survival (PFS) as assessed by the investigator and an independent reviewer for participants who had a BRAF V600E mutation

End point description:

PFS is defined as the interval between the first dose of study medication and the earliest date of disease progression or death due to any cause. The length of this interval is estimated as the date of death or progression minus date of first dose plus 1 day. Kaplan-Meier model was used to estimate the median and 95 percent confidence interval (CI). For participants who received subsequent anti-cancer therapy prior to the date of documented progression or death, PFS was censored at the last adequate assessment. For participants who did not have a documented date of progression or death, PFS was censored at the date of last adequate assessment.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	76[4]			
Units: Weeks				
median (confidence interval 95%)				
Weeks	6.3 (4.6 to 8.1)			

Notes:

[4] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) as assessed by the investigator and an independent reviewer for participants who had a BRAF V600K mutation

End point title	Progression-free Survival (PFS) as assessed by the investigator and an independent reviewer for participants who had a BRAF V600K mutation

End point description:

PFS is defined as the interval between the first dose of study medication and the earliest date of disease progression or death due to any cause. The length of this interval is estimated as the date of death or progression minus date of first dose plus 1 day. Kaplan-Meier model was used to estimate the median and 95 percent CI. For participants who received subsequent anti-cancer therapy prior to the date of documented progression or death, PFS was censored at the last adequate assessment. For participants who did not have a documented date of progression or death, PFS was censored at the date of last adequate assessment.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	16[5]			
Units: Weeks				
median (confidence interval 95%)				
Weeks	4.0 (2.6 to 6.2)			

Notes:

[5] - Secondary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response as assessed by the investigator and an independent reviewer for participants who had a BRAF V600E mutation

End point title	Duration of response as assessed by the investigator and an independent reviewer for participants who had a BRAF V600E mutation

End point description:

Duration of response for participants with either a CR or PR is defined as the time from the first

documented evidence of a PR or CR until the first documented sign of disease progression or death due to any cause. Duration of response was estimated using Kaplan-Meier model and the median and 95 percent CI was presented. The analysis was performed on Primary efficacy Population and only those participants who had a CR or PR were analyzed.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	45[6]			
Units: Weeks				
median (confidence interval 95%)				
Weeks	6.6 (3.9 to 11.1)			

Notes:

[6] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response as assessed by the investigator and an independent reviewer for participants who had a BRAF V600K mutation

End point title	Duration of response as assessed by the investigator and an independent reviewer for participants who had a BRAF V600K mutation

End point description:

Duration of response for participants with either a CR or PR is defined as the time from the first documented evidence of a PR or CR until the first documented sign of disease progression or death due to any cause. Duration of response was estimated using Kaplan-Meier model and the median and 95 percent CI was presented. The analysis was performed on Secondary efficacy Population and only those participants who had a CR or PR were analyzed.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	3[7]			
Units: Weeks				
median (confidence interval 95%)				
Weeks	5.6 (3.7 to 6.8)			

Notes:

[7] - Secondary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival for participants who had a BRAF V600E mutation

End point title	Overall survival for participants who had a BRAF V600E mutation

End point description:

Overall survival is defined as the time from the first dose of study medication until death due to any cause. For participants who did not die, overall survival was censored at the date of last contact. Overall survival was estimated using kaplan-Meier model and median and 95 percent CI was presented. The estimated value for the percentage of participants was 20 with 95% CI as 11.6-29.8.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	76[8]			
Units: Weeks				
median (confidence interval 95%)				
Weeks	13.1 (9.5 to 21.9)			

Notes:

[8] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival for participants who had a BRAF V600K mutation

End point title	Overall survival for participants who had a BRAF V600K mutation

End point description:

Overall survival is defined as the time from the first dose of study medication until death due to any cause. For participants who did not die, overall survival was censored at the date of last contact. Overall survival was estimated using Kaplan-Meier model and median and 95 percent CI was presented. The estimated value for the percentage of participants was 13 with 95% CI as 2.2-34.6.

End point type	Secondary

End point timeframe:

From the first dose to death due to any cause (up to 60 months)

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	16[9]			
Units: Weeks				
median (confidence interval 95%)				
Weeks	12.9 (4.2 to 17.1)			

Notes:

[9] - Secondary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AEs and Serious Adverse Events (SAEs)

End point title	Number of participants with AEs and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs including systemic allergic and non-allergic reactions as well as local site injection-related reactions were counted throughout treatment phase and follow up phase. Systemic allergic reactions included facial paralysis, flushing, hypersensitivity and rash pruritic. Injection related reactions were considered as systemic non-allergic reactions. Local site reactions included injection site bruising, erythema, pain and reaction. The analysis was performed on All treated Population which comprised of all participants that receive at least one dose of dabrafenib.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	92[10]			
Units: Participants				
Any AE	87			
Any SAE	33			

Notes:

[10] - All treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change from Baseline in clinical chemistry and hematology toxicity grades

