TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An Open-Label, Multicentre, Corollary Study of Pre-Operative Therapy with Dabrafenib and the Combination of Dabrafenib with Trametinib in Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain

Compound Number: GSK1120212+GSK2118436

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2011N129968_00	2012-MAY-23	Original
2011N129968_01	2013-AUG-28	Amendment No. 1
Clarified age requirement and other eligibility criteria; reduced dabrafenib monotherapy cohort to 15 subjects and included cohort of 15 subjects who will be treated with dabrafenib and trametinib; changed post-op treatment to dabrafenib plus trametinib; updated dose modification guidelines; updated contraindicated and cautionary medications; updated translational research to include assessment of mRNA and miRNA expression, and, when feasible, for DNA methylation and copy number variation; clarified post-craniotomy assessment schedule.		
2011N129968_02	2013-NOV-08	Amendment No. 2
Updated medical monitor contact information; revised IND number to reflect submission to dabrafenib + trametinib IND; Added ophthalmic examinations to be performed at the Screening Visit, Week 4 Visit, and as clinically indicated; updated dose modification guidelines for QTc prolongation; removed collection of alcohol information at baseline; updated guidelines for missed doses of trametinib		
2011N129968_03	2015-APR-15	Amendment No. 3
Revised Author list. Updated medical monitor contact information. Changed the resection of extracranial metastases to optional from required; analyses related to the concordance of cranial to extracranial have been categorized as exploratory. Sequence of enrollment for first 10 patients changed to 5 for cohort A and 5 for cohort B. (Sequence for next 20 defined as groups of 5 in same order). Interim review planned after first 10 patients. Exclusion criteria have been amended to no longer include presence of leptomeningeal disease or dural metastases; or history of another active malignancy within the past 5 years; or any malignancy with a confirmed activating RAS mutation. Papsmear no longer required prior to enrollment. Clarified that SUVmax is recorded for PET-CT scans, not size of tumor lesions. Clarified that FDG-PET may not be performed in lieu of bone scans. Removed 18-NaF- PET as an alternate to bone scans. Option to use core biopsy for extracranial tumor added. Allow option to collect the optional extracranial tissue ± 1 day craniotomy procedure. Third optional extracranial biopsy corrected from every 8 weeks to at study discontinuation. Revised guidelines for visual changes for the dabrafenib and trametinib combination arm to replace CSR with RPED and align with asset standard language.		

SPONSOR SIGNATORY

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15. April 2015
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Regulatory Agency Identifying Number(s):

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol BRV116521

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
ATS	All treated subjects
BBB	Blood-brain barrier
BID	Twice a day
BUN	Blood urea nitrogen
CL_{Cr}	Creatinine clearance
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPK	Creatinine phosphokinase
CR	Complete response
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE v4.0	Common Terminology Criteria for Adverse Events, version 4.0
CYP	Cytochrome P450
dL	Deciliter(s)
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
EIAED	Enzyme-inducing antiepileptic drug
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin fixed, paraffin embedded
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
G	Gram
GCP	Good Clinical Practice
GK	Gamma knife
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
G6PD	Glucose-6-phosphate dehydrogenase
H&E	Hematoxylin and eosin
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C Virus
HFSR	Hand-foot skin reaction

HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl methyl cellulose
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonization
IHC	Immunohistochemical
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
KA	Keratoacanthoma
kg	Kilogram
L	Liter(s)
LDH	Lactate dehydrogenase
Linac	Linear accelerator
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MALDI	Matrix Assisted Laser Desorption Ionization
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
miRNA	MicroRNA
mL	Milliliter
mm	Millimeter
MOA	Mode of action
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
nM	Nanomolar
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	Overall response rate
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
p-ERK	Phosphorylated ERK
PET	Positron emission tomography, FDG-PET, FDG-PET/CT unless stated otherwise
Pgp	p-glycoprotein
PK	Pharmacokinetic
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
OCT	Optimum cutting temperature solution
QTc	Corrected QT interval on electrocardiogram

RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumours
RPED	Retinal pigment epithelial detachment
RNA	Ribonucleic acid
RPPA	Reverse phase protein arrays
RVO	Retinal vein occlusion
SAE	Serious adverse event(s)
SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SPM	Study procedures manual
SRS	Stereotactic radiosurgery
SUV	Standard uptake value
TID	Three times a day
TIL	Tumor infiltrating lymphocyte
TMZ	Temozolamide
μL	Microliter
μM	Micromolar
ULN	Upper limit of normal
US/USA	United States
WBRT	Whole-brain radiation therapy

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PROTOCOL SUMMARY

Rationale

Cutaneous melanoma is the most aggressive form of skin cancer, with approximately 132,000 new cases and approximately 37,000 disease-related deaths worldwide each year. One of the most common complications of advanced melanoma is the development of brain metastasis. Brain involvement is detected in up to 80% of advanced melanoma patients in autopsy series, and up to 55% of advanced melanoma patients will die as a direct result of uncontrolled and progressive brain metastases. The prognosis of melanoma patients with brain metastasis is generally very poor, with a median overall survival ranging from 2.8 to 4 months. While local treatment options are generally preferred, the need for effective systemic treatments to also control peripheral melanoma manifestations and to ultimately prolong the overall survival of patients with melanoma metastatic to the brain is still very much unmet.

Dabrafenib (GSK2118436, TAFINLA™), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is a potent and selective inhibitor of BRAF kinase activity with a mode of action (MOA) consistent with adenosine triphosphate (ATP)-competitive inhibition. In May 2013, dabrafenib monotherapy was approved by the United States Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Clinical activity was reported in patients with BRAF V600E or K-mutation positive melanoma brain metastases [Long, 2012].

The clinical activity in the brain metastases may have resulted from the activity of the parent or of one (or more) of the metabolites of dabrafenib. In preclinical studies, dabrafenib failed to penetrate the intact blood-brain-barrier (BBB) but disruption of the BBB in patients with brain metastases may allow penetration of dabrafenib or its metabolites into the brain. In the Phase I trial with GSK2118436, as well in a Phase I trial with the BRAF inhibitor vemurafenib, correlative studies demonstrated the critical need to achieve specific parent drug concentrations in the plasma to achieve inhibition of signalling by the mutant BRAF V600E protein in extracranial metastases, which correlated with the achievement of clinical responses.

Trametinib (GSK1120212, MEKINIST™) is an orally available, small molecule, selective inhibitor of MEK1 and MEK2 that was approved in May 2013 by the United States FDA for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

In phase II studies, it was shown that dabrafenib can be safely combined with trametinib, and the anti-tumor activity of the combination of both agents given continuously at full approved dose levels for monotherapy was superior when compared to single-agent dabrafenib. Several phase III trials evaluating the safety and efficacy of the combination are currently ongoing.

In order to facilitate the understanding of dabrafenib and dabrafenib in combination with trametinib as a treatment option for patients with brain metastases, there is a critical need

to improve the understanding of the levels of the dabrafenib parent compound, its metabolites, and trametinib that are achieved in the central nervous system (CNS), the relationship of intracerebral concentrations to plasma levels, and pharmacodynamic effects in the brain metastases.

Objective(s)

The primary objective of this study is to determine levels and distribution of dabrafenib, its metabolites, and trametinib (Cohort B only) in parenchymal brain metastases, extracranial metastases (when available), and peripheral blood (plasma) within two cohorts of subjects with BRAF V600E/K mutation-positive melanoma that has metastasized to the brain.

The secondary objectives of this study are to determine: the levels of dabrafenib , its metabolites, and trametinib (as appropriate) in the cerebrospinal fluid (CSF)) and in extracranial metastases where possible; the activation status of the RAS-RAF-MEK-ERK signalling pathway in brain metastases and extracranial metastases; the activation status of other pro-survival signalling pathways in brain metastases and extracranial metastases; the relationship between these pharmacokinetic and pharmacodynamic measures and early clinical responsiveness of the brain metastases; the degree of concordance with respect to the presence of BRAF mutations in both the brain and extra-cranial metastases from the same subjects, the presence of other mutations that may be uniquely present and novel only for brain metastases; and the safety and tolerability of pre-operative treatment with dabrafenib or dabrafenib combined with trametinib prior to resection of brain metastases, as well as the surgical outcomes from the craniotomy itself. Efficacy will be assessed in terms of change from baseline to pre-surgery in the sum of the longest diameters of intracranial target lesions, maximum change from baseline in the sum of longest diameters of unresected intracranial target lesions, overall extracranial response rate in unresected lesions, and overall survival.

The exploratory objectives of this study are to determine, in available samples, the degree of concordance with respect to the presence of BRAF mutations in both the brain and extra-cranial metastases from the same subjects; the presence of other mutations that may be uniquely present and novel only for brain metastases; and to compare the status of signalling pathways and the immune response in brain metastases and extra-cranial metastases.

Study Design

This is a global, multi-centre, open-label, study that will be conducted evaluable subjects with resectable, BRAF V600E or V600K mutation-positive metastatic melanoma to the brain. The first cohort of 5 subjects will receive dabrafenib orally 150mg twice daily (BID) for 7 to 14 days prior to surgery (Cohort A); the second cohort of 5 subjects will receive the combination of dabrafenib 150 mg BID and trametinib 2 mg once daily for 7 to 14 days prior to surgery (Cohort B). An interim analysis will be performed after cohorts A and B have each enrolled 5 patients (with cohort A enrolling the first 5 patients and cohort B the second 5) to assess variability in PK results and determine whether projected total sample size of 30 subjects will be adequate or sample size will require

readjustment. Accrual will continue during this formal review. If variance in results suggests that a total sample size of 30 subjects is adequate, the planned assignment of subsequent patients to the two cohorts will be in groups of 5 with the first 5 subjects enrolling in cohort A, then the next 5 enrolling in cohort B; alternating between cohorts until up to 30 patients have been enrolled. Study treatment will be taken the night prior to surgery, but not on the day of surgery. Samples of the resected brain tumor(s) will be utilized for pharmacokinetic and pharmacodynamic analyses. Optional samples of accessible extracranial metastases may be collected prior to starting treatment and on the same day as the resection of the brain metastases. PK and PD levels in extracranial metastases if available will be compared with those observed in resected brain metastases. Plasma will be collected from all subjects on the day of the craniotomy for pharmacokinetic analysis, to determine the correlation with levels achieved in the brain and extracranial tumors. Optional CSF collected on the day of surgery will also undergo pharmacokinetic analysis, and results will be compared to plasma and intracranial pharmacokinetic levels. Radiographic assessment of early clinical responses by positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) will be performed in all subjects and compared with pharmacokinetic and pharmacodynamic analyses. Tissues and blood will also be utilized for exploratory translational objectives.

After surgery, all subjects with remaining intracranial and/or extracranial metastases will be able to resume treatment with the combination of dabrafenib and trametinib no earlier than 72 hours after surgery, provided the subject is able to tolerate oral medications and felt to be appropriate for treatment by the Principal Investigator. Subjects who resume treatment will be evaluated for safety 4 weeks after restarting treatment and every 4 weeks thereafter. Efficacy will be assessed 8 weeks after restarting treatment and every 8 weeks thereafter. Subjects will be permitted to remain on treatment until disease progression, unacceptable toxicity, investigator discretion, subject/proxy request, or administrative reasons. An optional tumor biopsy may be collected for subjects who discontinue treatment due to disease progression or recurrence.

Subjects who do not continue treatment after the craniotomy procedure will be evaluated for safety at the discontinuation visit 4 weeks after the procedure.

All subjects who permanently discontinue study treatment will be followed for survival and new anti-cancer therapy for a total of two years or until death or the subject wishes to withdraw from further follow-up. The study will be considered closed once the last subject reaches this milestone.

1. INTRODUCTION

1.1. Background

Cutaneous melanoma is the most aggressive form of skin cancer, with approximately 132,000 new cases and approximately 37,000 disease-related deaths worldwide each year. The prognosis of melanoma is primarily dependent on the disease stage at the time of initial diagnosis. The high risk of developing distant tumor metastases, and particularly brain metastases, negatively impacts the prognosis of advanced stage disease. In fact, after lung-, breast-, and cancer of unknown primary origin, melanoma results in the fourth highest number of patients who develop central nervous system (CNS) metastases detected by imaging each year (10% of all brain metastases) [Majer, 2007]. Moreover, autopsy series indicate that up to 75% of subjects who die from melanoma show evidence of metastatic disease in the CNS [McWilliams, 2008]. It is of major clinical relevance that subjects with malignant melanoma who initially respond to aggressive systemic therapy often relapse with metastases in the CNS.

The prognosis of melanoma patients with brain metastasis is generally very poor, with a median overall survival ranging from 2.8 to 4 months; up to 55% of these subjects will ultimately die as a direct result of their brain metastases [McWilliams, 2008; Staudt, 2010]. The initial clinical management of melanoma brain lesions depends largely on the number and size of the lesion(s), the presence of concurrent extracranial metastatic disease, and the patient's performance status. The neurological symptoms associated with melanoma brain metastasis can be severe and therefore, the supportive care is of particular clinical importance. The use of corticosteroids to reduce intracerebral edema is well established, and high initial doses can be frequently weaned as anti-tumor therapy is delivered. Anti-convulsants are primarily used in subjects with symptomatic brain metastases and documented seizures since several studies have demonstrated the lack of use of these medications in a prophylactic setting [McWilliams, 2008]. While local treatment options are generally preferred [Staudt, 2010] the need for effective systemic treatments to also control peripheral melanoma manifestations is still very much unmet. Neurosurgical tumor resection usually followed by radiotherapy is the current gold standard in the local control of melanoma brain metastases [Fife, 2004; Samlowski, 2007]. Unfortunately, only a small proportion of patients are suitable candidates for surgical tumor resection, and the overall survival in these patients remains poor [Davies, 2011]. Similar rates of local tumor control of brain metastases have been demonstrated for stereotactic radiosurgery (SRS), using either linear accelerator (Linac-) or gamma-knife (GK) based treatment approaches [Majer, 2007]. Patients who are not suitable for neurosurgical resection or SRS, including those with poor prognostic factors (uncontrolled primary tumor and/or extracranial metastases, or those patients with either >3 or surgically inaccessible lesions) are frequently treated with palliative whole-brain radiation therapy (WBRT).

So far, the efficacy of systemic treatment approaches, and especially chemotherapy, in the treatment of melanoma metastatic to the brain is limited. Most attempts to control the progression of metastatic brain lesions with single-agent or combination regimens alone or in combination with local modalities, have been largely unsuccessful [McWilliams,

2008; Samlowski, 2007]. Although multiple chemotherapeutic agents such as the nitrosoureas carmustine and fotemustine or the dacarbazine analogue temozolamide (TMZ) can theoretically penetrate the blood-brain-barrier, only limited activity against melanoma CNS metastases has been demonstrated in clinical trials [McWilliams, 2008]. The convincing efficacy data that led to the regulatory approval of TMZ for the use in subjects with primary brain tumors were not reproduced for the treatment of melanoma brain metastases in a phase II study [Agarwala, 2004]. In this study, the response rate was low (7% in patients with no prior systemic treatment, 6% in those who had previously received systemic treatment), and the progression-free survival (1.2 months in patients with no prior systemic treatment, 1.2 months in those who had previously received systemic treatment) as well as the overall survival (3.5 months in patients with no prior systemic treatment, 2.2 months in those who had previously received systemic treatment) were short. However, multiple trials are currently ongoing to assess the efficacy of novel targeted- and immnuo-therapeutic agents alone or in combination with other systemic or localized treatment modalities in the clinical management of melanoma metastatic to the brain.