End point title	Number of participants with change from Baseline in clinical chemistry and hematology toxicity grades

End point description:

Blood samples were collected from participants for evaluation of change from Baseline in toxicity grades in clinical chemistry and hematology parameters. The clinical chemistry parameters included alkaline

phosphatase, Alanine amino transferase (ALT), Aspartate amino transferase (AST), total bilirubin, creatinine, glucose, potassium, magnesium, sodium and phosphorus. The hematology parameters included hemoglobin, total neutrophils, platelets and white blood cells (WBC). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. The change from Baseline was calculated as visit value minus Baseline value and was presented in the form of worst-case post Baseline value which was the maximum toxicity grade for a participant after the first dose of study drug over the treatment period. Only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	92[11]			
Units: Participants				
Alkaline phosphatase; n= 91	23			
ALT; n= 91	18			
AST; n= 91	18			
Total bilirubin; n= 91	3			
Creatinine; n= 91	11			
Glucose; n= 90	51			
Potassium; n= 91	2			
Magnesium; n= 89	2			
Sodium; n= 91	5			
Phosphorus; n= 91	36			
Hemoglobin; n= 91	0			
Total Neutrophils; n= 91	21			
Platelet; n= 91	12			
WBC; n= 91	24			

Notes:

[11] - All treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change from Baseline in temperature and pulse rate

End point title	Number of participants with change from Baseline in temperature and pulse rate

End point description:

Number of participants with change from Baseline in temperature and pulse rate were evaluated from the first dose of study treatment till discontinuation due to any reason. Change from Baseline in worst-case post Baseline value was presented as decrease to <=35, change to normal or no change and increase to >=38. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. The change from Baseline was calculated as visit value minus Baseline value and was presented in the form of worst case post-baseline value which was the maximum toxicity grade for a participant after the first dose of study drug over the treatment period.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[12]			
Units: Participants				
Temperature; Decrease to <=35	3			
Temperature; Change to normal or no change	84			
Temperature; Increase to >=38	4			
Pulse rate; Decrease to <=35	9			
Pulse rate; Change to normal or no change	66			
Pulse rate; Increase to >=38	16			

Notes:

[12] - All treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with increase from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point title	Number of participants with increase from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point description:

Number of participants with increase from Baseline in SBP and DBP were evaluated from the first dose of study treatment till discontinuation due to any reason. Change from Baseline in worst-case post Baseline value was presented as any increase to >=80 and increase to >=100 for DBP and as any increase to >=120 and increase to >=160 for SBP. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. The change from Baseline was calculated as visit value minus Baseline value and was presented in the form of worst-case post Baseline value which was the maximum toxicity grade for a participant after the first dose of study drug over the treatment period.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[13]			
Units: Participants				
DBP; Any increase to >=80	32			
DBP; Increase to >=100	6			
SBP; Any icrease to >=120	2			
SBP; Increase to >=160	7			

Notes:

[13] - All treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change from Baseline in Left Ventricular Ejection Fraction (LVEF) levels

End point title	Number of participants with change from Baseline in Left Ventricular Ejection Fraction (LVEF) levels

End point description:

LVEF was defined as the percentage of blood pumped out of the left ventricle. Change from Baseline in worst-case post Baseline was presented as no change or any increase and any decrease values. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. The change from Baseline was calculated as visit value minus Baseline value and was presented in the form of worst-case post Baseline value which was the maximum toxicity grade for a participant after the first dose of study drug over the treatment period.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	GSK2118436 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	92[14]			
Units: Participants				
No change or any increase	34			
Any decrease	54			

Notes:

[14] - All treated Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the first dose of investigational product until death of all participants or a follow-up till 60 months.

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in the All Treated Participants Population, comprised of all randomized participants who received at least one dose of study medication, according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	GSK2118436 150 mg

Reporting group description:

Participants received GSK2118436 (gelatin capsules) 150 mg orally twice a day and continued on treatment until disease progression, death, or unacceptable AEs . Participants who are benefiting from GSK2118436 at the time of study completion will have the option to enter Study BRF114144 (NCT01231594), which is a rollover study for GSK2118436.

Serious adverse events	GSK2118436 150 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 92 (35.87%)		
number of deaths (all causes)	71		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Keratoacanthoma			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Malignant neoplasm of eyelid			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences causally related to treatment / all	6 / 7		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Chills				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 92 (4.35%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Miscarriage of partner				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Epistaxis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				

subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Amylase increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Liver function test increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Post procedural haematoma				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia supraventricular				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Atrial fibrillation			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Localised infection			

subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GSK2118436 150 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 92 (90.22%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	10 / 92 (10.87%)		
occurrences (all)	14		
Seborrhoeic keratosis			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	13		
Skin papilloma			

subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	20		
Vascular disorders			
Hot flush			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	11		
Chills			
subjects affected / exposed	13 / 92 (14.13%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	22 / 92 (23.91%)		
occurrences (all)	27		
Oedema peripheral			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	24 / 92 (26.09%)		
occurrences (all)	58		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	13		
Dyspnoea			
subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	15		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Depression			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		