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers, including melanoma. This pathway can be constitutively activated by alterations in specific proteins, including BRAF, which phosphorylates MEK1 and MEK2 on two regulatory serine residues. Approximately 90% of all identified BRAF mutations that occur in human cancer result in a V600-E or -K amino acid substitution [Wan, 2004; Wellbrock, 2004]. This mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately >10-fold compared to wild type [Davies, 2002]. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 40-60% of melanoma [Hocker, 2007]. The frequency of this activating mutation and the pathway addiction to which it leads make mutated BRAF an extremely attractive target especially in melanoma. So far, only one putative RAF kinase small-molecule inhibitor, sorafenib, has achieved regulatory approval (for renal cell and hepatocellular carcinoma). However, sorafenib failed to demonstrate activity in melanoma as a single agent [Eisen, 2006] or in combination with systemic chemotherapy [Flaherty, 2013]. Clinical benefit from sorafenib in metastatic melanoma patients did not correlate with the presence of the activating V600E BRAF-mutation [Eisen, 2006], indicating that the compound lacks specificity and potency against BRAF kinase. The clinical activity of sorafenib is most likely due to inhibition of targets other than BRAF. The selective small molecule BRAF-inhibitor vemurafenib received FDA-approval in August of 2011, as the first molecularly-targeted agent for unresectable or metastatic melanoma harboring BRAF V600E mutations. In the pivotal Phase III study, treatment with vemurafenib resulted in a significant ($p<0.001$) improvement of progression-free survival (HR 0.26) and overall survival (HR 0.37) in the interim data analysis compared to DTIC chemotherapy [Chapman, 2011]. In addition to a strict dependence on BRAF mutation status for activity, vemurafenib also has notable pharmacologic requirements in that the drug failed to achieve clinical responses until doses were reached that achieved > 80% inhibition of phosphorylated (activated) ERK (p-ERK) levels in the tumors [Bollag, 2010]. This correlated with the achievement of plasma level that also induced tumor regression in preclinical models [Flaherty, 2010].

1.2. Dabrafenib

Dabrafenib (GSK2118436), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is a potent and selective inhibitor of BRAF kinase activity with a mode of action (MOA) consistent with adenosine triphosphate (ATP)-competitive inhibition. Excluding RAF enzymes, GSK2118436 demonstrated IC_{50} values <100 nM against only 8 kinases from ~300 protein and lipid kinases tested. GSK2118436 has demonstrated inhibition of a downstream pharmacodynamic biomarker (pERK) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutant tumor cell lines, and achieved biomarker inhibition and tumor regression in BRAF mutant xenograft models. Dabrafenib is metabolized sequentially to 3 metabolites, hydroxyl-dabrafenib (GSK2285403), carboxy-dabrafenib (GSK2298683), and desmethyl –dabrafenib (GSK2167542). Hydroxy- and desmethyl-dabrafenib are believed to contribute to the clinical activity of dabrafenib, although contribution of each metabolite to the overall clinical activity is unknown and dependent on potency and relative exposure. Additional background information is provided in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number CM2010/00010/03].

More than 700 patients have been treated to-date with dabrafenib monotherapy. Common AEs occurring in at least 20% of patients include hyperkeratosis, headache, pyrexia, arthralgia, alopecia, and palmar-plantar erythrodysesthesia syndrome. . Most cases of pyrexia have been mild, self limited, and have responded to anti-pyretic therapy. However, cases of complex pyrexia have been reported as serious adverse events (SAEs) in which patients have presented with high fever (up to 105 -106 degrees F), with severe rigors, and in some instances, hypotension. Most cases of pyrexia have presented within the first two months of therapy. A variety of skin effects have been noted in BRAF inhibitor treated patients including rash, hyperkeratosis, actinic keratosis, seborrheic keratosis, hand-foot skin reactions (HFSR), papillomas and cutaneous squamous cell carcinomas (SCC). Squamous cell cancers related to BRAF inhibitor therapy often have characteristic of keratoacanthoma type of SCC, which traditionally have a relatively benign prognosis. Among the rare AEs, renal insufficiency/failure was recently identified as a potential adverse drug reaction associated with dabrafenib. Most cases of renal insufficiency have been in the setting of dehydration and/or pyrexia; however there have been reports of acute renal failure suggestive of intrinsic renal disease. Dabrafenib, like other BRAF inhibitors, has been associated with reports of uveitis, with an incidence of 1%.

BRF113683 (BREAK-3) was a phase III clinical trial in subjects with BRAF V600E-mutation positive metastatic melanoma. 250 subjects were randomly assigned to receive either dabrafenib (187 patients) or dacarbazine (63 patients). Median progression-free survival was 5.1 months for dabrafenib and 2·7 months for dacarbazine, with a hazard ratio (HR) of 0·30 (95% CI 0·18–0·51; p<0·0001). The most common adverse events with dabrafenib were skin-related toxicities: fever, fatigue, arthralgia, and headache [Data from this trial were the basis for the recent FDA approval of dabrafenib as treatment for patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

BRF113929 (BREAK-MB) was a phase II clinical trial in subjects with BRAF V600E/K-mutation positive melanoma that had metastasized to the brain. 172 subjects were enrolled; 89 (52%) had not received prior local treatment to the brain (Cohort A) and 83 (48%) had progressive brain metastases after prior local intervention (Cohort B). Of the 74 subjects with V600E mutation-positive melanoma, 29 (39·2%, 95% CI 28·0–51·2) achieved an overall intracranial response, as did 20 (30·8%, 19·9–43·4) of 65 subjects in Cohort B. One (6·7%, 0·2–31·9) of 15 subjects with V600K mutation-positive melanoma achieved an overall intracranial response in Cohort A, as did four (22·2%, 6·4–47·6) of 18 subjects patients in Cohort B. Treatment-related adverse events of grade 3 or worse occurred in 38 (22%) patients. Eleven (6%) patients developed squamous-cell carcinoma. Four grade 4 treatment-related adverse events occurred in Cohort A: one blood amylase increase, one convulsion, one lipase increase, and one neutropenia. Two grade 4 events occurred in Cohort B: one agranulocytosis and one intracranial hemorrhage. 51 (30%) patients had a serious adverse event. The most frequent serious adverse events were pyrexia (6%), intracranial hemorrhage (6%) and squamous-cell carcinoma (6%) [Long, 2012].

1.3. Trametinib

Trametinib (GSK1120212), a pyrido-pyrimidine derivative, is a potent and highly selective allosteric i.e. non-ATP competitive inhibitor of MEK1 and MEK2 activation and kinase activity. In the pivotal study MEK114267 (METRIC), 322 patients who had metastatic melanoma with a V600E or V600K BRAF mutation were randomized in a 2:1 ratio to receive trametinib (2 mg orally) once daily or chemotherapy (either intravenous dacarbazine, 1000 mg per square meter of body-surface area or paclitaxel 175 mg per square meter every 3 weeks.) Median progression-free survival was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (hazard ratio 0.45; 95% confidence interval [CI], 0.33 to 0.63; P<0.001). At 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the chemotherapy group despite crossover (hazard ratio, 0.54; 95% CI, 0.32 to 0.92; P = 0.01). Rash, diarrhea, and peripheral edema were the most common toxic effects in the trametinib group and were managed with dose interruption and dose reduction; asymptomatic and reversible reduction in the cardiac ejection fraction and ocular toxic effects occurred infrequently. Secondary skin neoplasms were not observed [Flaherty, 2012a]. Data from this trial were the basis for the approval of trametinib for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
Trametinib monotherapy has been evaluated in well over 500 patients. Common AEs include rash, lymphedema, and diarrhea. In addition, a decrease in left-ventricular ejection fraction (LVEF) has been observed in approximately 10% of subjects receiving trametinib. Most of these cases were associated with no symptoms. Consequently, strict monitoring has been in place along with guidelines on management of patients with decreased LVEF.

1.4. Dabrafenib Combined with Trametinib

In a recent study of dabrafenib in combination with trametinib in patients without CNS metastases, a confirmed ORR of 76% was reported in patients with BRAF V600E/K-mutation-positive metastatic melanoma who were treated in the dabrafenib 150 mg BID combined with trametinib 2 mg once daily dose cohort. In this same cohort, efficacy outcomes were significantly improved when compared with dabrafenib monotherapy (ORR: 76% vs 54%; p=0.026; median PFS=9.4 vs 5.8 mo, HR 0.39; 95% CI (0.25, 0.62), p<0.0001) [Flaherty, 2012b].

1.5. Study Rationale

The current systemic therapeutic options for the management of melanoma metastatic to the CNS are limited and there is a high unmet medical need for additional treatment modalities. Although local therapies such as neurosurgical resection, SRS, and WBRT are considered standard, the ability of these modalities to control intracranial disease progression, and to improve neurological signs and symptoms, is limited to sub-populations of melanoma patients with limited tumor burden. In addition, CNS progression of melanoma is rarely independent of extracranial progression and therefore, innovative treatment approaches for patients with melanoma metastatic to the brain should ideally address both intracranial and extracranial disease [Cranmer, 2010].

Although encouraging results have been observed in BREAK-MB, the interpretation of this trial, and the design of future clinical trials for subjects with melanoma brain metastases with BRAF mutations, will be strengthened by an improved understanding of the pharmacokinetics and pharmacodynamic effects of dabrafenib in brain metastases. In preclinical studies, dabrafenib did not penetrate the intact blood-brain-barrier (BBB) following single dose administration in mice without brain metastases. It is currently unknown if the activity of dabrafenib in subjects with established brain metastases is due to BBB penetration of dabrafenib or one (or more) of its metabolites, and the relationship between the levels achieved in brain metastases and peripheral exposure in plasma and extracranial metastases. The degree of inhibition of BRAF achieved in brain metastases with doses of dabrafenib that were selected for their peripheral pharmacokinetic and pharmacodynamic characteristics is also unknown. We have designed this corollary study of pre-operative treatment of dabrafenib 150 mg BID monotherapy and dabrafenib 150 mg BID combined with trametinib 2 mg once daily in subjects with BRAF V600E or V600K-mutation positive melanoma with resectable brain metastases to address these important questions.

2. OBJECTIVES AND ENDPOINTS

Table 1 lists the study objectives and corresponding endpoints.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
The primary objective of this study is to determine levels and tissue distribution of dabrafenib, its metabolites and trametinib in parenchymal brain metastases peripheral blood (plasma) and, when possible, in extracranial metastases within two cohorts of subjects with BRAF V600E/K mutation-positive metastatic melanoma to the brain following pre-operative treatment.	Concentrations and tissue distribution of dabrafenib, its metabolites hydroxy-, carboxy- and desmethyl-dabrafenib and trametinib (Cohort B only) in parenchymal brain metastases, peripheral blood (plasma) and, when possible, in extracranial metastases.
Secondary	
The secondary objectives are as follows: Determine the levels of dabrafenib, its metabolites and trametinib in the CSF in subjects who undergo resection of BRAF V600E/K mutation-positive metastatic melanoma to the brain following pre-operative treatment. Determine the activation status of the MAPK pathway following pre-operative treatment in resected brain and, when available, extracranial metastases. Activation of the MAPK kinase pathway will also be determined in samples of readily accessible extracranial metastases obtained prior to starting treatment. Comparison of pharmacokinetics and pharmacodynamics to tumor response.	Concentrations of dabrafenib, its metabolites hydroxy-, carboxy- and desmethyl-dabrafenib) and trametinib (Cohort B only) in CSF samples. When available, changes in MAPK pathway markers in paired extracranial biopsies taken pre-treatment, during craniotomy, and at disease progression, and changes in markers between post-operative intracranial and extracranial biopsies. Changes in the radiographic characteristics of the tumors will be compared to (1) levels of dabrafenib, its metabolites and trametinib (where appropriate) in the brain metastases, plasma, and CSF, and (2) MAPK pathway activation status in tumors at the time of surgery. When available, results will also be compared to the analysis of early clinical responses in extracranial metastases, as determined by the PET-CT imaging.

Objectives	Endpoints
The clinical response objectives are to evaluate efficacy of study treatment in resected and unresected lesions.	Efficacy as measured by: • change from baseline to pre-surgery in the sum of the longest diameters of intracranial target lesions, • maximum change from baseline in the sum of longest diameters of unresected intracranial target lesions, • overall extracranial response rate in unresected lesions, and • overall survival
The safety objective is to further characterize the safety profile of study treatment in subjects with melanoma brain metastases.	Safety as measured by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), chemistry and hematology laboratory values, and adverse events (AEs).
Exploratory	
The exploratory research objectives are as follows:	
Characterize the prevalence of BRAF and other mutations in melanoma brain metastases and extracranial metastases when available.	Quantitative analysis of DNA from the brain and extracranial metastases to determine the degree of concordance of BRAF mutations between the two samples. Additional mutations found in the analysis of tumor samples will be summarized.
Evaluate the baseline and changes in the expression and activation of proteins and transcriptional cell signaling networks, including the MAPK kinase pathway, in readily accessible extracranial metastases when available in patients treated with dabrafenib and dabrafenib plus trametinib and compare changes where appropriate.	The expression and activation of protein signaling pathways and transcriptional networks, including the MAPK pathway, will be evaluated when available in extracranial biopsies taken pre-treatment, at/near the time of craniotomy, and at disease progression to understand changes induced by the given treatments and their correlation with other molecular features (i.e. mutations) and treatment outcomes.

Objectives	Endpoints
Compare the status of protein and transcriptional signaling pathways, including the the MAPK kinase pathway, in the brain metastases and readily accessible extracranial metastases when available.	The expression and activation of protein signaling pathways and transcriptional networks, including the MAPK pathway, in intracranial and, when available, extracranial biopsies collected at/near the time of craniotomy, and/or at disease progression, will be compared to identify differential molecular features and treatment effects. Results will also be compared to the analysis of early clinical responses in extracranial metastases, as determined by the PET-CT imaging, and drug levels in blood and tissue samples.

Encouraging efficacy has been reported in subjects with BRAF V600E/K-mutation positive melanoma that has metastasized to the brain who were treated with dabrafenib monotherapy; however, the degree of BRAF inhibition achieved in brain metastases with doses of dabrafenib that were selected for their peripheral pharmacokinetic and pharmacodynamic characteristics is unknown. Thus, it is critical to better understand whether levels and distribution of dabrafenib and/or trametinib in intracranial lesions differ from extracranial lesions and plasma. A secondary question would be to understand whether there is a variation of distribution of drug between intracranial tumors and plasma and, when possible, extracranial tumors and CSF. Potential intra-cohort variability and the small cohort sample sizes preclude any meaningful inter-cohort analysis, thus, there are no planned statistical comparisons between Cohort A and Cohort B.

3. STUDY DESIGN

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 19), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This international, multi-centre, open-label study will be conducted in up to 30 evaluable subjects with untreated, resectable brain metastases and when possible, readily accessible (i.e. cutaneous, subcutaneous, or superficial lymph node) extracranial metastases. Subjects with metastatic melanoma (Stage IV) and evidence of untreated brain metastases will be screened for eligibility. Subjects must have clinically certified testing results that indicate the presence of a BRAF mutation involving the V600 codon (V600E or V600K) in a sample of tumor tissue obtained at any time during the subject's disease course. Eligible subjects will have at least one intracranial metastasis of between 1.0 – 4.0 cm that is considered surgically resectable by a neurosurgeon but that does not require immediate removal for subject safety or symptom relief. Eligible subjects must not have received any prior radiation or surgical treatments to the brain in the region of the tumor (s) that will be resected to address the primary endpoint of the study.

This is a global, multi-centre, open-label, study that will be conducted in up to 30 evaluable subjects with resectable, BRAF V600E or V600K mutation-positive metastatic melanoma to the brain. Subjects in Cohort A will receive dabrafenib orally 150mg twice daily (BID) for 7 to 14 days prior to surgery (Cohort A); Subjects in Cohort B (the second cohort of 2 cohorts) will receive the combination of dabrafenib 150 mg BID and trametinib 2 mg once daily for 7 to 14 days prior to surgery (Cohort B). An interim analysis will be performed after cohorts A and B have each enrolled 5 patients (with cohort A enrolling the first 5 patients and cohort B the second 5). After the first 10 subjects have been enrolled the planned assignment of subsequent patients to the two cohorts will be in groups of 5 beginning with Cohort A then switching to the Cohort B until up to 30 patients have been enrolled. Subjects will be treated for at least 7 days prior to craniotomy, but not more than 14 days. This 7-14 day window is allowed for scheduling purposes, or if the interim or later analyses determines this duration is needed to meet the primary endpoint. The last dose of study treatment will be given the night prior to the craniotomy. The timing of the last dose prior to surgery may also be adjusted based on interim or later analyses to meet primary endpoint. Protocol specified guidelines for dose adjustments, interruptions and discontinuation due to adverse events are provided in Section 5.7. If available, subjects will undergo biopsy of an easily accessible extracranial metastasis within 14 days before starting treatment. All subjects will have an MRI of the brain and whole-body PET-CT imaging within 14 days before starting study treatment. All subjects will undergo physical exam and routine lab testing prior to starting therapy. Subjects will initiate study treatment on Day 1. On the day prior to the craniotomy, subjects will be assessed by physical exam and lab testing. MRI

of the brain and whole-body PET-CT imaging will also be performed between 1 to 3 days prior to surgery. On the day of surgery, blood samples will be collected for pharmacokinetic analysis. Two samples will be collected prior to surgery, and two samples will be collected after surgery; all samples will be separated in time by at least 1 hour. Optional collection of CSF will be obtained in the operating room on the day of brain metastasis resection; this procedure is described in Section 6.5 of the protocol. Portions of the resected brain metastasis(es) that in the clinical judgment of the neurosurgeon performing the operation are not required to be submitted for pathological confirmation of melanoma brain metastasis will be divided into sections to be used for pharmacokinetic, pharmacodynamic, and exploratory translational research studies. Optional collection of an easily accessible extracranial metastasis may be performed after the PET-CT scan and up to 1 day after the removal of brain metastasis(es); which will be similarly divided for studies. The time of collection of brain metastasis, the plasma samples, and the optional extracranial metastasis(es) and CSF will be recorded for the purpose of the pharmacokinetic analysis, as well as the time the last dose of study treatment was taken.

Subjects in either cohort with intracranial and/or extracranial metastases remaining after surgery may resume treatment with the combination of dabrafenib 150 mg BID and trametinib 2 mg once daily no earlier than 72 hours after surgery at the discretion of the Principal Investigator. Subjects continuing on treatment will be evaluated for safety 4 weeks after restarting treatment, and every 4 weeks thereafter. These subjects will be evaluated for efficacy eight weeks after restarting treatment, and every 8 weeks thereafter.

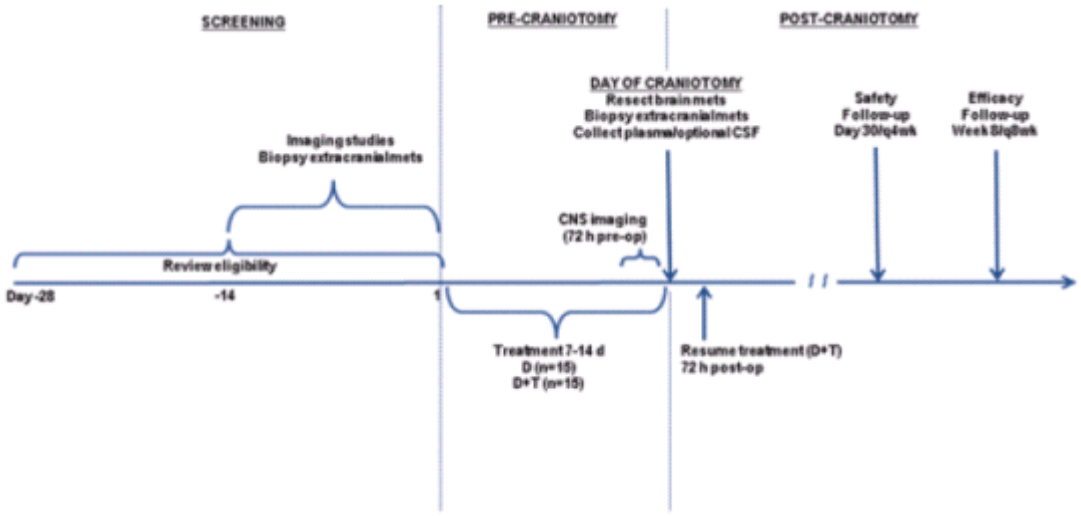
Subjects who do not continue treatment after the craniotomy procedure will be evaluated for safety at the discontinuation visit 4 weeks after the craniotomy.

All subjects who permanently discontinue study treatment will be followed for survival and new anti-cancer therapy for a total of two years or until death or the subject wishes to withdraw from further follow-up. The study will be considered closed once the last subject reaches this milestone.

This trial will prospectively evaluate the levels of dabrafenib and its metabolites that are achieved in melanoma brain metastases, the relationship between the drug levels achieved in the brain metastases and in the plasma, and the activation of the MAPK pathway and other cell signalling networks in the brain metastases. In subjects receiving dabrafenib in combination with trametinib, drug levels of trametinib will also be assessed, where feasible. Subjects may also undergo optional biopsies of readily accessible extracranial tumors (i.e. skin, subcutaneous, superficial lymph nodes) prior to initiating treatment and on the same day as the craniotomy. The activation status of the MAPK and other cellular signalling pathways will be determined in the pre- and post-treatment specimens to determine the degree of pathway inhibition achieved in the extracranial metastases, which will be compared to the activation status of the pathway in the brain metastases at the time of resection. The levels of dabrafenib and its metabolites will also be determined in the available extracranial metastases for comparison to the pharmacodynamic effects, and for comparison to the levels achieved in the brain metastases and the plasma. For subjects who consent to the optional procedure, we will

also determine the levels of dabrafenib and its metabolites in the CSF, which will be collected at the time of the craniotomy, and will be compared to the levels in the plasma and in the brain metastases. Exploratory studies of the activation status of other pro-survival pathways as well as for the prevalence of BRAF and activating mutations in other oncogenes will also be performed on the tissues obtained from the study. The study also incorporates imaging to detect early clinical responsiveness of the brain and extracranial lesions, for correlation with the results of the pharmacokinetic and pharmacodynamic studies, and the pathologic and immunological features of the tumor.

Figure 1 Study Schema



3.1. Discussion of Design

The trial will evaluate the pharmacokinetics, pharmacodynamics, exploratory translational research, and safety endpoints of preoperative treatment of dabrafenib and dabrafenib combined with trametinib in subjects with resectable metastatic melanoma to the brain.

3.1.1. Dose Rationale

Dabrafenib 150 mg BID was studied in Phase II and Phase III studies of patients with metastatic melanoma (including patients with melanoma that has metastasized to the brain), and was the basis for the dose level described in the current US Prescribing Information.

The dose combination of dabrafenib 150 mg BID combined with trametinib 2 mg once daily was clinically active and well-tolerated in a phase II study [Flaherty, 2012b], and is presently under study in three pivotal phase III trials.

3.1.2. Treatment Duration and Timing Rationale

The goals of the study include both pharmacokinetic and pharmacodynamic evaluations. Thus, the duration of pre-operative treatment is designed to result in surgery prior to significant tumor tissue degradation due to apoptosis and/or necrosis. Based on pharmacokinetic analyses from the FTIH study, dabrafenib exposure decreases with time and is near steady state after about 14 days of dosing. However, two of the dabrafenib metabolites accumulate with repeat dosing due to their long half-life and are generally stable after one week of dosing. Based on these PK data and the analysis of a selected number of tumor tissue biopsies performed between 8 to 15 days of treatment, it is estimated that the ideal duration of treatment will be 7 to 14 days. In the initial phase of the trial, the treatment duration goal will be for 7 days, with 24-48 hour variance allowed for scheduling conflicts. Study treatment will be taken until the evening before surgery. Concentrations of dabrafenib and hydroxyl-dabrafenib should be in the terminal, linear phase during surgery while concentrations of carboxy-dabrafenib and desmethyl-dabrafenib should be fairly constant. This will allow better estimations of brain to plasma equilibrium. A sample quality review will take place after 3 subjects have been treated to allow for evaluation of modifiable treatment logistics and the ability to complete the primary objective of the study. This sample quality review will include an assessment of the quality of the tissue samples from the resected brain and optional extracranial metastases for the planned pharmacokinetic and pharmacodynamic analyses. In addition, the results of the pharmacokinetic analysis of dabrafenib and its metabolites for the first 3 subjects will be reviewed. Adjustments may be made to the duration of the treatment before surgery, and/or the timing of the last dose of dabrafenib that is administered prior to surgery, based on the review of the results by the participating investigators. Subject safety and any unexpected toxicities will also be reviewed. Accrual will continue during this formal review. Additional analyses will be performed after the last patient in the dabrafenib cohort reaches the 4-week post-craniotomy assessment or withdraws from the study, whichever comes first.

Among all subjects treated with dabrafenib 150 mg BID on the phase I study, the most common adverse events documented to occur or start within the first 15 days on drug were pyrexia (19%; all grade 1 or 2), headache (17%; 1 grade 3), anemia (16%; 1 grade 3, 1 grade 4), and rash (14%; all grade 1-2). There were 2 cases of neutropenia (both grade 2), and no cases of thrombocytopenia. Of note, based on the adverse event reporting in that trial, it is not possible to tell if the grade 4 anemia actually occurred during the first 15 day or it rather started within this timeframe and at some point reached grade 4. In that same trial, 36 subjects underwent a total of 51 invasive procedures. The majority (n=28) of the procedures were biopsies or removal of cutaneous lesions. Other significant procedures included hemicolectomy (n=2), laminectomy (n=1), and tibia hardware replacement with debridement (n=1). One subject underwent gamma knife treatment of a brain metastasis. Three subjects underwent resection of intracranial lesions, one of whom underwent evacuation of an intracerebral hematoma that developed in the setting of disease progression more than 10 days after discontinuation of dabrafenib. Adverse events occurring within 15 days of surgery included the single intracerebral hemorrhage described above, one post-procedural complication (inflammation of a biopsy site), and one post-procedural pain. There were no wound healing or infectious adverse events observed [GlaxoSmithKline Document Number CM2010/00010/03].

4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

Up to 30 evaluable subjects (up to 15 per cohort) will be enrolled in this study. An interim analysis will be performed after both cohorts A and B have enrolled 5 subjects. Subjects may have received prior treatment for brain metastatses. If subjects do not complete the full pre-operative treatment regimen, or if their samples cannot be evaluated, they will be replaced with another subject until a total of 15 subjects per cohort have been treated and evaluated.

See Section 9.1.1 for sample size assumptions.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on study treatment that may impact subject eligibility is provided in the GSK2118436 IB [GlaxoSmithKline Document Number CM2010/00010/03] and the GSK1220212 + GSK2118436 IB [GlaxoSmithKline Document Number 2011N126811_01]

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Signed written informed consent
2. Histologically-confirmed metastatic melanoma (Stage IV), carrying BRAF V600E or V600K mutation as determined by testing certified for clinical diagnostic purposes. Previously performed certified BRAF testing is acceptable. If no prior BRAF mutation testing results are available, testing of a distant metastasis is preferred, but testing of a regional metastasis or primary tumor is also acceptable.
3. At least one previously untreated intracranial lesion $\geq$ 1.0 cm but $\leq$ 4.0 cm that can be treated with surgical resection in the opinion of the treating physicians, and for which immediate local therapy is not clinically indicated.
4. Age > 18 years of age.
5. Able to swallow and retain oral medication
6. Women with child-bearing potential must be willing to practice acceptable methods of birth control during the study (See Section 7.3.2).
7. Women of childbearing potential must have a negative serum pregnancy test within 14 days of first dose of study treatment.

8. Must be able to understand and comply with protocol requirements and instructions.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 [Oken, 1982].
10. Must have adequate organ function as defined by the following screening values in Table 2:

Table 2 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
ANC	≥ 1.2 × 10^9/L
Hemoglobin	≥ 9 g/dL
Platelet count	≥ 100 x 10^9/L
PT/INR[a] and PTT	≤ 1.3 x ULN
Hepatic	
Total bilirubin	≤ 1.5 x ULN
AST and ALT	≤ 2.5 x ULN
Renal	
Serum creatinine[b]	≤ 1.5 mg/dL
Cardiac	
Left Ventricular Ejection fraction (LVEF)[c]	≥ LLN by ECHO

1. Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; INR = international normalized ratio; LLN = lower limit of normal; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

a. Subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization.

b. If serum creatinine is > 1.5 mg/dL, calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 2). Creatinine clearance must be ≥ 50 mL/min to be eligible.

4.1.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Neurological symptoms related to brain metastasis that are not controlled with a stable or decreasing dose of oral steroids for at least 7 days prior to starting study treatment.
2. Prior whole brain radiation (WBRT). Prior treatment with stereotactic radiosurgery is permitted so long as there is one evaluable lesion which has not been treated with SRS.
3. Previous treatment with a BRAF or MEK inhibitor.
4. Cancer therapy (chemotherapy with delayed toxicity, extensive radiation therapy, immunotherapy, biologic therapy, or major surgery) or investigational anti-cancer

drugs within the last 3 weeks, or chemotherapy without delayed toxicity within the last 2 weeks, preceding the first dose of study treatment.

5. Current or expected use of a prohibited medication as described in Section 6.2, including enzyme-inducing antiepileptic drugs (EIAEDs) during treatment with dabrafenib.
6. Presence of leptomeningeal disease or dural metastases.
7. History of another active malignancy within the past 5 years, or any malignancy with a confirmed activating RAS mutation. Please note prospective RAS mutation testing is not required, however, if results of previous RAS testing are known, they must be used in assessing eligibility. Subjects with a history of completely resected non-melanoma skin cancer are eligible.
8. Known allergies against contrast agents required for MRI of intracranial lesions, or other contraindications for MRI, i.e., pacemaker.
9. Current use of therapeutic warfarin. Low-molecular-weight heparin and prophylactic low-dose warfarin are permitted.
10. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia.
11. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs.
12. History of a prior symptomatic stroke, dementia, or other significant central neurologic condition (i.e. multiple sclerosis).
13. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection.
14. Current acute infection requiring intravenous antibiotics.
15. A history or evidence of cardiovascular risk, including any of the following cardiac abnormalities:

    - A QT interval corrected for heart rate using Bazett's Formula; (QTcB) interval ≥ 480 msecs;
    - A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization;
    - A history or evidence of current Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) guidelines;
    - Abnormal cardiac valve morphology (≥ Grade 2) documented by echocardiogram (ECHO) (subjects with Grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
    - History of or evidence of clinically significant uncontrolled cardiac arrhythmias;

- Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;
- Patients with intra-cardiac defibrillators or permanent pacemakers;

16. A history or current evidence/risk of retinal vein occlusion (RVO) or CSR including:
    a. Presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or
    b. Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as:
        i. Evidence of new optic disc cupping;
        ii. Evidence of new visual field defects on automated perimetry;
        iii. Intraocular pressure >21 mmHg as measured by tonography.
17. Pregnant, lactating or breastfeeding females
18. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
19. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to dabrafenib, trametinib or their excipients that contraindicate their participation.

4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

All subjects will receive study treatment until the day prior to the resection of their brain metastasis (es), or until unacceptable adverse event, including meeting stopping criteria for hematologic and other non-hematologic toxicity. Subjects who have additional melanoma metastases after resection of their brain metastasis (es) and optional sampling of easily accessible extracranial metastases may resume treatment with the combination of dabrafenib 150 mg BID and trametinib 2 mg once daily no earlier than 72 hours after completion of their surgical procedures, at the discretion of the treating physician.

Subjects will be permitted to receive the combination of dabrafenib 150 mg BID and trametinib 2 mg once daily until disease progression, death, or unacceptable AE, including hematologic or other non-hematologic toxicity, and/or meeting stopping criteria for liver chemistry defined in Section 5.7.6. In addition, study treatment may be permanently discontinued at any time for any of the following additional reasons:

- deviation(s) from the protocol
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up

- study is terminated.

The primary reason that study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and follow-up as specified in Time and Events Table (Table 19) and Section 7.11.

All subjects will be followed for survival and new anti-cancer therapy for a total of two years or until the subject wishes to withdraw from further follow-up.

4.2.1. Subject Completion

A subject will be considered to have completed the study if the subject dies during the study, during the follow-up period or has been in survival follow-up for 2 years. The cause of death will be recorded in the eCRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, is no longer being followed at the investigator's discretion, or if the study is terminated.

5. STUDY TREATMENTS

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

5.1. Investigational Products

5.1.1. Dabrafenib

Dabrafenib will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

Dabrafenib study treatment will be provided for oral administration as 50 mg and 75 mg capsules. Each capsule contains 50 mg or 75 mg as free base (present as the mesylate salt). Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff upon request.

5.1.2. Trametinib

Trametinib will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

Trametinib study treatment will be provided as 0.5 mg and 2.0 mg tablets. Each tablet will contain 0.5 mg or 2.0 mg of trametinib parent (present as the DMSO solvate). The inactive ingredients will include mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, and film coating (Opadry, a titanium dioxide-based formulation with yellow or red iron oxide as colorant). Both tablet strengths are biconvex film coated tablets with a different shape and size to facilitate the visual identification. The 0.5 mg strength is a 4.8x8.7 mm yellow, oval tablet, and the 2.0 mg strength is a 7.5 mm diameter, pink, round tablet.

5.1.3. Study Treatment Dosage and Administration

Both study treatment cohorts should take their assigned treatment in the morning at approximately the same time every day. Study treatment should be taken orally with approximately 200 mL of water under fasting conditions, either one hour before or two hours after a meal. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose.

If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.

If a subject misses a dose of dabrafenib, the subject should not double the next regularly scheduled dose. However, the subject can take the missed dose immediately if the next scheduled dose is at least 6 hrs later. The subject should take the next dose at the usual time.

If a subject misses a dose of trametinib, the subject should not double the next regularly scheduled dose. However, the subject can take the missed dose immediately if the next scheduled dose is at least 12 hrs later. The subject should take the next dose at the usual time.

Refer to Section 5.7 for information on dose modifications of study treatment.

5.2. Handling and Storage of Study Treatment

No special preparation of study treatment is required.

Dabrafenib and trametinib must be dispensed and administered in accordance with the protocol, and only to subjects enrolled in the study. Dabrafenib and trametinib must be stored in a secure area under the appropriate physical conditions for the product at the temperature specified on the label. Maintenance of a temperature log (manual or automated) is required. Access to and administration of study treatment will be limited to the investigator and authorized site staff.

Procedures for final disposition of unused study treatments will be provided in the SPM.

5.3. Treatment Assignment

Subjects will be identified by a unique subject number for the duration of the study. Each site will be given a subject number range. The first 5 enrolled subjects will receive dabrafenib 150 mg twice daily (Cohort A). The second 5 enrolled subjects will receive dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily (Cohort B). After the first 10 subjects have been enrolled the planned assignment of subsequent patients to the two cohorts will be in groups of 5 beginning with Cohort A then switching to the Cohort B until up to 30 patients have been enrolled.

Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff. Study-specific instructional worksheets will be provided for the use of RAMOS. All calls to RAMOS are confirmed with a fax, which will be sent to the site upon completion of each call.

Subjects who begin, but discontinue treatment prior to the planned pre-operative treatment duration, or who fail to undergo surgical resection and collection of their brain metastasis (es) and extracranial metastases for pharmacokinetic analysis (the primary objective of the study will be replaced in the study. Once 30 subjects have completed the treatment and assessments described in the protocol, the study will be closed to further enrolment.

5.4. Blinding

This is an open-label study.

5.5. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

5.6. Treatment Compliance

Compliance with study treatment will be assessed through querying the subject during the site visits and documented in the source documents and electronic case report form (eCRF). A record of the number of dabrafenib capsules and trametinib tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates of dose modifications and/or interruptions will also be recorded in the eCRF.

5.7. Dose Modification Guidelines

The severity of AEs will be graded using the CTCAE, version 4.0. The section includes:

- general guidelines for clinically significant toxicities related to study treatments and
- specific guidelines for adverse events of special interest, which are events that have been observed with higher frequency or severity in subjects receiving dabrafenib, trametinib, or a combination of both therapies.

With the exceptions of pyrexia which is likely related to dabrafenib, and LVEF decrease, retinal vein occlusion (RVO), central serous retinopathy (CSR), and retinal pigment epithelial detachment (RPED) which are likely related to trametinib, guidance suggests that both therapies be reduced simultaneously in response to toxicities that are considered by the investigator to be treatment related.

Table 3 Categories of Dose Modification Guidelines

Adverse Event	Dabrafenib	Trametinib	Section
General Guidelines for Clinically Significant Toxicities	X	X	Section 5.7.2
Guidelines for Specific Adverse Events Cardiovascular Adverse Events			
LVEF		X	Section 5.7.3.1
Hypertension	X	X	Section 5.7.3.2
Prolonged QTc	X	X	Section 5.7.3.3
Skin–Related Adverse Events (Except cuSCC)[a]			
Rash	X	X	Section 5.7.4.1
Hand-Foot Skin Reaction	X	X	Section 5.7.4.2
Other Adverse Events			
Pyrexia	X		Section 5.7.5.1
Diarrhea	X	X	Section 5.7.5.2
Renal Insufficiency	X	X	Section 5.7.5.3
Visual Changes	X	X	Section 5.7.5.4
Pneumonitis	X	X	Section 5.7.5.5
Liver Chemistry Stopping Criteria	X	X	Section 5.7.6.1

a. Refer to Section 5.7.4.3 for management of cuSCC.

5.7.1. Dose Levels of Dabrafenib and Trametinib

Dose levels for this study are provided in Table 4.

Table 4 Dose Level Reduction Guidelines

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule
Starting Dose	150 mg BID	2 mg once daily
-1 (1st Dose reduction)	100 mg BID	1.5 mg once daily
-2 (2nd Dose reduction)	75 mg BID	1.0 mg once daily

1. Abbreviation: BID = twice daily

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, the dose may be increased to the previous dose level.

A dose reduction below 75 mg BID for dabrafenib and 1 mg once daily for trametinib is not allowed. If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued, but the subjects will be allowed to continue trametinib. If a dose reduction below1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib.

Note: Approval from the GSK Medical Monitor is required to restart study treatment after ≥21 days of interruption.

5.7.2. General Guidelines for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and which do not have specific guidelines (see Table 3) are provided in Table 5.

Table 5 Dose Modification Guidelines for Events Considered Related to Study Treatment

CTCAE Grade	Action and Dose Modification
Grade 1	• Continue study treatment at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Interrupt study treatment if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to grade 1 or baseline, restart study treatment at current dose level
Grade 3	• Interrupt study treatment • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by one dose level** • If the grade 3 toxicity recurs, interrupt study treatment • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by another dose level**
Grade 4	• Interrupt study treatment • Monitor closely • Provide supportive care according to institutional standards • Restart with study treatment **reduced by one dose level** once toxicity resolves to grade 1 or baseline • If the grade 4 toxicity recurs, either **permanently discontinue study treatment or**, if the subject is clinically benefiting, discuss continuation of study treatment with the GSK medical monitor.

For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.

5.7.3. Guidelines for Cardiovascular Adverse Events

Cardiovascular adverse events have been seen in subjects receiving, trametinib or dabrafenib in combination with trametinib.

5.7.3.1. Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Time and Events Table (Table 19). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6.

Table 6 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification

Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• Interrupt study treatment and repeat ECHO within 2 weeks[a]
		• If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline)
		  • Consult with the GSK medical monitor and request approval for restart
		  • Restart with trametinib reduced by one dose level
		  • Restart dabrafenib at previous dose level
		  • Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter
		• If LVEF **does not recover** within 4 weeks
		  • Consult with cardiologist
		  • **Permanently discontinue trametinib**
		  • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
		  • Consult with GSK medical monitor[c]

Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue study treatment.** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution

1. Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; GSK = GlaxoSmithKline; LLN = lower limit of normal; LVEF = left ventricular ejection fraction;

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
c. Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.

5.7.3.2. Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided in Section 5.7.3.2.1 and Section 5.7.3.2.2, respectively.

5.7.3.2.1. Monitoring of Hypertension

All blood pressure assessments should be performed under the following optimal conditions:

- the subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor
- the subject is relaxed comfortably for at least 5 minutes
- restrictive clothing has been removed from the cuff area and the right cuff size has been selected
- the subjects arm is supported so that the middle of the cuff is at heart level
- the subject remains quiet during the measurement.

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the eCRF.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the Time and Events Table (Table 19). Ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP >140 mm Hg and/or DBP >90 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension.

5.7.3.2.2. Management of Hypertension

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Table 7 Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
(Scenario A) • Asymptomatic and persistent [a] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Continue study treatment at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled [b] BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, • or • Failure to achieve well-controlled BP within 2 weeks in Scenario A	• Interrupt study treatment if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • Once BP is well controlled [b], restart study treatment **reduced by one dose level**
(Scenario C) • Symptomatic [c] hypertension or • Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• Interrupt study treatment • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP • Referral to a specialist for further evaluation and follow-up is recommended • Once BP is well controlled, restart study treatment **reduced by one dose level**
(Scenario D) • Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• Permanently discontinue study treatment • Continue follow-up per protocol.

1. Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure
a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

5.7.3.3. Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in Table 8.

Table 8 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Recommend testing serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b] • If event recurs, permanently discontinue study treatments.

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and GSK medical monitor agree that the subject will benefit from further treatment.

5.7.4. Guidelines for Skin-related Adverse Events

Cutaneous adverse events have been observed in subjects receiving dabrafenib, trametinib or both therapies in combination (see the Investigator Brochures for more information). Recommendations for supportive care and guidelines for dose modifications are provided (Section 5.7.4.1, Section 5.7.4.2 , and Section 5.7.4.3). The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the GSK Medical Monitor may be required. In addition, the Sponsor may require biopsies of any new skin lesions especially those suspicious of cuSCC for further study.

5.7.4.1. Rash

Rash is a frequent AE observed in subjects receiving trametinib, dabrafenib, or the combination of both therapies. Guidelines for rash management are based on experience with other MEK inhibitors and EGFR inhibitors [Balagula, 2010; Lacouture, 2011] and are provided below (Table 9 and Table 10).

Table 9 Guidelines for Supportive Care of Rash

Type of Care	Action
Prevention/Prophylaxis: Start from Day 1	• Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
Prevention/Prophylaxis: Start from Day 29 and implement for a total of 6 weeks	• Topical steroids and antibiotics should be applied at least twice daily starting on Day 29 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) and • topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID)
Symptomatic Care[a]	• Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics

1. Abbreviations: BID = twice daily; SPF = sun protection factor
a. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided in Table 10.

Table 10 Management and Dose Modification Guidelines for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures • Use moderate strength topical steroid[a] • Reassess after 2 weeks	• Continue study treatment • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce study treatment by one dose level[c]**

Grade 2	• Initiate prophylactic and symptomatic treatment measures
	• Use moderate strength topical steroid[a]
	• Reassess after 2 weeks
		• **Reduce study treatment by one dose level**
		  • If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level
		  • If no recovery to ≤grade 1 within 2 weeks, interrupt study treatment until recovery to ≤grade 1
		• **Restart study treatment at reduced dose level[b]**

Grade ≥3	• Use moderate strength topical steroids[a] PLUS oral methyl-prednisolone dose pack • Consult dermatologist	• Interrupt study treatment until rash recovers to grade ≤1 • **Restart[b] with study treatment reduced by one dose level[c]** • If no recovery to grade ≤2 within 4 weeks**, permanently discontinue study treatment**

1. Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events
a. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
b. Approval of GSK medical monitor is required to restart study treatment after ≥21 days of interruption.
c. Escalation of study treatment to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

5.7.4.2. Guidelines for Hand-foot Skin Reactions (HFSR)

Episodes of Hand-Foot Skin Reaction (HFSR) have been observed in subjects receiving dabrafenib. Guidelines for management of HFSR are based on experience with other kinase inhibitors [Lacouture, 2008; McLellan, 2011] and are listed Table 11.

Table 11 Management and Dose modification Guidelines for Hand-Foot Skin Reaction (HFSR)

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1[a]	• Life style changes recommended[b] • Initiate symptomatic treatment[c] if clinically appropriate	• Continue study treatment at current dose level
Grade 2	• Life style changes recommended[b] • Initiate symptomatic treatment[c]	• Interrupt study treatment until recovery to ≤grade 1[d] • Recovery to ≤grade 1 within 7 days: Restart study treatment at previous dose level • No recovery to grade ≤1 within 7 days or ≥ 2nd occurrence: **restart with study treatment reduced by one dose level[e]**
Grade ≥3	• Life style changes recommended[b] • Initiate symptomatic treatment[c] • Consult dermatologist	• Interrupt study treatment until recovery to ≤ grade 1[d] • Restart with study treatment **reduced by one dose level[e]** • If 3rd occurrence, discontinue study treatment permanently

1. Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events
a. A full-body skin examination and a removal of pre-existing calluses and keratotic skin is recommended prior to initiation of study treatment
b. Life-style changes: (1)reduce exposure of hands and feet to hot water, (2) avoid traumatic activity including vigorous exercise especially in the first 4 weeks after start of study treatment, (3) avoid constrictive footwear, (4) avoid excessive friction on the skin, when applying topical treatments, (5) wear thick cotton socks and gloves, and shoes with padded insoles
c. Symptomatic Treatments: (1) use moisturizing creams frequently and especially on hands and feet (2) consider topical keratolytics: urea 20-40 % cream, or salicylic acid 6%, or tazarotene 0.1% cream, or fluorouracil 5% cream; (3) erythrematous areas: clobetasol propionate 0.05% ointment; (4) Pain: topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin
d. Approval of GSK medical monitor is required to restart study treatment after ≥21 days of interruption
e. Escalation of study treatment to the previous dose level is allowed if no HFSR is observed in the 4 weeks subsequent to dose reduction.

5.7.4.3. Guidelines for cuSCC

Cutaneous squamous cell carcinoma has been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib. These treatment-related cuSCC should be surgically removed according to institutional practice. Dose modifications or interruptions of the study treatment are not required for cuSCC. Occurrence of cuSCC must be reported as an SAE. Submit tumor tissue from cuSCC or other suspected new primary cancers for analysis (including RAS-mutation status and other mutations as appropriate) as directed in the SPM.

5.7.5. Guidelines for Other Adverse Event of Special Interest

5.7.5.1. Guidelines for Pyrexia

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy or in combination with trametinib (see dabrafenib and dabrafenib and trametinib combination IBs). In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Pyrexia accompanied by ≥ Grade 3 hypotension, or hypotension that is clinically significant in the judgment of the investigator, or dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE per Section 7.3.2.2.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully (see Section 5.7.5.3).

Guidelines regarding management and dose reduction for pyrexia considered to be related to study treatment are provided in Table 12.

Table 12 Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification

Pyrexia[a]	1st Event[b]:
	• Clinical evaluation for infection and hypersensitivity[c]
	• Laboratory work-up[c]
	• Hydration as required[d]
	• Blood sample for cytokine analysis[e]
	• Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f]
	
	2nd Event[g]
	• Clinical evaluation for infection and hypersensitivity[c]
	• Laboratory work-up[c]
	• Hydration as required[d]
	• Blood sample for cytokine analysis[e]
	• Within 3 days of onset of pyrexia
	  • Optimize anti-pyretic therapy
	  • Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[f]
	
	Subsequent Events:
	• Clinical evaluation for infection and hypersensitivity[c]
	• Laboratory work-up[c]
	• Hydration as required[d]
	• Blood sample for cytokine analysis[e]
	• within 3 days of onset of pyrexia:
	  • Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[g]
	  • If corticosteroids have been tapered and pyrexia recurs, restart steroids
	  • If corticosteroids cannot be tapered consult medical monitor
		1st Event:
		• Interrupt dabrafenib
		• Continue trametinib
		• Once pyrexia resolves to baseline, restart dabrafenib at the same dose level
		  • If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
		
		2nd Event:
		• **Interrupt dabrafenib**
		• Continue trametinib
		• Once pyrexia resolves to baseline, restart dabrafenib at the same dose level
		  • If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
		
		Subsequent Events:
		• **Interrupt dabrafenib**
		• Continue trametinib
		• Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[h]**
		• If dabrafenib must be reduced to <75 mg BID, permanently **discontinue dabrafenib**

a. Pyrexia is defined as a body temperature equal to or above 38.5 Celsius or 101.3◦ Fahrenheit.
b. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended. For subjects experiencing rigors/chills without pyrexia, work-up and supportive care, including interruption of study treatment, are recommended.
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
e. Blood samples for cytokine analysis should be taken immediately at the start of fever (i.e., when the subject is being evaluated for fever), and after the fever has disappeared (i.e., during the next routine visit). Blood samples for cytokine analysis must be sent to the central laboratory
f. Anti-pyretic treatment may include ibuprofen, or suitable anti-pyretic medication according to institutional standards. Acetaminophen should be used with caution, especially in subjects with elevated liver enzymes. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
g. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
h. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

5.7.5.2. Guidelines for Diarrhea

Episodes of diarrhea have occurred in subjects receiving dabrafenib, trametinib, or both therapies in combination. Other, frequent causes for diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, partial bowel obstruction, etc., should be clinically excluded.

Guidelines regarding management and dose reduction for diarrhea considered to be related to study treatment by the investigator are provided in Table 13.

Table 13 Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhea[a] Grade 1 or 2	• Diet: stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics	• Continue study treatment • If diarrhea is grade 2 for > 48h, interrupt study treatment until diarrhea resolves to grade ≤1 • Restart study treatment at the same dose level
Uncomplicated Diarrhea[a] Grade 3 or 4 Any Complicated Diarrhea[b]	• Clinical evaluation mandatory • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Oral antibiotics and second-line therapies if clinically indicated • Hydration: intravenous fluids if clinically indicated • Antibiotics (oral or intravenous) if clinically indicated • Intervention should be continued until the subject is diarrhea free for ≥ 24 hours • Intervention may require hospitalization for subjects at risk of life-threatening complications	• Interrupt study treatment until diarrhea resolves to grade ≤1 • Restart with study treatment reduced by one dose level [d] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study treatment**

1. Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

a. **Uncomplicated diarrhea** defined by the absence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution

b. **Complicated diarrhea** defined by the presence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution

c. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea

d. Escalation of study treatment to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

5.7.5.3. Guidelines for Renal Insufficiency

Cases of renal insufficiency have occurred in subjects receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Guidelines regarding management and dose reduction for renal insufficiency considered to be related to study treatment by the investigator are provided in Table 14.

Table 14 Management and Dose Modification Guidelines for Renal Insufficiency

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
Serum creatinine increase >0.2 mg/dL (18 umol/L) but ≤ 0.5 mg/dL (44 umol/L) above baseline	• Recheck serum creatinine within 1 week • Serum creatinine increase > 1 week: contact GSK Medical Monitor • If pyrexia is present, treat pyrexia as per guidelines[a]	• Continue study treatment at the same dose level

Serum creatinine increase >0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L)	• Monitor serum creatinine ≥ 2-times per week
	• Hospitalization may be necessary if serum creatinine cannot be monitored frequently
	• If pyrexia is present, treat pyrexia per guidelines[a]
	• Consult nephrologist if clinically indicated
	• Perform renal biopsy if clinically indicated, for example:
	  • Renal insufficiency persists despite volume repletion
	  • Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)
		• Interrupt study treatment until serum creatinine recovers to baseline
		• Restart with study treatment[b]

1. Abbreviations: GSK = GlaxoSmithKline; NSAIDS = non-steroidal anti-inflammatory drugs
a. NSAIDs can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia 5.7.5.1.
b. Investigator may restart at either the same or a reduced dose level. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Consultation with GSK Medical Monitor is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

5.7.5.4. Guidelines for Visual Changes

Episodes of visual changes have been observed in subjects receiving trametinib, dabrafenib, and combination therapy. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination.

Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO). For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in Table 15.

Table 15 Management and Dose Modification Guidelines for Visual Changes

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1	• Consult ophthalmologist within 7 days of onset •	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification table Y below; **report as SAE if diagnosed.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued. •	• If RPED and RVO excluded, restart trametinib at same dose level. • If RPED diagnosed, see RPED dose modification table below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE** •
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued. •	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • **If RVO or RPED diagnosed, permanently discontinue trametinib and report as SAE.**

1. Abbreviations: CSR = central serous retinopathy; CTCAE = Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; SAE = serious adverse event

a. Refers to CTCAE Version 4.0 'Eye disorders – Other, specify

b. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

5.7.5.5. Guidelines for Pneumonitis

Pneumonitis has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in Table 16.

Table 16 Management and Dose Modification Guidelines for Pneumonitis

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation of pulmonologist recommended	• Continue study treatment at current dose
Grade 2	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests -if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt study treatment until recovery to grade ≤1 • Restart with study treatment **reduced by one dose level** • Escalation to previous dose level after 4 weeks and consultation with medical monitor possible • If no recovery to grade ≤1 within 4 weeks, **permanently discontinue study treatment**
Grade 3	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL if possible • Symptomatic therapy including corticosteroids as clinically indicated	• Interrupt study treatment until recovery to grade ≤1 • After consultation with medical monitor, study treatment may be restarted **reduced by one dose level** • If no recovery to grade ≤1 within 4 weeks, **permanently discontinue study treatment**
Grade 4	• Same as grade 3	• **Permanently discontinue study treatment**

1. Abbreviations: BAL= bronchoalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

5.7.6. Liver Chemistry Stopping and Follow-Up Criteria

5.7.6.1. Liver Chemistry Stopping Criteria

These liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event aetiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov).

Phase II liver chemistry stopping criteria 1-5 are defined as follows:

1. Alanine aminotransferase (ALT) ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and international normalized ratio (INR)>1.5, if INR measured)

   NOTE: If serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is not available, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. ALT ≥5xULN
3. ALT ≥3xULN, if associated with symptoms (new or worsening) believed to be related to hepatitis, such as fatigue, nausea, vomiting, right upper quadrant pain, tenderness or jaundice), or hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥3xULN persists for ≥4 weeks
5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks.

When any of the liver chemistry stopping criteria 1 - 5 is met, do the following:

- **Immediately discontinue** investigational product
- Report the event to GSK within **24 hours** of learning its occurrence
- Complete the liver event case report form (CRF) and serious adverse event (SAE) data collection tool if the event also meets the criteria for an SAE
  - All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
  - **NOTE:** If serum bilirubin fractionation is not immediately available, and if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN, discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury

- Complete the liver imaging and/or liver biopsy CRFs (provided by GSK) if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Withdraw the subject from the study (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment.
- Do not rechallenge with investigational product.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic **within 24** hours for repeat liver chemistries, liver event follow up assessments (refer to Section 5.7.6.3), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for subjects meeting any of the criteria 2 - 5:

- Make every reasonable attempt to have subjects return to clinic within **24-72 hrs** for repeat liver chemistries and liver event follow up assessments (refer to Section 5.7.6.3)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
    - Subjects meeting criterion 5 should be monitored as frequently as possible.

5.7.6.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety
- Continue study treatment
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time the subject meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Refer to Appendix 3 for an algorithm of liver chemistry monitoring, interruption, stopping and follow-up criteria.

5.7.6.3. Liver Event Follow Up Assessments

For subjects meeting any of the liver chemistry stopping criteria 1 - 5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 96 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following assessments are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct), but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1. Permitted Medications and Non-Drug Therapies

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment. Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior surgical procedures will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted provided that INR is monitored in accordance with local institutional practice.

6.2. Prohibited Medications and Non-Drug Therapies

The use of certain medications and illicit drugs within 28 days or 5 half lives, whichever is shorter, prior to randomization and for the duration of the study will not be allowed.

The following medications or non-drug therapies are also prohibited while on treatment in this study:

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known HIV are ineligible for study participation);
- Herbal remedies (e.g., St. John's wort);
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors

or inducers of CYP3A and CYP2C8 (see list in Table 1) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data. Refer to the SPM for the most current list.

Table 17 Prohibited Medications

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St-John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

6.3. Medications to be Used with Caution

The following medications should be used with caution as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 18 and in the SPM.
- Therapeutic level dosing of warfarin can be used with approval by the GSK Medical Monitor and close monitoring of PT/INR by the site. Exposure decreased by 37% due to enzyme induction when on treatment, thus warfarin

dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.

- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

Table 18 Medications to be used with Caution

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib.	
pH altering agents	Dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine

Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

6.4. Treatment after Discontinuation of Study Treatment or Withdrawal from/Completion of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment.

Please refer to Section 7.12 for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinuing study treatment

6.5. Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300mg as a single dose or 600mg daily (the highest dose tested in clinical studies to date), and/or a trametinib overdose, defined as administration of more than 3.0 mg once daily (the maximum tolerated dose defined in the MEK111054 study), the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. GSK does not recommend specific treatment. The investigator will use clinical judgment to treat any overdose.

Decisions regarding dose interruptions or modifications should be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

A plasma sample for PK analysis may be requested by the Medical Monitor on a case-by-case basis. This plasma sample should be collected as soon as possible.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

Refer to the Time and Events Table for the timing of all assessments (Table 19). Details on efficacy and safety assessments are presented in Section 7.2 and Section 7.3, respectively. Further details of study procedures and assessments can be found in the study procedures manual (SPM).

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study. Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

Table 19 Time and Events Table

Study Assessments[1]	Screen[2]	1 to 3 Days prior to surgery	Day prior to surgery	Day of surgery	Day 3 after surgery	Every 4 weeks after restart	Every 8 weeks after restart	Discontinuation	Survival
Informed consent	X								
Inclusion/exclusion criteria[3]	X								
Demographic data	X								
Serum pregnancy test[4]	X								
Register subject	X								
Disease characteristics[5]	X								
Prior anti-cancer therapy, radiotherapy, surgical procedures	X								
Past and current medical conditions, family history	X								
Past and current tobacco consumption	X								
Dispense oral study treatment, assess compliance[6]	X		X		X	X			
Neurological assessment	X					X		X	
Height/weight[7]	X					X		X	
Blood pressure, vital signs[8]	X		X			X		X	
Performance status (ECOG)	X					X		X	
Physical examination[9]	X					X		X	
Dermatologic assessment[10]	X						X	X	
ECG[11]	X								
ECHO[12]	X						X		
Ophthalmic examination	X					X (only week 4)			
Concomitant medications	X					X		X	
Blood products and blood supportive care products	X					X		X	
Adverse events[13]		X							
Chemistry and Haematology[14]	X		X			X		X	
Coagulation	X		X						

Study Assessments[1]	Screen[2]	1 to 3 Days prior to surgery	Day prior to surgery	Day of surgery	Day 3 after surgery	Every 4 weeks after restart	Every 8 weeks after restart	Discontinuation	Survival
PET-CT/CT, disease assessment[15]	X	X					X	X	
MRI Brain[16]	X	X			X		X	X	
Biopsy extracranial metastasis(es) (Optional) [19]	X			X[19]				X[19]	
Removal of brain metastasis(es)				X					
Plasma collection for PK studies[17]				X					
CSF collection for PK studies (Optional)				X					
Photographic skin lesion assessment[18]	X						X	X	
Blood Sample for immunologic monitoring[20]	X					X	X		
Pharmacogenetics		X							

1. MRI = magnetic resonance imaging; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; ECHO = echocardiogram; PK = pharmacokinetic.
2. Screening procedures may be performed up to 14 days prior to first dose of study drug, except for ECG and echocardiogram, which may be performed up to 28 days prior to the first dose of study drug. Tumor biopsy may be performed up to 14 days prior to the first dose of the study drug. Testing results for BRAF V600E and V600K mutation via a CLIA-certified testing center at any time prior to enrolment is acceptable.
3. Only subjects who meet all inclusion and exclusion criteria will be eligible to enter into the study.
4. A negative serum pregnancy test will be required within the 14 days prior to the first dose of study treatment. Subsequent tests may be urine tests, and should be performed as clinically indicated.
5. Disease characteristics: Record date of diagnosis, primary tumor type, histology, stage, etc.
6. Record dose reductions, dose interruptions/delays and/or dose escalations. Subject treatment diary to be reviewed for dosing compliance.
7. Measurements should be in Metric scale. Height is only measured at screening.
8. Record body temperature, pulse rate, respirations.
9. Physical examination performed at visits listed.
10. Dermatologic exams should be performed by the Investigator, or may be referred to a dermatologist, at the discretion of the Investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow-up dermatologic assessments) to ensure consistency between evaluations.
11. ECG assessments must be performed within 28 days prior to starting treatment. Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary.
12. Echocardiogram assessments must be performed within 28 days prior to starting treatment, and then repeated at Week 8 and every 16 weeks thereafter.
13. Adverse events assessment should be continuous.
14. Chemistry and hematology evaluations are performed by the central laboratory.
15. PET-CT imaging will be performed on all subjects within 14 days of starting treatment. Imaging is repeated 1-3 days prior to surgery (optimally 1 day prior to surgery). After surgery, disease assessments will be performed by CT will be performed every 8 weeks.
16. Contrast-enhanced MRI will be performed on all subjects within 14 days of starting treatment. Imaging is repeated 1-3 days prior to surgery; day 3 after surgery and every 8 weeks thereafter.
17. A total of 4 PK samples will be obtained on the day of surgery. Two samples should be obtained prior to surgery and separated by at least 1 hr. Two samples should be obtained after surgery and separated by at least one hour. The date and time of PK samples and of the dose taken the evening before must be recorded.
18. Skin photography of new non-melanoma skin lesions or non-melanoma lesions that change during treatment must be obtained at each reassessment while the subject is on study medication.
19. Optional collection of extracranial tumor may be performed after the PET-CT scan and up to 1 day after the removal of brain metastasis(es), and at the time of disease progression
20. 1 genomic DNA Yellow/ACD tube at baseline; 3 x 10cc red top serum tubes and 10 x 10 cc heparin/green top tubes for peripheral blood mononuclear cell PBMC isolation at baseline, Week 4 and 8 post-craniotomy.

7.1. Critical Baseline Assessments

Subjects with histologically-confirmed metastatic melanoma (Stage IV) to the brain will be screened for eligibility within 28 days prior to the first dosing day.

Testing for BRAF V600E and V600K mutations may be performed at each participating site using a certified clinical test. Prior CLIA-certified testing result for the presence of a BRAF V600E or V600K mutation in a tumor sample from the subject will be acceptable for screening.

Cardiovascular medical history/risk factors will be assessed at baseline.

The assessments of brain and (optional) extracranial metastases conducted at baseline and during the study are described in Section 7.1.1.

The safety assessments conducted at baseline and during the study are described in Section 7.3.

The pharmacokinetic assessments are described in Section 7.3.11.

The pharmacodynamic assessments are described in Section 7.5.

Exploratory research assessments are described in Section 7.7.

7.1.1. Baseline Assessment of Target and Non-target Lesions

All baseline lesion assessments must be performed within 14 days of the first dose of study treatment.

All brain metastases that are planned for surgical resection and are ≥ 1.0 cm should be defined as target lesions, with their size by MRI.

All other intracranial lesions should be identified as non-target and should also be recorded at baseline. Measurements of non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

For subjects with extracranial metastases, up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeat measurements (either by imaging techniques or clinically). Extracranial lesions that are identified for optional biopsy after treatment should be identified as target lesions if the lesion is assessable for response.

Lymph nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed. Pathological lymph nodes with <15 mm and but ≥10 mm short axis are considered non measurable. Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions. However lymph nodes should not be selected as target lesions when other suitable target lesions are available.

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions. Lytic bone lesions or mixed lytic-blastic lesions will not be considered for response by PET-CT.

All other lesions (or sites of disease, excluding the brain) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.2. Efficacy

7.2.1. Efficacy Endpoints

Efficacy is a secondary objective for this trial. Efficacy endpoints include:

- Overall Survival: defined as the time from first dose of study treatment until death due to any cause.
- Overall Extracranial Response Rate: defined as the percentage of subjects with CR or PR at anytime as per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [Eisenhauer, 2009].
- Change from baseline to pre-surgery in the sum of longest diameters of intracranial target lesions.
- Maximum change from baseline in the sum of longest diameters of unresected intracranial target lesions.

7.2.2. Efficacy Assessment

Disease progression and response will be determined according to the definitions established in modified RECIST 1.1 guidelines.

See the Time and Events Table (Table 19) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and will not be affected by dose interruptions/delays. For post-baseline assessments, a window of ± 7 days is permitted to allow for flexible scheduling.

7.2.3. Assessment of Treatment Response in Intracranial and Extracranial Metastases

For this study, treatment responses will be assessed in both the brain and extracranial metastases when feasible and will be considered separately. PET-CT imaging will be performed within 14 days before the start of treatment, and 1 to 3 days prior to resection of brain metastasis(es). Changes in tumor size of the intracranial target lesions will be assessed by MRI of the brain and changes in SUVmax in total-body PET-CT imaging; changes in changes in SUVmax of extracranial target lesions will be assessed by total-body PET-CT.

Given the planned surgical intervention for brain metastases after 7-14 days of treatment, response may be evaluated in extracranial lesions.

7.2.4. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the eCRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required [Eisenhauer, 2009].

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are

clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

7.2.5. Guidelines for Evaluation of Disease

7.2.5.1. Measurable and Non-measurable Definitions

Measurable lesion:

A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable-only disease: The presence of only non-measurable lesions. **Note: non-measurable only disease is not allowed per protocol.**

7.2.6. Response Criteria

7.2.6.1. Evaluation of extracranial target lesions

Definitions for assessment of response for extracranial target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% 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).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): any target lesions at baseline.
- Not Evaluable (NE): cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions, the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are <u>not</u> assessed, sum of the diameters <u>cannot</u> be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status

then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

7.2.6.2. Evaluation of intracranial or extracranial non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): any non-target lesions at baseline.
- Not Evaluable (NE): cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

7.2.6.3. New intracranial and/or extracranial lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

7.2.6.4. Evaluation of overall extracranial response

Table 20 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable extracranial disease at baseline.

Table 20 Evaluation of Overall Extracranial Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigator's assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 56 days.
- If the minimum time for SD is not met, best extracranial response will depend on subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

7.3. Safety

The safety endpoint of this study is the evaluation of safety assessments during treatment with dabrafenib or the combination of dabrafenib with trametinib, as measured by the nature and frequency of adverse events, laboratory abnormalities, vital signs, echocardiograms, 12-lead electrocardiograms (ECG), and clinical monitoring /observation.

7.3.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that a lead to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

7.3.1.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Protocol-Specific SAEs:

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

- NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury
- Protocol-specific SAEs:
  - SCC,
  - Pyrexia accompanied by ≥ Grade 3 hypotension, or hypotension that is clinically significant in the judgment of the investigator, or dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE ;
  - CSR and RVO
- Additionally, new primary cancers (excluding basal cell carcinoma) and laboratory abnormalities as referenced in Section 7.3.1.3 are considered to be serious events by virtue of being medically important. These should be reported in the same manner as other serious adverse events. Please refer to Section 5.7.4.3.

7.3.1.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

7.3.1.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

7.3.1.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.3.1.6.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any adverse event that they believe possibly related to study treatment.

7.3.1.6. Prompt Reporting of SAEs and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities Phase II:				
ALT≥3xULN and bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and bilirubin <2xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

1. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. Liver Event Documents (i.e., "Liver Event CRF" and/or "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible
3. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Please refer to the liver chemistry stopping rules and follow-up criteria in Section 5.7.6 for additional details.

Methods for detecting, recording, evaluating, and following up on AEs and SAEs and procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs and SAEs are provided in the SPM.

7.3.1.7. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy Testing, Prevention and Reporting

7.3.2.1. Pregnancy Test and Prevention

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum β-hCG pregnancy test performed within 14 days prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 4 weeks following the last dose of study treatment.

GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 4 weeks after the last dose of study treatment.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

Hormonal-based methods (e.g., oral contraceptives) are not permitted due to potential drug-drug interactions with dabrafenib.

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

7.3.2.2. Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

7.3.3. Laboratory Assessments

Laboratory assessments must be conducted in accordance with the Time and Events Table (Table 19).

Table 21 Laboratory Assessments

Hematology	**Standard Chemistry**[1]
Hemoglobin	Sodium
Hematocrit	Potassium
Red blood cell count	Calcium
Platelets	Glucose
White blood cell count with differential	Blood Urea Nitrogen or Urea
Total neutrophils	Creatinine[2]
Lymphocytes	AST
Monocytes	ALT
Eosinophils	Alkaline phosphatase
Basophils	Total bilirubin
	Lactate dehydrogenase
Coagulation	Magnesium
PT	Phosphate
PTT	
INR	
Serum Pregnancy[3]	
serum β-hCG (human chorionic gonadotrophin)	

1. Chemistry evaluation of bicarbonate, chloride, and uric acid are not required where there are logistical constraints
2. If serum creatinine is >1.5 mg/dL, calculate creatinine clearance using standard Cockcroft and Gault method (Appendix 2).
3. Refer to Section 7.3.2 for further details on serum pregnancy testing.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator. A subject with a laboratory value outside the reference range(s) may be included only if the investigator and GSK Medical Monitor agree that it is unlikely to introduce additional risk factors and will not interfere with study procedures. However, subjects with laboratory values outside eligibility criteria in Section 4.1 should be excluded.

All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.3.4. Physical Examinations

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. Height and weight will also be measured and recorded. A complete physical exam including a thorough genitourinary examination for female subjects, inspection of the head and neck region, and digital rectal examination for both male and female subjects must be performed at Screening, and Month 12 or at discontinuation if discontinuation occurs prior to Month 12. If the subject has had a genitourinary and rectal exam within 6 months of screening, these assessments do not need to be repeated at screening. Physical examinations will be obtained at each time point as noted in the Time and Events Table (Table 19).

7.3.5. Neurological Examinations

Neurological exams should be performed by the Investigator as per the Time and Events Table (Table 19). Alternatively, subjects may be referred to a neurologist or neurosurgeon, at the discretion of the investigator.

A thorough neurological assessment is required at baseline focusing on:

- mental status
- cranial nerves
- motor system
- sensory system
- the deep tendon reflexes
- coordination and the cerebellum
- gait

During study conduct, an orientating neurological assessment should be conducted at the timepoints indicated in the Time and Events Table (Table 19) in order to detect potential early neurological symptoms, such as:

- Headache
- Nausea and/or vomiting
- Vertigo and/or dizziness
- Restlessness and/or irritability
- Fatigue or sleeplessness
- Hearing loss
- Muscle weakness
- Balance problems
- Speech problems
- Others

7.3.6. Dermatologic Examinations

A full skin assessment must be performed at baseline and at various timepoints throughout the study, as noted in the Time and Events Table (Table 19). Dermatologic exams should be performed by the investigator or may be referred to a dermatologist, at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e., if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.

7.3.7. Vital Signs

Vital sign measurements will include temperature, respiratory rate, systolic and diastolic blood pressure, and pulse rate, and will be obtained at each time point as noted in the Time and Events Table (Table 19).

7.3.8. Performance Status

Eastern Cooperative Oncology Group performance status should be assessed per the Time and Event Table (Table 19).

7.3.9. Electrocardiogram (ECG)

12-lead ECGs will be obtained at screening as noted in the Time and Events Table (Table 19) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after at least a five-minute rest with the subject in a semi-recumbent or supine position.

7.3.10. Echocardiograms

ECHO should include an evaluation for LVEF and both right- and left-sided valvular lesions. ECHO will be performed at the time points specified in the Time and Events Table (Table 19).

Additional ECHO assessments may be performed if clinically warranted.

7.3.11. Ophthalmic Examination

At certain time points in the trial and if visual changes develop, an eye exam is indicated. (Refer to Section 5.7.5.4 for visual changes stopping criteria). The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

7.4. Pharmacokinetics

7.4.1. Pharmacokinetic Endpoints

- Brain tumors (All subjects): The concentrations and tumor tissue distribution of dabrafenib and its metabolites, including hydroxy-, carboxy, and desmethyl-dabrafenib, in samples of the resected brain metastases will be determined in all subjects. Concentration of trametinib will also be determined in Cohort B.
- Plasma (All subjects): The concentrations of dabrafenib, its metabolites, including hydroxy-, carboxy, and desmethyl-dabrafenib, and trametinib in plasma samples collected on the day of the brain tumor resection will be determined. Levels in 2 plasma samples collected before surgery and 2 samples collected after surgery will be determined to allow accurate estimate of the pharmacokinetics at the time of the tumor resection.
- Extracranial metastases (if available): The concentrations and tumor tissue distribution of dabrafenib, its metabolites, including hydroxy-, carboxy, and desmethyl-dabrafenib, and trametinib (as appropriate in Cohort B) in samples of extracranial metastases collected on the same day as the brain tumor resection will be determined.
- Cerebrospinal fluid (CSF) (in subjects who agree to optional collection of CSF): The concentrations of dabrafenib, its metabolites, including hydroxy-, carboxy, and desmethyl-dabrafenib, and trametinib (as appropriate in Cohort B), in the CSF of subjects who give consent for optional collection of this fluid at the time of brain tumor resection will be determined.

7.4.2. Brain Tumor Sample Collection for Pharmacokinetics

Tissue for pharmacokinetic analysis will be isolated from the remaining portion of the resected melanoma brain metastasis(es) that in the clinical judgment of the neurosurgeon is not required to be submitted for pathologic confirmation of CNS melanoma metastases. 100 mg to 1 gm of the remaining tissue will be snap-frozen for pharmacokinetic analysis. If the tumor is bloody, the tissue will be blotted on gauze to dry prior to snap freezing in liquid nitrogen. A second portion (up to 500 mg) of the tumor will be inserted into a tissue cassette, and embedded in Optimum Cutting Temperature (OCT) solution, and frozen. A third portion of tumor tissue (up to 100 mg) will be fixed in formalin for paraffin embedding (FFPE). Additional tumor tissue may be used to establish an immortalized cell line and/or snap-frozen. The remaining portion from the adjacent "normal" CNS tissue that has been confirmed by the neuropathologist using frozen sections OR the overlying normal CNS tissue that is required to be resected by the neurosurgeon in order to gain access to the underlying CNS melanoma metastasis will be processed in a similar fashion. The time the tumor was resected will be recorded to facilitate the comparative pharmacokinetic analyses. Concentrations of dabrafenib, its metabolites, hydroxy-, carboxy, and desmethyl-dabrafenib, and trametinib (as appropriate) and possibly other drug-related species will be quantified in the PK tissue sample by an investigative LC-MS/MS method. The spatial distribution of dabrafenib, its metabolites, hydroxy-, carboxy, and desmethyl-dabrafenib, and trametinib (as appropriate in Cohort B), and possibly other drug-related species in the tissue samples will be determined using an investigative matrix assisted laser desorption ionization (MALDI) analysis method.

7.4.3. CSF Collection for Pharmacokinetics

Collection of CSF will be an optional procedure; subjects must provide consent for this procedure. CSF will be collected either right before cutting the dura, on condition that there is no evidence of intracranial hypertension, or using the lumbar puncture approach (following completion of craniotomy and repositioning the subject while under general anesthesia during the same operation OR postoperatively), or accessing the Ommaya reservoir, if present. Three ml of CSF will be processed for pharmacokinetic analysis and quantified using an investigative LC-MS/MS method. The time of CSF collection will be recorded for the comparative pharmacokinetic analyses.

7.4.4. Extracranial Tumor Sample Collection for Pharmacokinetics

Optional sampling of readily accessible extracranial metastases will be performed on the day of the removal of the brain metastasis (es), or up to one day before or after the craniotomy if necessary for scheduling. Sampling will consist of an excisional biopsy, core needle biopsy, or a 6 mm punch biopsy. 100 mg to 1 gm of the biopsy material of the extracranial metastasis (es) will be snap-frozen for pharmacokinetic analysis and quantified using an investigative LC-MS/MS method. If the tumor is bloody, the tissue will be blotted on gauze to dry prior to snap freezing in liquid nitrogen. A second portion of the tumor (up to 500 mg) will be inserted into a tissue cassette, embedded in OCT solution, and frozen. A third portion of the tumor (up to 100 mg) will be fixed in formalin for paraffin embedding (FFPE). Additional tumor tissue may be used to establish an immortalized cell line and/or snap-frozen. The remaining portion of any

adjacent "normal" tissue that has been confirmed by the pathologist using frozen sections or the underlying normal tissue that is required to be resected in order to gain access to the underlying metastasis will be processed in a similar fashion. The time of tumor collection will be recorded for comparative pharmacokinetic analyses.

7.4.5. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic analysis of dabrafenib and its active metabolites, including hydroxy-, carboxy-, and desmethyl-dabrafenib and trametinib (as appropriate), will be collected on the day of surgical resection of the brain metastasis(es). Two samples will be collected prior to surgery; two samples will be collected after surgery. Each sample must be collected at least one hour after the prior sample. The collection time of each blood sample collection will be recorded. The time of the last dose of study treatment will also be recorded. Upon collection blood will be placed on wet ice. Plasma will be isolated within 60 minutes of collection and frozen at -20°C

The timing of pharmacokinetic samples may be altered and/or pharmacokinetic samples may be obtained at additional time points to ensure thorough pharmacokinetic monitoring. No more than 160 mL of blood will be collected over the duration of the study for pharmacokinetic blood sample collection, including any extra assessments that may be required.

7.4.6. Pharmacokinetic Sample Analysis

Plasma sample analysis will be performed under the management of Bioanalytical Science and Toxicokinetics and tissue sample analysis, under Biotransformation and Drug Disposition, Drug Metabolism and Pharmacokinetics, Platform Technology and Science, GlaxoSmithKline. Concentrations of dabrafenib, its metabolites, hydroxy-, carboxy, and desmethyl-dabrafenib, and trametinib (as appropriate) will be determined in plasma samples using the most current approved and validated analytical methodology, and their presence will be determined in tissue and CSF samples using investigative assay methodology. Plasma raw data will be stored in the Good Laboratory Practices (GLP) Archives, GlaxoSmithKline.

7.4.7. Meals and Dietary Restrictions

Either dabrafenib monotherapy or dabrafenib combined with trametinib should be administered under fasting conditions, either one hour prior to or at least two hours after a meal. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.

7.5. Pharmacodynamics

Dabrafenib inhibits the BRAF kinase, which is a component of the RAS-RAF-MEK-ERK signalling pathway. Activation of the pathway may be determined by measuring the expression of phosphorylated (activated) proteins in the pathway, including phospho (p)-MEK and p-ERK.

7.5.1. Pharmacodynamic Analysis of Brain Metastases

After sufficient tissue is collected for necessary pathological analysis and pharmacokinetic analysis, up to 500 mg of tumor tissue, optimally with adjacent normal brain tissue, will be formalin-fixed, paraffin-embedded (FFPE). Tissue will undergo immunohistochemical (IHC) analysis for the expression of p-MEK and p-ERK.

OCT-embedded tissue will be used to prepare a hematoxylin and eosin (H&E) slide for review. The tissue will undergo H&E-guided macrodissection to isolate specimens enriched for ≥ 80% viable tumor cell content. The tissue will be processed for reverse phase protein array analysis (RPPA) as previously described [Davies, 2009]. The quantitative ratio of p-MEK: Total MEK and p-ERK:Total ERK will be determined using the results of the RPPA analysis.

7.5.2. Pharmacodynamic Analysis of Extracranial Metastases

Optional sampling of easily accessible extracranial metastases will be performed (1) prior to starting treatment with dabrafenib alone or in combination with trametinib, and (2) on the day of the craniotomy, or up to one day prior or one day after the craniotomy procedure if needed for scheduling. The pre-treatment tumor sampling may include a 6 mm punch biopsy, core needle biopsy, or an excisional biopsy. For the pre-treatment sample, excisional biopsy may only be performed if another easily accessible lesion can be identified for sampling on the day of the craniotomy. Approximately two-thirds of the pre-treatment tumor tissue will be inserted into a tissue cassette and embedded in OCT solution; the remaining tissue will be processed by FFPE. Collection of the extracranial metastasis on the day of craniotomy is described in Section 7.4.4. After sufficient tissue is collected for pharmacokinetic analysis (Section 7.4.6), approximately two-thirds of the tissue will be inserted into a tissue cassette and embedded in OCT solution; the remaining tissue will be processed for FFPE. Tissue will undergo IHC analysis for the expression of p-MEK and p-ERK. IHC staining and quantitation will be performed under the management of GlaxoSmithKline.

OCT-embedded tissue will be used to prepare an H&E slide for review. The tissue will undergo H&E-guided macrodissection to isolate specimens enriched for ≥ 80% viable tumor cell content. The tissue will be processed for RPPA, as previously described [Davies, 2009]. The quantitative ratio of p-MEK: Total MEK and p-ERK:Total ERK will be determined using the results of the RPPA analysis.

7.6. Pharmacogenetics

Information regarding pharmacogenetic (PGx) research is included in Appendix 1: Pharmacogenetic Research.

7.7. Translational Research

7.7.1. Prevalence of BRAF and Other Mutations in Brain Metastases and Extracranial Metastases

A requirement for inclusion into the study is the presence of a BRAF mutation (V600-E or –K) in tumor tissue of subjects being screened. For each subject, DNA will be extracted from (1) FFPE slides of the resected brain metastasis(es), and if available (2) FFPE slides from extracranial metastases. All samples will be dissected to isolate DNA from isolates consisting of ≥ 90% tumor cells. The prevalence of the known BRAF mutation in DNA from both tumors will be determined by mass-spectroscopy-based genotyping using the Sequenom platform [Davies, 2009; Davies, 2008], or by next generation sequencing (NGS) approach if the amount of DNA isolated is feasible for this analysis. When feasible the mutational analysis will also analyze other gene, including but not limited to *Nras, Kras, Mek1/2, Akt1/2/3, Pik3ca, c-Kit,* and *Egfr* DNA samples may also be analyzed for other mutations implicated in responsiveness to BRAF inhibitors or melanoma pathogenesis by subsequent investigations. DNA from frozen samples, or from FFPE samples if feasible, may also be analyzed using whole-genome and/or whole-exome sequencing, depending on the results of other molecular analyses. Please refer to the SPM for additional details on translational research.

7.7.2. Tumor Biomarker Analysis

RPPA analysis will be performed using OCT-embedded tissue from brain and available extracranial metastases. In addition to MEK and ERK, analysis will be performed for the expression of ~150 validated protein markers (http://www.mdanderson.org/education-and-research/resources-for-professionals/scientific-resources/core-facilities-and-services/functional-proteomics-rppa-core/index.html). This will include analysis of the PI3K-AKT pathway, which has been implicated both in melanoma brain metastasis and in resistance to BRAF inhibitors, as well as other critical regulators of melanoma growth and survival [Villanueva, 2009; Davies, 2009].

FFPE tissue may undergo IHC analysis of additional markers, including Ki67 and P27, or other markers that are identified in ongoing or future studies.

Tissue samples collected during the conduct of the study may also undergo analysis for patterns of mRNA and miRNA expression, and, when feasible, for DNA methylation and copy number variation.

Cells may be isolated from fresh melanoma biopsies for the establishment of immortal cell lines and/or xenografts. These cells will be used to examine mechanisms of drug action and resistance efficiently. Patients will be required to sign a separate consent for this analysis.

Optional tumor biopsies collected at progression will also allow for further analysis of changes in biomarkers to facilitate understanding of mechanisms of treatment resistance.

Details on the analytical methods and biomarkers under study can be found in the SPM.

7.7.3. Immunologic Monitoring

For screening potential serum biomarkers, 3 x 10cc red top serum tubes at each time point will be drawn, enabling multiple marker screens at each time point (Baseline, Week 4 post-surgery, and Week 8 post-surgery). These may include circulating cytokines, chemokines and growth factors, C-reactive protein, and testing LDH and autoimmune antibodies (if not performed directly in clinical labs).

For assessment of anti-tumor immunity and immune suppression, up to 10 x 10cc heparin/green top tubes for isolation of PBMC will be drawn. PBMC assays may include immune suppressive Treg and myeloid-derived suppressor cell frequency assessment (to determine if elevated frequencies negatively impact outcomes), testing of melanoma antigen-specific immunity (for example, CD8+ and CD4+ T cell responses to MART-1, NY-ESO-1, gp100) and other potential immune responses. Absolute counts and percentages of lymphocyte and myeloid subsets may be performed.

For assessment of RNA and mRNA, up to six cc of blood will be collected in PAXgene tubes.

A genomic DNA Yellow/ACD tube will be drawn to assure quality of the DNA.

Plasma will be isolated from the green top tubes before PBMC purification, which will allow for miRNA studies.

To allow for centralized processing, banking and testing of these blood samples, the UPCI Immunologic Monitoring Laboratory will serve as a central lab.

Blood collected into the appropriate tubes should be sealed, wrapped and placed in the specimen shipper kit and shipped on the same day they are drawn by Federal Express overnight courier using the air bill provided in the kit. The green top tubes should be shipped at ambient temperature (no wet or dry ice). The red, yellow, and PAXgene RNA tubes should be refrigerated immediately and shipped at 2-8C. Shipments must be timed to arrive during normal working hours.

The laboratory will be open Monday through Friday to receive samples. Samples should not be shipped on Fridays, Saturdays, or the day before a legal holiday. Ship by overnight courier Monday-Thursday only to:

Immunologic Monitoring and Cellular Products Laboratory
University of Pittsburgh Cancer Institute
UPCI-IMCPL, Suite L 1.26
Study Coordinator
Hillman Cancer Center
5117 Centre Avenue
Pittsburgh, PA 15213
Tel: PPD
Fax: PPD

7.7.4. T-Cell Receptor Sequencing

Immune profiling can provide a precise characterization of the complete immune repertoire in each of the tissues being collected for this study, including brain tissue, CSF, and blood. Immune profiling may also contribute meaningful data to help construct combination or sequential therapy for BRAF inhibitors, given the frequent development of resistance.

Approximately 2 micrograms of extracted DNA, a 25 micron slice from an FFPE block, or a frozen punch biopsy (depending on available volume of tumor tissue) will be utilized for the immunoSEQ assay (Adaptive Biotechnologies, Seattle, WA, USA). This assay employs a novel method that amplifies rearranged T-Cell Receptor 3 sequences and exploits the capacity of high-throughput sequencing technology to sequence tens of thousands of TCR CDR3 chains simultaneously. Approximately 80% of the sample collected will be used for this assay; the remaining tissue will be used for tumor infiltrating lymphocyte analysis (Section 7.7.5).

Samples will be collected as per extracranial metastases biopsy schedule as described in Table 19.

7.7.5. Tumor Infiltrating Lymphocyte Analysis

Tumors contain variable numbers of lymphocytes, referred to as tumor infiltrating lymphocytes (TILs). In melanoma, the intensity of this lymphocytic infiltrate is believed to correlate with outcome though there is some debate about the applicability of this finding for all melanomas present in the tissue samples from these patients. Therefore, considerable research is needed to better elucidate the function and prognostic significance of TILs in both untreated melanoma and tumors treated with biological therapy [Oble, 2009].

QuanTILfy (Adaptive Biotechnologies, Seattle, WA, USA) is an assay utilized to measure the quantity and clonality of TILs. This platform uses a new technology, droplet digital PCR, to directly measure Tumor Infiltrating Lymphocytes (TILs). Remaining material from the immunoSEQ assay (FFPE or frozen tissue biopsy, Section 7.7.4) will be used for this assay.

Samples will be collected as per extracranial metastases biopsy schedule as described in Table 19.

7.8. Days 1-3 Post-Craniotomy

Subjects will undergo follow-up imaging as part of routine surgical follow-up within 72 hours of craniotomy. Subjects in either cohort for whom continued treatment is considered appropriate by their treating investigator will be permitted to continue on the combination of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily after no less than 72 hours have passed.

7.9. Post-Craniotomy Safety Assessments

For subjects continuing on study treatment after the craniotomy procedure, the following safety assessments must be performed 4 weeks after the procedure and every 4 weeks thereafter (±7 days):

- Complete physical examination (including weight, ECOG PS)
- Vital signs (blood pressure, pulse rate, and temperature)
- Clinical laboratory tests: hematology and clinical chemistry
- Dermatological examination
- Neurologic examination
- Treatment dispensing and treatment compliance

Echocardiograms will be performed at Week 8 and every 16 weeks thereafter.

7.10. Post-Craniotomy Disease Assessments

Subjects continuing on study treatment after the craniotomy procedure must have radiologic disease assessments performed 8 weeks after the procedure and every 8 weeks thereafter (±14 days).

7.11. Discontinuation Visit

If a subject does not resume treatment after surgery, or discontinues study treatment after surgery at a time other than a regularly-scheduled follow-up visit as described in Section 7.10, the following assessments will be performed within 28 days of the last dose of study treatment and prior to initiation of other anti-cancer therapy:

- Brief physical examination (including weight, ECOG PS)
- Vital signs (blood pressure, pulse rate, and temperature)
- Clinical laboratory tests: hematology and clinical chemistry
- Dermatological examination
- Neurologic examination
- Radiologic assessment of disease

7.12. Survival Follow-up Visits

If a subject discontinues study treatment and begins new anti-cancer therapy, investigators will report on the survival status of the subject every 8 weeks.

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system. Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to

ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Study Design Considerations

9.1.1. Sample Size Assumptions

For the objective of estimating the levels of dabrafenib its metabolites, and trametinib in brain metastases, the average level for the parent drug and each metabolite along with the range and 95% confidence interval for the brain metastases, extracranial metastases, and plasma will be reported. A sample size of 15 patients per cohort was chosen to characterize concentrations with reasonable precision (within 0.7 standard deviation) within each cohort. The correlation and corresponding 95% confidence interval between concentrations in the brain metastases and concentrations in the plasma, and in the optional extracranial metastases and CSF, for the parent drug and each metabolite will also be estimated. Additionally, the ratio between the concentrations in the brain metastases and in the extracranial metastases and the plasma concentrations within each subject for each metabolite will be estimated and summarized with 95% CI's.

9.1.2. Sample Size Re-estimation

No formal sample size re-estimation is planned.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

All subjects who receive at least one dose of study treatment will be evaluable for both efficacy and safety and will comprise the All Treated Subjects (ATS) population.

9.2.2. Analysis Data Sets

The primary datasets for the planned pharmacokinetic, pharmacodynamic, exploratory translational, and early response analyses will include subjects in the ATS population who complete the planned surgical resection of their brain metastasis(es), and biopsies of extra-cranial metastases.

The datasets for assessing overall survival, extracranial response, maximum change from baseline in unresected intracranial lesions, and all safety endpoints will include efficacy and safety data collected on subjects in the ATS population.

9.2.3. Interim Review

There is no stopping rule to allow for early termination for lack of efficacy. An interim review will take place after 5 subjects in each of Cohorts A and B have undergone a craniotomy and have completed one follow-up post-craniotomy assessment. This review will allow for evaluation of modifiable treatment logistics and the ability to complete the primary objective of the study. This interim review will include an assessment of the quality of the tissue samples from the resected brain and optional extracranial metastases for the planned pharmacokinetic and pharmacodynamic analyses. In addition, a sample quality review will take place where the results of the pharmacokinetic analysis of dabrafenib and its metabolites for the first 3 subjects will be reviewed. Adjustments may be made to the duration of the treatment before surgery, and/or the timing of the last dose of dabrafenib that is administered prior to surgery, based on the review of the results by the participating investigators. Subject safety and any unexpected toxicities will also be reviewed. Accrual will continue during this formal review. Similar analyses will be performed after the last subject in Cohort A completes one post-craniotomy assessment, or withdraws from the study, whichever comes first.

9.2.4. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that summaries of data by center would be unlikely to be informative, data from participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis.

The length of treatment for each subject will depend on the efficacy and toxicity of the treatment, so the duration of treatment and follow-up will vary among subjects. All available overall survival data will be analyzed using appropriate statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing data. Consequently there will be no imputation of overall survival data.

Demographic and baseline characteristics will be summarized according to current GSK standards.

For the analysis of overall survival, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored.

9.2.4.1. Primary Analysis

9.2.4.1.1. Pharmacokinetics

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GlaxoSmithKline. Levels of dabrafenib, its metabolites, and trametinib (Cohort B only) will be summarized for each tissue (brain metastases, optional assessment of extracranial metastases, and mandatory assessment of plasma for all subjects. Concentrations in plasma will be summarized by nominal times and the average concentrations calculated and summarized. Both absolute concentrations and ratios relative to plasma will be determined for the different sample types. Total and free concentrations may be reported. If necessary, the plasma concentration at time of the surgery or collection may be interpolated.

9.2.4.2. Secondary Analyses

9.2.4.2.1. Pharmacokinetics in CSF

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GlaxoSmithKline. Levels of dabrafenib, its metabolites, and trametinib (Cohort B only) will be summarized for CSF for subjects with available samples. Concentrations in plasma will be summarized by nominal times and the average concentrations calculated and summarized. Both absolute concentrations and ratios relative to plasma will be determined for the different sample types. Total and free concentrations may be reported. If necessary, the plasma concentration at time of the surgery or collection may be interpolated.

9.2.4.2.2. Pharmacodynamics

The percent change in p-MEK, p-MEK:Total MEK ratio, p-ERK, and p-ERK:Total ERK ratios will be determined for the paired assessment of optional extracranial metastases obtained before and after treatment. The absolute levels and ratios of p- and total-MEK and –ERK will also be compared to the brain metastasis tissue for those subjects. Paired t-tests will be used to determine the significance of differences between samples.

Absolute levels and ratios of expression of the same markers will be determined in the assessment of optional extracranial metastases, and will be compared to the results observed in the post-treatment extracranial metastases. In addition, results will be compared to a retrospective collection of BRAF V600-mutation-positive brain metastases that were collected independently from this study [Davies, 2009].

9.2.4.2.3. Mutational Analysis

Paired *t*-tests will be used to determine if there is a significant difference in the relative prevalence of the BRAF V600 mutation in the brain and optional extracranial metastases. In addition, the presence of activating mutations in other genes (i.e. *Nras, Kras, Akt1/2/3,*

Pik3ca, c-Kit, Egfr) will be compared. If indicated, samples may also be compared using whole-genome and/or whole-exome sequencing.

If there are significant differences noted, the correlation with pharmacodynamic results (Section 9.2.4.2.2) will be assessed.

9.2.4.2.4. Exploratory Biomarkers (others)

The percent change of additional protein markers, as determined by IHC and/or RPPA will be determined for the paired pre-treatment and post-treatment extracranial metastases. The absolute levels and ratios of phospho-total-proteins will be determined. The pre- and post-treatment levels will be compared to the brain metastasis tissue for those subjects. Paired t-tests will be used to determine the significance of differences between samples.

In addition, results will be compared to a retrospective collection of BRAF V600-mutation-positive brain metastases that were collected independently from this study [Davies, 2009].

9.2.4.2.5. Change from Baseline to Pre-Surgery in Intracranial Target Lesions

The change from baseline to the pre-surgery intracranial disease assessment in the sum of the longest diameters (SLD) of intracranial target lesions will be calculated as a percentage change from the baseline SLD. It will be reported for the V600E and V600K analysis populations for each cohort and also aggregately if appropriate.

9.2.4.2.6. Maximum Change from Baseline in Unresected Intracranial Target Lesions

The maximum change from baseline in the sum of the longest diameters (SLD) of unresected intracranial target lesions will be calculated as a percentage change from the baseline SLD. It will be reported for the V600E and V600K analysis populations for each cohort and also aggregately if appropriate.

9.2.4.2.7. Overall Response in Extracranial Lesion(s)

The overall extracranial response rate in unresected lesions is defined as the percentage of subjects with a confirmed overall CR or PR by investigator assessment using modified RECIST 1.1 guidelines. Subjects who have an overall extracranial response of NE (not evaluable) or a missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage. A two-sided 95% confidence interval will be reported along with the point estimate. The ORR will be reported for the V600E and V600K analysis populations for each cohort and also aggregately if appropriate.

9.2.4.2.8. Duration of Response

The duration of extracranial response will be summarized descriptively using Kaplan-Meier quartiles, along with two-sided 95% confidence intervals, for the V600E and V600K analysis populations for each cohort and also aggregately if appropriate. Only the subset of subjects who show a complete or partial tumor response will be included in this analysis. If a subject receives subsequent anti-cancer therapy prior to the date of documented progression or death (other than planned craniotomy), duration of extracranial response will be censored at the last adequate assessment (that is, the last assessment in which the visit level response is CR, PR, or SD) prior to the initiation of that anti-cancer therapy. Otherwise, if the subject does not have a documented date of progression or death, the duration of extracranial response will be censored at the date of the last adequate assessment.

9.2.4.2.9. Overall Survival

Overall survival (OS), defined as the time from first dose of study treatment to death for any reason, will be summarized using Kaplan-Meier quartile estimates along with two-sided 95% confidence intervals. OS will be censored using the date of last known contact for those who are alive at the time of analysis.

9.2.4.3. Safety Analyses

The ATS population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP. Safety assessments that will be summarized are described in Section 7.3.

9.2.4.3.1. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy.

9.2.4.3.2. Adverse Events

Adverse events (AEs) will be coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to NCI-CTCAE (version 4.0).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation of study treatment.

If the AE is listed in the NCI CTCAE Version 4.0 table, the maximum grade will be summarized.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of AEs of special interest will be summarized separately. Please refer to Section 7.3.1 for additional details.

The incidence of deaths and the primary cause of death will be summarized.

9.2.4.3.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade. The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

9.2.4.3.4. Other Safety Measures

The results of scheduled safety assessments (e.g., body weight, vital signs, 12-lead ECG, echocardiogram, and ECOG performance status) will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). All data will be listed. Further details will be provided in the RAP.

9.2.4.4. Pharmacogenetic Analyses

Further details on PGx analyses are described in Appendix 1: Pharmacogenetic Research

10. STUDY CONDUCT CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1: Pharmacogenetic Research unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to

all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified

10.5. Study and Site Closure

The study will be considered complete when all evaluable subjects have completed the study as per Section 4.2.1.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

10.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

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APPENDICES

Appendix 1: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* 5701	Carriage of the HLA-B*5701 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*5701 screening and exclusion of HLA-B*5701 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*5701 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*5701 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	HLA-B*1502	Independent studies indicated that patients carrying HLA-B*1502 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis and that this marker is prevalent in some populations, particularly with Asian ancestry. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects, that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood/saliva samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to treatment.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to treatment. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject who is enrolled in the clinical study can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled

Study Assessments and Procedures

Blood samples can be taken for PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~10mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx sample is labeled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of study treatment has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to study treatment.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- The sample is retained for PGx research.
- Any PGx sample is destroyed.

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters, or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to treatment. The genes that may code for these proteins may also be studied.

Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) analysis plan or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood/saliva being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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Appendix 2: Cockcroft-Gault Formula

CL_{cr}(mL/min) =	Q x (140-age[yr]) x ideal body wt [kg]*
	72 x serum creatinine [mg/dL]
Q = 0.85 for females	
Q = 1.0 for males	
OR	
CLcr(mL/min) =	K x (140-age[yr]) x ideal body wt [kg]*
	Serum creatinine [umol/L]
K = 1.0 for females	
K = 1.23 for males	

*Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]
Ideal body weight

Males =	50.0 kg + (2.3 kg x each inch over 5 feet) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Females =	45.5 kg + (2.3 kg x each inch over 5 feet) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)
Example 1:	Male, actual body weight = 90.0 kg, height = 68 inches.
	Ideal body weight = 50.0 + (2.3) (68-60) = 68.4 kg.

This subject's actual body weight is > 30% over ideal body weight. Therefore, in this case, the subject's ideal body weight of 68.4 kg should be used in calculating estimated creatinine clearance.

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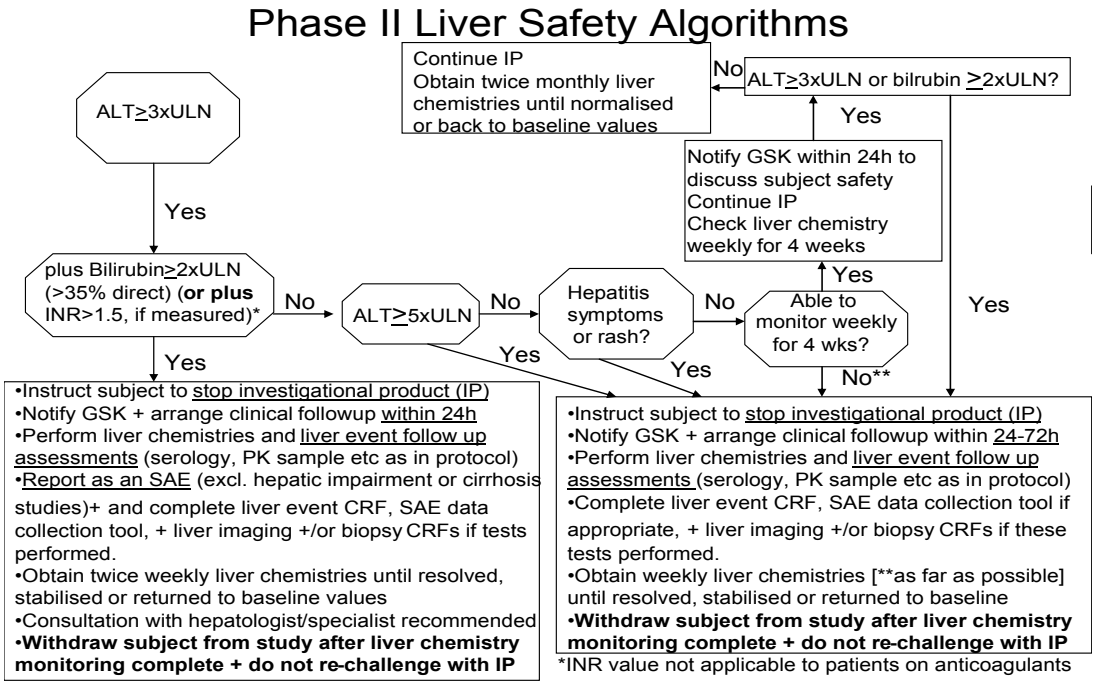
Appendix 3: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria



Appendix 4: Country Specific Requirements

No country-specific requirements exist.

Appendix 5: Collection of CSF

Cerebrospinal fluid may be collected as an optional procedure on the same day as the resection of the melanoma brain metastasis(es). Signed, informed consent must be obtained prior to the surgical procedure. At the time of surgery, up to 3 mL of CSF can be collected only if the neurosurgeon attests that there are not any signs of intracranial hypertension (e.g. bulging of brain tissue through the craniotomy site due to recent intratumoral hemorrhage). Any of the four ways described below can be followed to collect CSF

1. In select cases after the dura is opened, the neurosurgeon will determine if there is a sulcus that is large enough to permit puncture with a 25 gauge butterfly needle attached to a 1 mL tuberculin syringe such that CSF can be slowly withdrawn (see figure on the following page).
2. If the operative exposure permits the surgeon will access one the basal cisterns, in a similar manner as above, CSF will be withdrawn after puncture with a 25 gauge butterfly.
3. Depending on the craniotomy exposure, an image-guided trajectory to the lateral ventricles may be possible. In these cases, if there is no access using the above methods, the pia/arachnoid will be coagulated with bipolar cautery and image guidance will determine a trajectory to allow ventricular puncture with a ventricular catheter and CSF will be withdrawn. The trajectory may be through the cortical surface or after the resection, through the tumor cavity into the ventricle.

If the above methods are not possible, a lumbar puncture will be performed while still under general anesthesia following the completion of the craniotomy and resection of the CNS tumor. The patient will thus be placed in lateral position on the operating table and standard sterile technique for lumbar puncture will be done to withdraw up to 3 mL of CSF.

Appendix 6: Summary of Protocol Amendment Changes

AMENDMENT 2

Summary of Amendment Changes

Updated medical monitor and sponsor contact information; revised IND number to reflect submission to dabrafenib + trametinib IND; added ophthalmic examinations to be performed at the Screening Visit, Week 4 Visit, and as clinically indicated; updated dose modification guidelines for QTc prolongation; removed collection of alcohol information at baseline; updated guidelines for missed doses of trametinib

List of Specific Changes

Sponsor Information Page

Previous text

IND 105,032

Revised text

IND 113357

Rationale for Change

Inclusion of combination arm warranted submission to combination IND.

Section 5.1.3

Previous Text

If a subject misses a dose, the subject should not double the next regularly scheduled dose. However, the subject can take the missed dose immediately if the next scheduled dose is at least 6 hrs later. The subject should take the next dose at the usual time.

Revised text

If a subject misses a dose of dabrafenib, the subject should not double the next regularly scheduled dose. However, the subject can take the missed dose immediately if the next scheduled dose is at least 6 hrs later. The subject should take the next dose at the usual time.

If a subject misses a dose of trametinib, the subject should not double the next regularly scheduled dose. However, the subject can take the missed dose immediately if the next scheduled dose is at least 12 hrs later. The subject should take the next dose at the usual time.

Rationale for Change

Clarification and updates to recommendations for missed trametinib doses.

Section 5.7.3.3

Previous Text

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec, OR • uncorrected QT>600 msec, OR • QTcB>530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline • If event resolves, restart study treatment at current dose level[b] • If event does not resolve, permanently discontinue study treatment • If event recurs, permanently discontinue study treatment

1. Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and GSK medical monitor agree that the subject will benefit from further treatment.

Revised Text

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec, OR • uncorrected QT>600 msec, OR • QTcB>530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If <LLN correct with supplements to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level [b] • If event recurs, permanently discontinue study treatment

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and GSK medical monitor agree that the subject will benefit from further treatment.

Rationale for Change

Text has been revised across all protocols to reflect additional monitoring requirements.

Table 19

Previous Text

Alcohol consumption data were collected at baseline

Ophthalmic exams were not included in the table.

Revised Text

Alcohol consumption data are no longer being collected at baseline.

Ophthalmic exams are included as a required assessment during Screening and at Week 4.

Rationale for Change

Alcohol consumption data are not longer required for collection.

Ophthalmic exams were included per recent FDA guidance and subsequent revision of standard assessments.

Section 7.3.11

Previous Text

N/A; new section

Revised Text

Ophthalmic Examination

Subjects are required to have a standard ophthalmic examination performed by an ophthalmologist at baseline, at week 4, and as clinically warranted per guidance for visual changes (Section 5.8.5.4). The exam will include indirect fundoscopic examination, visual acuity (with correction), visual field examination, and tonometry with special attention to retinal abnormalities that are predisposing factors for RVO or CSR. Direct fundoscopy may be performed but is not required. In subjects with clinical suspicion of RVO or CSR, flourescein angiography and/or optical coherence tomography are highly recommended.

Rationale for Change

New section added per FDA recommendations.