Insomnia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	6		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 92 (20.65%)		
occurrences (all)	23		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	13		
Lymphopenia			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	9		
Diarrhoea			

subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	19 / 92 (20.65%)		
occurrences (all)	24		
Vomiting			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	17		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	10		
Alopecia			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	15		
Dry skin			
subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	11		
Erythema			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	8		
Hyperhidrosis			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	7		
Hyperkeratosis			
subjects affected / exposed	27 / 92 (29.35%)		
occurrences (all)	61		
Palmoplantar keratoderma			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	8		
Pruritus			
subjects affected / exposed	9 / 92 (9.78%)		
occurrences (all)	10		
Pruritus generalised			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		

Rash			
subjects affected / exposed	10 / 92 (10.87%)		
occurrences (all)	11		
Transient acantholytic dermatosis			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	33 / 92 (35.87%)		
occurrences (all)	64		
Back pain			
subjects affected / exposed	9 / 92 (9.78%)		
occurrences (all)	11		
Musculoskeletal pain			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	8		
Myalgia			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	14		
Pain in extremity			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	19		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	13 / 92 (14.13%)		
occurrences (all)	18		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 92 (15.22%)		
occurrences (all)	16		
Hyperglycaemia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	6		

Hypophosphataemia subjects affected / exposed occurrences (all)	9 / 92 (9.78%) 20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2010	Country specific amendment for France to add valvular toxicity stopping criteria and to add that an Independent data monitoring committee (IDMC) will be established to review data from the study.
01 September 2010	Applies to all study sites. Modification of overall statistical design to include V600E mutant participants as the primary efficacy population and V600K in secondary efficacy assessments and updated primary and secondary objectives, endpoints, etc. accordingly; removal of V600D population; updates to First time in humans (FTIH) clinical activity and safety data and reference to the current version of the investigational brochure (IB); addition of IDMC to review data from interim analysis and periodically throughout the study; addition of valvular toxicity and Correction in QT interval (QTc) stopping criteria; changes to inclusion criteria to include treatment naïve participants and add computed tomography (CT) as a method for detecting brain metastases if magnetic resonance imaging (MRI) is contraindicated; deletion of exclusion criteria that excludes participants with a presence of rheumatoid arthritis, addition of exclusion criteria to exclude participants with history of alcohol or drug abuse within 6 months of screening and participants with known ocular or primary mucosal melanoma; changes to GSK2118436 storage temperature; modification of the frequency of efficacy assessments to every 8 weeks Week 20 to 52 and every 12 weeks from Week 52 until discontinuation; modifications to pregnancy section to address contraception requirements for female and male participants separately with a subsection on pregnancy; addition of mandatory cfDNA sample at discontinuation; addition of central reading of electrocardiogram (ECG) and Echocardiogram (ECHO)s; correction of minor typographical errors; administrative revisions to add/delete authors and update references.
14 November 2011	Footnote added to Table 4 Dose Modification that an ophthalmologic consultation is required if uveitis, blurry vision, eye pain, or erythema develops. A guideline for renal insufficiency was added for the management of renal toxicities; minor administrative change corrections; and correction of minor typographical errors.
19 December 2013	Updated study objectives to include secondary efficacy objective of long-term overall Survival; Updated definition of study completion throughout to allow for collection of long term survival data; Removed option for ongoing participants to transition to rollover study BRF114144 at the time of study completion; Updated dabrafenib dosing instructions; Updated dose modification guidelines for general toxicities and adverse events of special interest; Updated Liver Chemistry Stopping and Follow-up criteria to permit rechallenge/restart following liver toxicity; Updated permitted, prohibited and cautionary concomitant medication information; Updated treatment of dabrafenib overdose information; Updated visit schedule and dermatologic skin assessment frequency; As requested by the European Regulatory Authority, information for new malignancies will be collected throughout study treatment and follow-up; Removed male contraception requirement; As requested by French Regulatory Authority, additional monitoring following discontinuation of dabrafenib was incorporated; Minor administrative changes and typographical corrections throughout.
11 March 2014	Country specific amendment for Germany to incorporate additional monitoring for cutaneous squamous cell carcinoma, new primary melanoma and non-cutaneous secondary/recurrent malignancy at the request of the German Federal Institute for Drugs and Medical Devices (BfArM).

14 September 2015	Study will be closed out early. Reason for closure: As the primary endpoint of the study has been achieved and reported, (5 July 2012) it is believed that no significant new data or Overall Survival (OS) follow-up data will be generated in this study; Re-inserted the option for ongoing participants to transition to the roll-over study BRF114144 at the time of study completion or switch to commercially available Dabrafenib; FDA, EMA and other regulatory agencies approved dabrafenib for the treatment of participants with unresectable or metastatic melanoma with BRAF V600E mutation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported