NOVARTIS

Clinical Development

GSK2118436+GSK1120212

Protocol BRF117277 / NCT02039947

A Phase II, Open-Label, Multicentre Study of Dabrafenib plus Trametinib in Subjects with BRAF Mutation- Positive Melanoma that has Metastasized to the Brain

Authors	[redacted]
Document type	Amended Protocol Version (clean)
EUDRACT number	2013-003452-21
Version number	9.0
Development phase	Phase II
Document status	Final
Release date	21-JUN-2017
Novartis internal reference number	CDRB436B2204

Amendment 7

Amendment rationale

The main purpose of this protocol amendment, is to extend the study length, as the current protocol (amendment 5) mandates the study to close when 70% of all enrolled patients have died or are lost to follow up. (This has now been met and 9 patients are still on treatment.) The extension is required due to immaturity of cohort A data, the primary efficacy population, which is a result of slow recruitment in this cohort.

Protocol amendment 7 defines study close when 70% of all cohort A patients have died or been lost to follow up, or when all cohort A patients have been on study for three years, whichever is earlier. This will allow for adequate time for all cohort A patients to be followed up, as the last patient recruited has only be on study for 21 months.

It is expected that 70% of cohort A patients (a further 3 patients) will be complete within 3-6 months, as historic data shows completion rate at one patient per month. Thus, upon implementation of protocol amendment 6, the new LPLV for this study will be around October 2017.

In addition to the above change two note to files applicable to protocol amendments 4 and 5, and minor typographical errors have been updated.

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2013N168437_00	2013-OCT-04	Original
2013N168437_01	2014-APR-27	Amendment No. 1
2013N168437_02	2014-AUG-20	Amendment No. 2
2013N168437_03	2014-SEP-04	Amendment No. 2
2013N168437_04	2015-MAR-16	Amendment No. 3
2013N168437_05	2015-DEC-06	Amendment No. 4
2013N168437_06	2015-DEC-14	Amendment No. 4
2013N168437_07	2016-JUL-13	Amendment No. 5
2013N168437_08	16-MAY-2017	Amendment No. 6
2013N168437_09	21-JUN-2017	Amendment No. 7

1) Minor administrative changes and correction to typographical errors throughout the document.
2) Survival follow-up period has been extended in order to collect additional long-term overall survival data.
3) Addition of secondary objective of long-term (particularly 5-year) OS.
4) Additional information available: Dabrafenib, another small molecule BRAF- inhibitor received FDA-approval in May 2013 and EMA approval in August 2013.
5) Reference to abstaining to any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pommelos was removed.
6) Additional information available: In Jan 2014 the combination of dabrafenib and trametinib received FDA approval, and in February 2014 the combination received approval in Australia.
7) Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least (changed from 3 weeks) 1 month prior to first dose of study treatment.
8) Typographical correction of neurologist to neuroradiologist and the addition of appropriately qualified radiologist /neurosurgeon based upon country requirements.
9) Revised Definitions for Adequate Baseline Organ Function- Albumin removed, PT/INRa and PTT was updated from ≤ 1.5 x ULN to ≤ 1.3 x ULN to align with the updated asset standard language for the dabrafenib and trametinib combination.
10) Revised inclusion criteria for Women of childbearing potential to include having to use effective contraception 14 days prior to enrollment, and for 4 months after the last dose of study treatment.
11) Revised exclusion criteria:
    - Prior treatment with a BRAF inhibitor or a MEK inhibitor.
    - Known ocular or primary mucosal melanoma.
    - Prior systemic anti-cancer treatment.
    - History of malignancy with confirmed activating RAS mutation at any time.
    - A history or current evidence of retinal vein occlusion (RVO).
12) Removal of exclusion criteria:
    - Acute infection requiring intravenous antibiotics.
13) Clarification that 5 years follow up is from the date of first dose of study treatment.

14) Updated the following sections to align with the updated asset standard language for the dabrafenib and trametinib combination.

- Section 5.2.1 Dabrafenib and Trametinib Combination to align with the updated asset standard language for the dabrafenib and trametinib combination.
- Section 5.8.4.3 Guidelines for cuSCC and treatment emergent melanomas.
- Section 6.1 Permitted Medications and Non-drug Therapies.
- Section 6.4 Treatment of Study Treatment Overdose updated.
- Table 24 Clinical Chemistry and Hematology Parameters.
- Section 7.4.2.2 Definition of a SAE.
- Section 7.4.5 Ophthalmic Examination.

15) Update Table 3 to correctly reflect categories of dose modification guidelines.

16) Updated Table 18 Medications to be used with Caution.

17) Revised Dose Modification Guidelines for:

Events Considered Related to Study Treatment (Dabrafenib and Trametinib Combination Treatment)

- LVEF
- QTc-Prolongation
- Pyrexia
- Visual Changes and/or Ophthalmic Examination Findings
- Retinal pigment epithelial detachments (RPED)Updated guidelines for cuSCC and new cases of secondary melanomas
- Pneumonitis

18) Changes to the Time and Events Tables including modification to frequency of ECHO in the table to match the footnote reference, update to instruction for screening, ophthalmology exam, dispensation of study treatment, follow-up contact, and week 1 changed to Day 1.

19) Addition of Appendix 9: Country Specific Requirements for France and Germany.

- The following subjects are excluded from the study; subjects with HIV, under guardianship / under supervision or deprived of liberty, present with electrolyte abnormalities, and taking medications known to induce QT prolongation.

Guidelines added;Valvular Toxicity and Non-cutaneous secondary/recurrent malignancy

2013N168437_02	2014-AUG-20	Amendment No. 2

1) A country-specific amendment as requested by the French regulatory agency.

- Removed footnotes under the pneumonitis guidelines as they did not pertain to pneumonitis guidelines.
- Updated Table 8 Withholding and Stopping Criteria for QTcB-Prolongation.
- Updated Appendix 6 – removal of Phase III to IV algorithm and placement of phase II algorithm.

2013N168437_03	2014-SEP-04	Amendment No. 2
Republishing (Table number was wrong)		
2013N168437_04	2015-MAR-16	Amendment No. 3

1) Revised list of authors.
2) Clarification Protocol Amendment 2 is a country-specific amendment as requested by the French regulatory agency.
3) Minor administrative changes and correction to typographical errors throughout the document.
4) Table of Contents Updated with Section 1.3, Appendix 11 and 12 references.
5) Section 1.3 header added for clarity between study and dose rationale.
6) Study design revised for clarity around treatment discontinuation and follow up of subjects.
7) Exclusion HIV removed per March 2014 updates to Inc/Exc (combination).
8) Permanent discontinuation from study treatment revised for clarity around treatment discontinuation and follow up of subjects.
9) Dosage and administration section revised based on combination dosage and administration March 2014.
10) Table 3 added footnotes for consistency across MEK/BRAF protocols.
11) Dose Level Reduction Guidelines revised for consistency across MEK/BRAF protocols.
12) Table 6 superscript b and c added to symptomatic LVEF for consistency across MEK/BRAF protocols.
13) Table 7 well controlled BP revised for consistency across MEK/BRAF protocols.
14) Section 5.8.4 added 'keratoacanthoma for consistency across MEK/BRAF protocols.
15) Section 5.8.4.3 added 'keratoacanthoma for consistency across MEK/BRAF protocols.
16) Table 11 revised dabrafenib dose reduction for consistency across MEK/BRAF protocols.
17) Section 5.8.5.4 added reference Section 7.5.5.
18) Table 14 added footnote for PK reference.
19) Table 16 added footnotes for consistency across MEK/BRAF protocols.
20) Section 6.1 revised for clarity to time requirements for concomitant medications.
21) Table 17 header revised for clarity on prohibited medications.
22) Table 19 revised for clarity on required assessments.
23) Section 7.3.2.1 revised for consistency between updated Image Acquisition Guidelines for Brain MRI.

24) Section 7.3.2.2 revised for clarity around treatment discontinuation and follow up of subjects.

25) Section 7.5.3.1 revised serium pregnancy test to 7 days prior to enrolment in accordance with Oct 2014 safety guidance.

26) Section 7.5.5 revised with new ophthalmic criteria from July 2014 trametinib safety guidance.

27) Section 9.2.1 revised with description on how sample size of 75 was calculated.

28) Section 9.3.3 Treatment comparison clarified as NA for this study.

29) Table 25 revised for clarity between row 1 and row 2 in a superiority binomial trial.

30) Section 9.3.5.1.1 Secondary Analyses added line for clarification to interpretation.

31) Appendix 11 added to reflect amendment 02 changes.

32) Appendix 12 added to reflect amendment 03 changes

2013N168437_05	2015-DEC-06	Amendment No. 4

1) Updating contact details of Medical Monitor

2) Table 1 Study Objectives – 1. Primary endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and 2 secondary endpoint number 9 OS changed from 5 to 3 year.

3) Section 3 Study design – cohort A patient population updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts). And definition of study closure updated from "where all subjects still in follow up have had at least 5 years follow up…" to "where all subjects still in follow up have had at least 3 years follow up…"

4) Section 3.1 Discussion of Design – primary efficacy objective endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts).

5) Section 4.1.2 Inclusion Criteria 4 updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and Inclusion criteria 10 - period for contraception amended from 14 days prior to baseline to 7 days to be consistent with all other sections of protocol and current IB 7 safety update.

6) Section 4.2.1 reference to 5 year survival changed to 3.

7) Section 4.2.2 reference to 5 year survival changed to 3.

8) Section 5.2,1 Duplicated sentence deleted.

9) Section 5.8.1 Amended from dose reductions below 50 to dose reductions below 75 mg BID.

10) Table 5 "or greater occurrence" deleted.

11) Table 19 Time and Events Table – footnotes 2 and 3 amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts).

12) Section 7.2.1.1 secondary endpoint reference to 5 year survival changed to 3.

13) 7.4.3.1 Pregnancy Testing and Prevention – section updated period for contraception amended from 14 days prior to baseline to 7 days to be consistent with all other sections of protocol and current IB 7 safety update.

14) 7.6.2 BRAF mutation assay section amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts).

15) Section 9.3.5.1.1 Primary Analysis reference to 5 year survival changed to 3.

16) Section 10.5 Study and Site Closure reference to 5 year survival changed to 3.

17) Appendix 13 added to reflect amendment 04 changes.

2013N168437_06	2015-DEC-14	Amendment No. 4

1Minor administrative changes found during pOPRC review:

1) Section 4.1.2 Inclusion Criteria 4 typographical duplication error removed "cohorts"

2) Section Objectives/primary objective Typo updated in scentence beginning "The primary efficacy endpoints will be accessed changed to assessed.

3) Section 10.5 Study and Site Closure number 3 added to scentence starting:" The study will be considered.

2013N168437_07	2016-JUL-13	Amendment No. 5

1) Delete or replace references to GSK or its staff with that of Novartis/Novartis and it's authorized agents.

2) Make administrative changes to align with Novartis processes and procedures

2013N168437_08	16-MAY-2017	Amendment No. 6

Amendment 6 did not incorporate amendment 5, as it was only for submission in countries that had not submitted GSK to Novartis sponsoship change

1. Study design section (page 22 and 36) amended to define study close as when 70% of cohort A patients are lost to follow up or completed or when all cohort A patients have been followed up for 3 years, whichever is earlier.

2. Section 10.5 (page 114) – Study closure definition amended from 70% of all enrolled study population to 70% of primary efficacy population (cohort A) and addition of at least three years follow up for all cohort A patients. Estimation of study length amended to approximately 5 years from study start.

3. Administrative errors from protocol amendment 4:
   - Table of assessment transcription error rectification
   - Discrepancy with window from pregnancy testing prior to screening in section 7.4.3.1
4. Section 3.1 page 37 & 106 Statistical power amended from 84% to 82% to align with final statistical analysis plan.

2013N168437_09	21-JUN-2017	Amendment No. 7

Amendment 7 did incorporate amendment 5, as it was for submission in countries that had already submitted GSK to Novartis sponsoship change

1. Study design section (page 22 and 34) amended to define study close as when 70% of cohort A patients are lost to follow up or completed or when all cohort A patients have been followed up for 3 years, whichever is earlier.

2. Section 10.5 (page 108) – Study closure definition amended from 70% of all enrolled study population to 70% of primary efficacy population (cohort A) and addition of at least three years follow up for all cohort A patients. Estimation of study length amended to approximately 5 years from study start.
3. Administrative errors from protocol amendment 4:
    - Table of assessment transcription error rectification
    - Discrepancy with window from pregnancy testing prior to screening in section 7.4.3.1
4. Section 3.1 page 35 & 100 Statistical power amended from 84% to 82% to align with final statistical analysis plan.

Sponsor Signatory: **Signature:** **Date:**

[redacted]
Novartis Pharmaceuticals Corporation.

SPONSOR INFORMATION PAGE

Clinical Study Identifier: BRF117277

Sponsor Contact Information

Novartis Pharmaceuticals Corporation

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Serious Adverse Events (SAE) Contact Information:

Please refer to the study procedures manual.

For study conduct questions not related to patient safety that need to be addressed to the sponsor, the first line of contact should be with the designated local country company contact. In the event that the designated company contact is not available, please contact the Medical Lead.

Medical Lead Contact Information

[redacted]

Novartis Pharmaceuticals Corporation

One Health Plaza, 337/A11.6F

East Hanover, NJ 07936-1080

USA

Telephone Number: [redacted]

Email: [redacted]

Novartis Pharma AG

Postfach

CH-4002 Basel

SWITZERLAND

Clinical Trial Head Contact Information

[redacted]

Telephone Number: [redacted]

Email: [redacted]

If you have any questions regarding the protocol, please contact your local Novartis office.

Regulatory Agency Identifying Number(s):

Investigational New Drug (IND) Number	113557
European Drug Regulatory Authorities Clinical Trials (EudraCT) Number	2013-003452-21

INVESTIGATOR AGREEMENT PAGE

For protocol BRF117277 amendment number 05.

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

ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event(s)
ALT	Alanine transaminase (SGPT)
ANC	Absolute neutrophil count
ASPCR	Allele-specific polymerase chain reaction
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BCRP	Breast cancer resistance protein
BID	Twice daily
BIRC	Blinded Independent Review Committee
BP	Blood pressure
BRAT	Banana, rice, apples, toast
BUN	Blood urea nitrogen
CAF	Cytokines and angiogenic factors
[redacted]	[redacted]
CI	Confidence interval
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
CNS	Central nervous system
CPK	Creatinine phosphokinase
CR	Complete response
CRO	Clinical Research Organization
CrCl	Creatinine clearance
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte antigen
cuSCC	Cutaneous Squamous Cell Carcinoma
CV%	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DER	Duration of Extracranial Response
DIR	Duration of Intracranial Response
DOR	Duration of Overall Response
DTIC	Dacarbazine
E	Glutamate
EC	Extracranial Disease
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERR	Extracranial Response Rate
EudraCT	European Drug Regulatory Authorities Clinical Trials
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FSH	Follicle-stimulating hormone
FTIH	First time in humans
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GCPH	Global Clinical Program Head
GCL	Global Clinical Lead
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
G6PD	Glucose-6-phosphate dehydrogenase
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HFSR	Hand-foot skin reaction
Hg	Mercury
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPMC	Hydroxypropyl methylcellulose
HR	Hazard ratio
HRQOL	Health-related quality of life
HRT	Hormone-replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDC	Intracranial Disease Control
IDE	Investigational Device Exemptions
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
INR	International normalized ratio
IUO	Investigational Use Only
IC	Intracranial Disease
IR	Intracranial Response Rate
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive voice response system
K	Lysine
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LSLV	Last subject's last visit

LSM	Least square means
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter(s)
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NSAIDS	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ODC	Overall Disease Control
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
Pgp	P-glycoprotein
[redacted]	[redacted]
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	Corrected QT interval on electrocardiogram
QTcB	QT interval on electrocardiogram corrected using the Bazett's formula
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic acid
RPED	Retinal pigment epithelial detachment
RVO	Retinal vein occlusion
SAE	Serious adverse event(s)
SBP	Systolic blood pressure
SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SOP	Standard Operating Procedure(s)
SPF	Skin protection factor
SPM	Study Procedures Manual
ULN	Upper limit of normal
UP	Upper Providence
US/USA	United States
V	Valine
VAS	Visual analogue scale
V/F	Volume of distribution
WBC	White blood cell

PROTOCOL SUMMARY

Rationale

One of the most common and serious complications of cutaneous melanoma is the development of metastatic sites in the central nervous system (CNS). Up to 20% of patients are diagnosed with brain metastases at the time of initial diagnosis, and up to 75% of patients are found to have brain metastases throughout the course of their disease [Davies, 2011]. Clinical outcomes are usually quite poor, with median overall survival estimated to be between 3.8 and 4.7 months [Sampson, 1998] [Fife, 2004] [Davies, 2011]. Treatment selection is driven by clinical and disease criteria, including number of cerebral metastases, performance status, and extent of extracranial disease [Hong, 2012]. Surgical intervention and radiation have demonstrated improved local control, but historically systemic treatments have been generally ineffective, with response rates of less than 10% and disease stabilization rates of around 20-30% [Agarwala, 2004] [Margolin, 2012].

Approximately 40 to 60% of cutaneous melanomas carry mutations in *BRAF* that lead to constitutive activation of downstream signalling through the MAPK pathway. Approximately 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (BRAF V600E), although other activating mutations are known (e.g., BRAF V600K and BRAF V600R) [Davies, 2002]. Dabrafenib is an orally available, reversible, ATP-competitive inhibitor that selectivelyinhibits BRAFV600E kinase with a concentration required for 50% inhibition of the kinase activity (IC50) five times lower than the IC50 for wild-type BRAF or CRAF. A recent study of dabrafenib monotherapy (BREAK-MB) in 172 patients with BRAF V600E/K-mutation positive melanoma that has metastasized to the brain in reported encouraging results. An overall intracranial response rate of 39% and overall disease control rate of 80% was reported in patients with V600E-mutation positive tumours who had not received prior local (brain) treatment. Similar results (overall intracranial response rate = 31%; overall disease control rate = 83%) were observed in patients with V600E- mutation positive tumours whose disease had progressed after previous intervention with surgery, whole-brain radiation, or stereotactic radiosurgery. In patients with V600K- mutation positive tumours, overall disease control rates of 47% and 50% were reported in the local- treatment naive and previous-local treatment cohorts, respectively[Long, 2012].

In a recent study of dabrafenib in combination with trametinib, an orally available, small molecule, selective inhibitor of MEK1 and MEK2, a confirmed ORR of 76% was reported in patients with BRAF V600E/K mutation positive metastatic melanoma without evidence of CNS metastases who were treated at full dose levels of both agents. In this same cohort, no patient had a best overall response of PD, and 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<0.001). www.gsk.com/content/dam/gsk/globals/documents/pdf/Investors/presentations/2012/ESMO-analyst-presentation-1-oct-2012.pdf.

While the BREAK-MB trial demonstrated activity in patients with active brain metastases, all of the patients in that trial were asymptomatic from CNS disease. Vemurafenib, another elective inhibitor of oncogenic BRAF kinase that specifically targets cancer cells harbouring mutated BRAFV600, was recently studied in a cohort of 24 patients with symptomatic brain metastases. Median PFS in the brain was 4.3 months and for other sites was 4.6 months. In addition, an improvement in performance status (decrease from baseline of at least 1 point of ECOG score) was seen in 83.3% of patients, and 66.7% reported a reduction of ≥30% (compared with baseline dose) or complete discontinuation of corticosteroids.Dummer, 2013].

This current trial is expected to build upon the current body of evidence of targeted therapy in melanoma brain metastases through an evaluation of the combination of dabrafenib and trametinib in patients with V600-mutation positive melanoma brain metastases.

Objectives

Primary Objective

The primary objective of the study is to assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, ***asymptomatic***, without prior local therapy and ECOG score of 0-1 (Cohort A). IR is defined as the proportion of subjects with a confirmed intracranial complete response (CR) or partial response (PR) by investigator assessment using modified RECIST 1.1 guidelines [Eisenhauer, 2009].

The primary efficacy endpoints will be investigator assessed via local MRI scans. Radiological scans will be collected via AGMednet, stored via Vesalius and may be centrally reviewed to support independent assessment of efficacy if needed.

The study is designed to provide evidence to support the null hypothesis, H_0: IR ≤ 35% or to reject it in favor of the alternative hypothesis, H_A: IR ≥ 50% for BRAF V600E mutation-positive subjects in Cohort A.

Secondary Objective

Safety endpoints will be evaluated in all cohorts and efficacy endpoints will be evaluated in 3 additional cohorts.

The following endpoints will be assessed as secondary endpoints in all cohorts (unless stated otherwise)

1. IR in Cohort B, C and D
2. Intracranial disease control (IDC)
3. Extracranial response rate (ERR)
4. Overall response rate (ORR)
5. Duration of intracranial, extracranial and overall response (DIR, DER and DOR respectively)
6. Progression-free survival (PFS)
7. Overall survival (OS) and long-term (particularly 3-year) OS
8. Safety of dabrafenib and trametinib combination therapy

Long-term survival, in particular 3year survival, is of interest for the population of V600E and V600K BRAF mutation-positive metastatic melanoma patients treated with dabrafenib and trametinib combination therapy.

Study Design

This is a multi-cohort, open label, Phase II study with dabrafenib (GSK2118436) and trametinib (GSK1120212) combination therapy in subjects with BRAF Mutation-Positive Melanoma that has metastasized to the Brain. This study will evaluate the safety and efficacy of 4 cohorts. Local therapy is ***defined*** as therapy to the brain ***wherever it is mentioned*** throughout this protocol even if not identified as such.

- **Cohort A:** Seventy-five subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, **without prior local (brain) therapy** and ECOG score of 0-1.
- **Cohort B:** Fifteen subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, **with prior local (brain) therapy** and ECOG score of 0-1.
- **Cohort C:** Up to fifteen subjects with locally confirmed BRAF **V600 D/K/R** cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, **with or without** prior local (brain) therapy and ECOG score of 0-1.
- **Cohort D:** Fifteen subjects with locally confirmed BRAF **V600 D/E/K/R** cutaneous melanoma with metastases to the brain confirmed by MRI, **symptomatic**, **with or without** prior local (brain) therapy and ECOG score of 0-2.

Subjects will receive dabrafenib capsules 150 mg twice daily and trametinib tablets 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity.

Subjects will be required to meet all eligibility criteria and return to clinic on a monthly basis for clinical and laboratory assessments. Intracranial and extracranial disease will be assessed at baseline, Week 4, Week 8, and every 8 weeks thereafter. After Week 40, disease assessments may be performed every 12 weeks. Response to treatment will be evaluated using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [Eisenhauer, 2009].

All subjects who permanently discontinue study treatment will have monthly skin assessments, survival follow up and new anti-cancer therapy (including radiotherapy and surgery follow up) through month 6 after treatment discontinuation. If they start new anti-cancer therapy or at the end of the 6 month follow up visit, they will be followed every 12 weeks for survival follow up and new anti-cancer therapy (including radiotherapy and surgery) until death, have withdrawn consent or are lost to follow-up, or study closure. Study closure is defined by where all cohort A subjects still in follow up have had the opportunity for at least 3 years follow-up from the date of first dose of study treatment or 70% of cohort A patients have died or are lost to follow up, whichever is earlier.

Either dose of the study treatments may be modified and/or interrupted for management of associated toxicities (Section 5.8).

Study Assessments

The primary endpoint is IR. Intracranial response (IR), extracranial response (ER), overall response (OR), disease control (intracranial, extracranial, and overall), PFS, OS and duration of all response endpoints will be determined based on the investigator's assessment of target- and non-target lesions as evaluated by the modified Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Safety will be evaluated by clinical assessments including monthly skin assessments, vital signs and physical examinations, neurological exams, 12-lead electrocardiograms (ECG), echocardiograms (ECHO), chemistry and haematology laboratory values, and adverse events (AEs). The subjects will be followed for survival.

1. INTRODUCTION

1.1. Background

Cutaneous melanoma is the most aggressive form of all skin cancers. Worldwide, it is expected that over 132,000 people will be diagnosed with melanoma each year and more than 37,000 people are expected to die of this tumour disease annually. In the USA and most countries of the Western World including Australia, the incidence of melanoma continues to rise faster than any other type of cancer in men and the annual increase in the incidence of melanoma in women is second only to lung cancer [Linos, 2009] [Ries, 2008].

In the past 40 years, the median survival time for patients with unresectable melanoma has remained short with approximately only 6 to 9 months from the time of diagnosis and with only 10-15 % of subjects alive after 3-years Although, combination therapies of chemotherapeutic agents and cytokines such as interferon-alpha and interleukin-2 have resulted in an increase of response rates, the overall survival (OS) of patients with unresectable melanoma had so far not been improved[Hodi, 2010].

However, much has changed in the treatment landscape of melanoma since 2011 with the regulatory approval of two new agents which demonstrated a significant survival benefit in well-controlled Phase III trials. Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen or CTLA-4, was approved by the US-Food and Drug Administration (FDA) 25-March-2011 and European Medicines Agency (EMA) 13-Jul- 2011 for unresectable or metastatic melanoma based on a significant ($p=0.003$) prolongation of OS (HR0.68) compared to gp100 tumour vaccine [Hodi, 2010]. In addition, ipilimumab in combination with standard dacarbazine (DTIC) chemotherapy significantly ($p<0.001$) improved the OS of previously untreated metastatic melanoma patients as compared to DTIC alone (HR 0.72). [Robert, 2011]. While ipilimumab was approved for the clinical use in unselected patients, the selective small molecule BRAF- inhibitor vemurafenib received FDA-approval in August of 2011 and EMA-approval February 2012 as the first molecular-targeted agent for unresectable or metastatic melanoma harbouring BRAF V600E mutations. Oncogenic mutations of the BRAF serine-threonine occur in approximately 50% of tumours in melanoma and result in a constitutive activation of the MAP-kinase pathway through

downstream phosphorylation and activation of the MEK1 and MEK2 kinases. In the pivotal Phase III study BRIM-3 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]. Dabrafenib, another small molecule BRAF-inhibitor received FDA-approval in May 2013 and EMA approval in August 2013.

Despite this major initial progress in the clinical management of unresectable melanoma, immune-mediated toxicities and the lack of a validated biomarker for patient selection may restrict the use of ipilimumab [Sondak, 2011]. As has been the pattern with other highly selective small molecule kinase inhibitors (e.g. imatinib in bcr-abl chronic myeloid leukaemia (CML); erlotinib and gefitinuib in EGFR-mutant non-small cell lung cancer (NSCLC) the rapid onset of drug resistance restricts the efficacy of vemurafenib and limits the median duration of response to only 6.7 months [Chapman, 2011] . It is widely believed, that combination therapies of targeted agents can further improve the survival currently achieved with ipilimumab- and vemurafenib- single agent-therapies [Eggermont, 2011]. . In Jan 2014 the combination of dabrafenib and trametinib received FDA approval, and in February 2014 the combination received approval in Australia.

For melanoma patients whose tumour harbour a BRAF-activating mutation, a combination of a selective and potent BRAF- and a MEK-inhibitor is favoured to address specific molecular mechanisms of intrinsic and acquired resistance to a BRAF-inhibitor monotherapy [Nissan, 2011]. Understanding these specific mechanisms of resistance to BRAF-inhibitors is critical for the development of more effective strategies in BRAF- mutant melanoma. Recently, several distinct mechanisms of resistance to BRAF- inhibition have been proposed based on data obtained in experimental melanoma cell models and small series of tumour samples. In a majority of cell models and melanoma samples, acquired and potentially primary resistance to BRAF-inhibitors was associated with a reactivation of the MAPK-pathway indicating that the 'addiction' to this pathway in BRAF-mutant melanoma remains unchanged. In these resistant BRAF-mutant melanomas the MAPK-pathway can be reactivated through secondary activating mutations of the upstream NRAS- or the downstream MEK1-kinase or an over expression of the RAF1- and COT-kinase. Although the frequency of specific resistance mechanisms is currently not known, alterations that restore MAP kinase pathway activity downstream of BRAF (e.g. MAP kinase pathway dependent mechanisms) may render melanoma cells susceptible to a combined BRAF- and MEK-inhibition.

Data from the ongoing Phase I/II study BRF113220 suggest that the small-molecule BRAF-inhibitor dabrafenib can be safely combined with the small molecule MEK-inhibitor trametinib. In addition, the anti-tumour activity of the combination of both agents given continuously and at full-single-agent dose appears to be superior as compared to single-agent dabrafenib.

1.1.1. The BRAF Inhibitor Dabrafenib as Monotherapy

Dabrafenib, a selective BRAF inhibitor, has shown activity with a manageable safety profile in phase 1 and 2 studies in patients with BRAF V600E/K-mutation positive metastatic melanoma. The BREAK-3 (BRF113683) global phase III trial was conducted in patients with BRAF V600E mutation-positive advanced or metastatic melanoma randomized (3:1) to

receive treatment with either dabrafenib [150 mg , twice daily (BID)] or dacarbazine (DTIC). Subjects were randomized by disease stage (unresectable Stage III, IVM1a and IVM1b versus IVM1c). Subjects randomized to the DTIC arm were allowed to crossover to receive dabrafenib after confirmation of progressive disease (PD). The primary endpoint was progression free survival (PFS) based on investigator assessment in the intent-to-treat (ITT) population comprised of all randomized subjects, regardless of whether or not treatment was administered. Secondary endpoints were overall survival (OS), overall response rate (ORR) in both groups and after crossover, PFS for subjects randomized to the DTIC treatment groups after crossover, duration of response, safety/tolerability and BRAF mutation assay validation.

Two hundred and fifty subjects were enrolled; including 187 that were randomized to dabrafenib and 63 to DTIC. At the time of data cut-off for the primary analysis, 141 subjects were on study treatment (dabrafenib n=127; DTIC n=14) including 21/28 DTIC subjects that crossed over to dabrafenib. Median age was 52 years; 31% had an Eastern Cooperative Oncology Group (ECOG) performance status ≥1, 66% were M1c, and 33% lactate dehydrogenase (LDH) greater than the upper limit of normal (>ULN) [Hauschild, 2012].

At the time of the primary analysis, there were 118 events (77 dabrafenib and 41 DTIC). The hazard ratio (HR) for PFS was 0.30 (95% CI: 0.18-0.53; p<0.0001). Median PFS was 5.1 months for dabrafenib and 2.7 months for DTIC by investigator assessment. OS data were immature. Confirmed response rate (RR) was 53% for dabrafenib and 19% for DTIC. Benefits in PFS and RR were observed in all subgroups evaluated. The most frequent adverse events (≥20%) in the dabrafenib arm were hyperkeratosis (39%), headache (35%), arthralgia (35%), pyrexia (32%), alopecia (29%), nausea (28%), skin papillomas (25%), fatigue (23%) palmar-plantar erythrodysaesthesia syndrome (20%), asthenia (20%).

Serious adverse events (SAEs) (>1%) on the dabrafenib arm included squamous cell carcinomas (10%), pyrexia (5%), Basal cell Carcinoma (2%) atrial fibrillation (2%), chills (2%), ejection fraction decreased (2%) , malignant melanoma (2%).

Further evidence for the safety and efficacy of dabrafenib has been established in a large (N=172) study of patients BRF113929 (BREAK-MB) where subjects were assessed for metastatic melanoma to the brain. Subjects with V600E without previous local therapy (Cohort A) demonstrated 39.2% overall intracranial response rate and 81.1% intracranial disease control (IDC); patients with V600E with previous local therapy (Cohort B) demonstrated 30.8% overall intracranial response rate and 89.2% intracranial disease control (IDC) with a cohort median survival of 33.1 and 31.4 weeks, respectively. This study demonstrates that dabrafenib has activity and acceptable manageable safety profile in patients with melanoma metastases to the brain. [Long, 2012].

1.1.2. The MEK Inhibitor Trametinib as Monotherapy

Trametinib is a reversible, highly selective allosteric inhibitor of MEK1/2 activation and kinase activity. A Phase 3 trial, METRIC (MEK114267), was conducted in patients with BRAF V600E/K mutation positive advanced or metastatic melanoma. Subjects were randomized 2:1 to trametinib (2mg once daily) or chemotherapy (DTIC or paclitaxel). Subjects were stratified by baseline LDH level and prior chemotherapy; subjects in the

chemotherapy arm were allowed to crossover to receive trametinib after confirmation of PD. The primary endpoint was PFS in subjects with BRAF V600E mutation-positive metastatic melanoma and no prior brain metastases; PFS was also evaluated in the ITT population. Secondary endpoints were OS, ORR in the primary and ITT population and safety in the safety population.

Three hundred and twenty-two subjects were randomized to trametinib (n=214) or chemotherapy (n=108); 273 subjects were BRAF V600E mutation-positive with no prior brain metastases. Median age was 54 years; all had an ECOG performance status of 0 (64%) or 1 (36%), and 65% were M1c [Flaherty, 2012].

The HR for the primary efficacy population for PFS by investigator was 0.44 (95% CI 0.31–0.64; p<0.0001) in favor of trametinib with a median PFS of 4.8 months vs. 1.4 months with chemotherapy. The confirmed ORR was 24% with trametinib and 7% with chemotherapy. HR for interim OS was 0.53 (95% CI 0.30–0.94; p=0.0181), in favor of trametinib.

The most frequent AEs (≥20%) with trametinib were skin rash (57%), diarrhea (43%), fatigue (26%), and edema (26%). Known MEK inhibitor class effects were observed in this study including chorioretinopathy (<1%) and decreased ejection fraction (7%).

1.1.3. BRAF and MEK Inhibitors as Combination Therapy

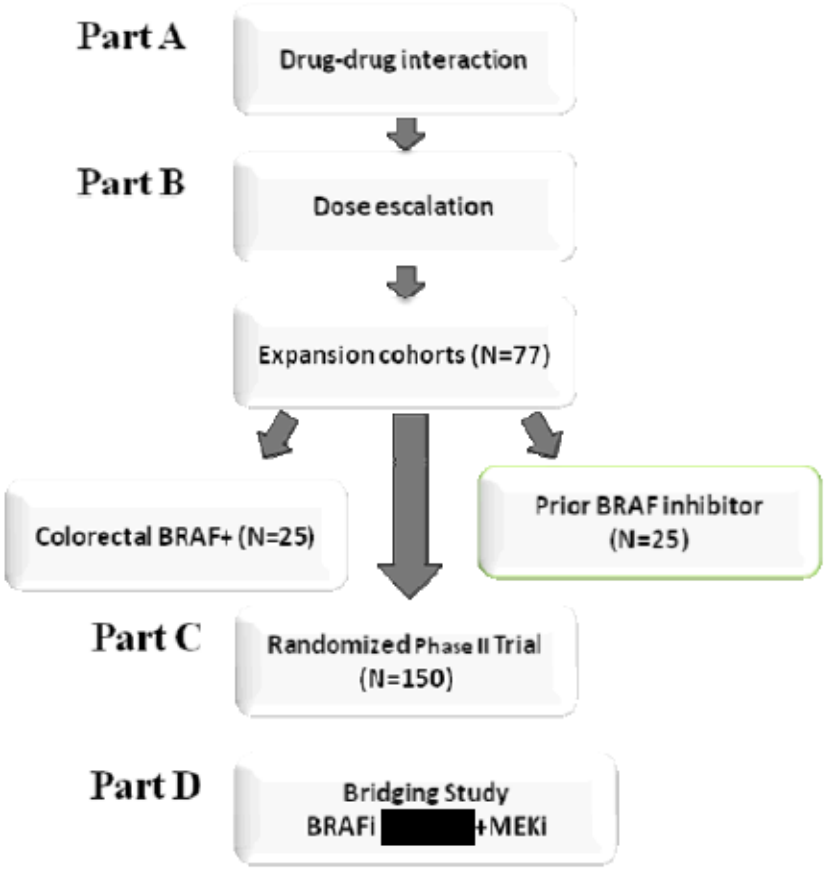
1.1.3.2. Dabrafenib and Trametinib Combination

The combination of dabrafenib and trametinib is in development for the treatment of BRAF mutant advanced and metastatic melanoma. As of 8 April 2013, the combination of dabrafenib and trametinib has been under evaluation in 6 clinical trials and 2 completed

single-patient compassionate care protocols (BRF115015, BRF115262), and one multi-patient compassionate program (MEK117341) is ongoing.

A 4-part Phase I/II study (BRF113220; Figure 1) investigating the dabrafenib/trametinib combination for metastatic melanoma is discussed below.

Figure 1 ***BRF113220 Study Design***



In Part B, subjects were treated on 4 escalating dose levels of dabrafenib/trametinib (mg BID/mg once daily): 75/1, 150/1, 150/1.5, 150/2. Demographic and efficacy data for the melanoma subjects and safety data for all 125 Part B subjects were reported [Weber, 2012].

Among 77 treatment-naïve subjects with BRAF V600 mutation-positive melanoma and measurable disease according to Response Evaluation Criteria in Solid Tumours version 1.1(RECIST 1.1), median age was 52 years, 61% male, 57% ECOG performance status of 0, 91% V600E, 65% M1c stage, 26% prior brain metastases, and 52% LDH > ULN. Confirmed ORR was 56% (95% CI: 44.1%-67.2%) with 4 complete response (CR), 39 partial response (PR), 29 stable disease (SD) and, 3 PD. Confirmed response rates for each dose level tested in Part B were 67% (n=6), 64% (n=22), 44% (n=25), and 63% (n=24), respectively. Median PFS was 7.4 months overall (95% CI: 5.5-9.2), and 10.8 months (95% CI: 5.3, NR) in the cohort treated with 150/2. Median duration of response for the entire cohort was 11.3 months (95% CI: 9.2, not reached) with a median duration on treatment of 10.7 months (including 38% of

subjects ongoing at the time of the analysis). The most common adverse events (AE) were pyrexia (52%), rash (45%), chills (38%), fatigue (37%), and nausea (34%). There were two grade 5 adverse events (AEs), pneumonia and hyponatremia. The most common Grade 3/4 AEs were pyrexia (n=6, 5%), fatigue (n=6, 5%) and dehydration (n=6, 5%). Skin toxicity ≥ Grade 2 occurred in 17 (14%) subjects. Cutaneous squamous cell carcinoma occurred in 3 (2%) subjects and actinic keratoses in 2 (2%). The most common treatment related AEs (≥20%, all grades) among subjects in Part B receiving 150 mg BID dabrafenib and 2 mg once daily trametinib (n=79) were pyrexia (58%), skin toxicities including rash (42%), chills (37%), fatigue (38%) and nausea (34%).

1.2. Study Rationale

- Clinical data from Phase I, II and III studies for dabrafenib and trametinib monotherapies have demonstrated single-agent clinical activity in subjects with BRAF-V600E- or BRAF-V600K-mutant melanoma.

  • Study BRF113929 (BREAK-MB): Results of investigator assessed metastatic melanoma to the brain demonstrated that patients without previous local therapy (Cohort A) demonstrated 39.2% overall intracranial response rate and 81.1% intracranial disease control (IDC); patients with previous local therapy (Cohort B) demonstrated 30.8% overall intracranial response rate and 89.2% intracranial disease control (IDC) with a cohort median survival of 33.1 and 31.4 weeks, respectively. This study demonstrates

that dabrafenib has activity and managable safety profile in patients with melanoma metastases to the brain. [Long, 2012]

- Preclinical studies and clinical data indicate that primary- and acquired resistance to a BRAF-inhibitor single-agent therapy may be addressed and potentially overcome by a combination of a BRAF- and MEK-inhibitor
- Clinical data from the Phase I/II study BRF113220 that evaluated the combination of dabrafenib and trametinib demonstrated good clinical activity and a manageable clinical safety profile.

[redacted]

[redacted]

[redacted]

2. OBJECTIVE AND ENDPOINTS

Table 1 lists the study objectives and corresponding endpoints.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
• To assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E-mutation positive melanoma that has metastasized to the brain without symptoms and have not undergone prior local therapy for brain metastases, ECOG score of 0-1 (Cohort A).	• IP is defined as the proportion of subjects with a confirmed intracranial complete response (CR) or partial response (PR) as per investigator assessment using modified RECIST 1.1 guidelines [Eisenhauer, 2009].
Secondary	
1. To assess cohort B for IR of subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic with prior local therapy for brain metastases; ECOG score of 0-1.	• IR is defined as the percentage of subjects with a confirmed intracranial complete response (CR) or partial response (PR) as per investigator assessment using modified RECIST 1.1 guidelines [Eisenhauer, 2009].
2. To assess cohort C for IR of subjects with locally confirmed BRAF V600 D/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with or without prior local therapy; ECOG score of 0-1.	
3. To assess cohort D for IR of subjects with locally confirmed BRAF V600 D/E/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, symptomatic; with or without prior local therapy; ECOG score of 0-2.	
4. To assess Cohorts A, B, C and D for Disease Control for intracranial, extracranial and overall response (IDC, EDC and ODC respectively)	• Intracranial Disease Control (IDC) is defined as CR+PR+SD for intracranial, extracranial, and overall disease control.
5. To assess Cohorts A, B, C and D for extracranial response rate (ER)	• Extracranial response (ER), defined as the percentage of subjects with a best extracranial response of a confirmed CR or PR by investigator assessment using modified RECIST 1.1
6. To assess Cohorts A, B, C and D for overall response rate (OR)	• Overall response (OR), defined as the percentage of subjects with a best overall confirmed response of CR or PR by investigator assessment.
7. To assess Cohorts A, B, C and D for overall response rate (OR)	• Duration of intracranial, extracranial and overall response (DIR, DER and DOR), defined as the time from first documented evidence of CR or PR until time of first documented intracranial, extracranial and overall disease progression.

Objectives	Endpoints
8. To assess Cohorts A, B, C and D for progression-free survival (PFS). 9. To assess C Cohorts A, B, C and D for overall survival (OS) and long-term (particularly 3-year) OS. 10. To assess Cohorts A, B, C and D to characterize the safety of dabrafenib and trametinib combination therapy	• PFS, defined as the interval between first dose and the earliest date of disease progression or death due to any cause • Overall survival (OS), defined as the time from first dose until death due to any cause. • Assessment of safety of dabrafenib and trametinib measured by the frequency and severity of adverse events, skin assessments, laboratory abnormalities, vital signs, and assessment data (12-lead electrocardiograms (ECG), echocardiograms, and clinical monitoring/observation including neurological examination)
[redacted]	

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 19) are essential and required for study conduct.

This is a multi-cohort, open label, Phase II study with dabrafenib (GSK2118436) and trametinib (GSK1120212) combination therapy in subjects with BRAF Mutation-Positive Melanoma that has metastasized to the brain. This study will evaluate the safety and efficacy of 4 cohorts. **Cohort A:** Seventy-five subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local (brain) therapy and ECOG score of 0-1. **Cohort B:** Fifteen subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with prior local (brain) therapy and ECOG score of 0-1. **Cohort C:** Up to fifteen subjects with locally confirmed BRAF V600D/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with or without prior local (brain) therapy and ECOG score of 0-1. **Cohort D:** Fifteen subjects with locally confirmed BRAF V600D/E/K or R cutaneous melanoma with metastases to the brain confirmed by MRI, symptomatic, with or without prior local (brain) therapy and ECOG score of 0-2.

Melanoma Metastatic Brain			
Dabrafenib and Tramatinib			
Cohort A (75):	Cohort B (15):	Cohort C (up to 15):	Cohort C (15):
Locally Confrimed	Locally Confrimed	Locally Confrimed	Locally Confrimed
V600E	V600E	V600D/K/R	V600DE//K/R
Asymptomatic	Asymptomatic	Asymptomatic	Symptomatic
Without Prior Local therapy	With Prior Local therapy	With or Without Prior Local therapy	Withor Without Prior Local therapy
ECOG 0-1	ECOG 0-1	ECOG 0-1	ECOG 0-2

Corticosteroid/Anti-epileptic Use and Prior Local Therapy in Cohorts

Cohort A:

- Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least **1 month** prior to first dose of study treatment. (Refer to Section 6.3 Cautionary Medications).

- No prophylactic or preventive anti-epileptic therapy. **Exception:** anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a pre- existing condition and not related to brain metastasis is allowed.

Cohort B:

- Must have received at least one local therapy for brain metastases including but not restricted to brain surgery, Whole Brain Radiotherapy (WBRT) or Stereotactic Radiosurgery (SRS e.g. gamma knife, linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local (brain) therapies or combinations of local therapies are allowed. For subjects receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions are required. For subjects receiving local (brain) therapy for some but not all lesions, disease progression based on RECIST 1.1 is not required as long as there are remaining brain lesions that are measurable and not previously treated.

- Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least **1 month** prior to first dose of study treatment. (Refer to Section 6.3 Cautionary Medications).

- No prophylactic or preventive anti-epileptic therapy. **Exception:** anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a pre- existing condition and not related to brain metastasis is allowed.

Cohort C:

- Not required to have prior local therapy but if subject has had prior local therapy for brain metastases could include but not restricted to brain surgery, Whole Brain Radiotherapy (WBRT) or Stereotactic Radiosurgery (SRS e.g. gamma knife, linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local (brain) therapies or combinations of local therapies are allowed. For subjects receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions are required. For subjects receiving local (brain) therapy for some but not all lesions, disease progression based on RECIST 1.1 is not required as long as there are remaining brain lesions that are measurable and not previously treated.

- Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least **1 month** prior to first dose of study treatment. (Refer to

Section 6.3 Cautionary Medications).

- No prophylactic or preventive anti-epileptic therapy. **Exception:** anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a pre- existing condition and not related to brain metastasis is allowed

Cohort D:

- Not required to have prior local therapy but if subject has had prior local therapy for brain metastases could include but not restricted to brain surgery, Whole Brain Radiotherapy (WBRT) or Stereotactic Radiosurgery (SRS e.g. gamma knife, linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local (brain) therapies or combinations of local therapies are allowed. For subjects receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions are required. For subjects receiving local (brain) therapy for some but not all lesions, disease progression based on RECIST 1.1 is not required as long as there are remaining brain lesions that are measurable and not previously treated.
- Concomitant corticosteroids: permissible and stability of dosing not required.
- Prophylactic or preventive anti-epileptic therapy is allowed (Refer to Section 6.3 Cautionary Medications).

Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity. Subjects will be required to meet all eligibility criteria and return to clinic on a monthly basis for clinical, skin and laboratory assessments. Intracranial and extracranial disease will be assessed at baseline, Week 4, Week 8, and every 8 weeks thereafter. After Week 40, disease assessments may be performed every 12 weeks. Response to treatment will be evaluated using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [Eisenhauer, 2009].

An Independent Data Monitoring Committee (IDMC) will be used in this study.

Protocol-specified guidelines for dose adjustments, interruptions and discontinuation due to adverse events are provided below. All subjects who permanently discontinue study treatment will have monthly skin assessments, survival follow up and new anti-cancer therapy (including radiotherapy and surgery follow up) through month 6 after treatment discontinuation. If they start new anti-cancer therapy or at the end of the 6 month follow up visit, they will be followed every 12 weeks for survival follow up and new anti-cancer therapy (including radiotherapy and surgery) until death, have withdrawn consent or are lost to follow-up, or study closure. Study closure is defined by where all cohort A subjects still in follow up have had the opportunity for at least 3 years follow-up from the date of first dose of study treatment or 70% of cohort A patients have died or are lost to follow up, whichever is earlier

.

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.

3.1. Discussion of Design

The efficacy of the combination of dabrafenib 150 mg twice daily and trametinib 2 mg once daily in patients with metastatic melanoma has been described above, but has not been characterized fully in patients with melanoma that has metastasized to the brain.

The primary efficacy objective of this study is to assess the investigator-reported intracranial response (IR) in locally-confirmed BRAF V600E mutation-positive melanoma subjects who have not previously received local treatment for brain metastases (Cohort A) using modified RECIST 1.1 guidelines.

The study is designed to provide evidence to support the null hypothesis, H_0: IRR $\leq$ 35% or to reject it in favor of the alternative hypothesis, H_A: IRR $\geq$ 50% for BRAF V600E mutation-positive subjects in Cohort A.

The null hypothesis is based on results of BRF113929, a study of dabrafenib in two cohorts of patients with histologically confirmed metastatic melanoma to the brain [Long, 2012]. The IR in patients with no prior local treatment for brain metastases was 39%; in patients with prior local treatment, the IR was 31%. The alternative hypothesis was selected as the IR that would be clinically relevant for this combination therapy. The study is designed to have 82% statistical power to detect an IR of 50% in V600E mutation-positive subjects who receive dabrafenib in combination with trametinib in Cohort A. This hypothesis will be tested using a one-sided test for superiority with α=0.05. There will be no other testing; therefore, there will be no adjustment of the Type I error for multiple testing.

While the BREAK-MB trial demonstrated activity in patients with active brain metastases, all of the patients in that trial were asymptomatic from CNS disease. Vemurafenib, another selective inhibitor of oncogenic BRAF kinase that specifically targets cancer cells harbouring mutated BRAFV600, was recently studied in a cohort of 24 patients with symptomatic brain metastases. Median PFS in the brain was 4.3 months and for other sites was 4.6 months. In addition, an improvement in performance status (decrease from baseline of at least 1 point of ECOG score) was seen in 83.3% of patients, and 66.7% reported a reduction of $\geq$30% (compared with baseline dose) or complete discontinuation of corticosteroids. [Dummer, 2013].

The current trial is expected to build upon the current body of evidence of targeted therapy in melanoma brain metastases through an evaluation of the combination of dabrafenib and trametinib in patients with V600-mutation positive melanoma brain metastases.

4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

Approximately 120 subjects will be enrolled in this study: Cohort A (n=75); Cohort B (n=15); Cohort C (n=up to 15); and Cohort D (n=15). See Section 9.2.1 for sample size assumptions. Cohorts will be closed to enrollment as they are filled.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the investigational products that may impact subject eligibility is provided in the trametinib (GSK1120212), dabrafenib (GSK2118436), and dabrafenib and trametinib combination IBs.

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. Is ≥18 years of age.
2. Has signed written informed consent.
3. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 for Cohorts A, B and C and ECOG score of 0-2 for Cohort D. See Appendix 4 [Oken, 1982] (See Appendix 3).
4. Histologically confirmed cutaneous melanoma that is Stage IV (metastatic to the brain), and determined to be BRAF V600E/K/D/R mutation-positive [redacted] The assay will be conducted by a central reference laboratory. Subjects with ocular or mucosal melanoma are not eligible. Subjects in ALL cohorts are eligible to enroll based on local test results. Certified local test results will be subjected to retrospective central confirmation by a designated assay.
5. May be systemic naïve or received up to two previous systemic treatment regimens for metastatic melanoma including chemo-, cytokine-, immune-, biological- and vaccine therapy. Prior temozolomide for brain metastases and adjuvant interferon are acceptable and does not count toward the two previous systemic treatment regimens.
6. Must be able to undergo MRI and have at least one measurable intracranial lesion for which all of the following criteria have to be met:
   a. Previously untreated or progressive according to RECIST 1.1 (>/= 20% increase in longest diameter on baseline scan) after previous local therapy.

b. Largest diameter of >/= 0.5cm diameter but </= 4cm as determined by contrast-enhanced MRI.

c. For target lesions with diameter of > 0.5cm but ≤ 1 cm documented measurement by a neuroradiologist/appropriately qualified radiologist /**neurosurgeon** is required.

d. For all lesions with a diameter of ≥ 3cm but ≤ 4 cm documented measurement by a neuroradiologist / appropriately qualified radiologist /**neurosurgeon** is required.

7. All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 1) must be ≤ Grade 1 according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.0; National Cancer Institute (NCI, 2009) at the time of entry.

8. Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

9. Must have adequate organ function as defined 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[c]
AST and ALT	≤ 2.5 x ULN
Renal	
Serum creatinine[b]	≤ 1.5 mg/dL
Cardiac	
Left Ventricular Ejection fraction (LVEF)[d]	≥ LLN by ECHO

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 enrollment.

b) If serum creatinine is > 1.5 mg/dL, calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 4). Creatinine clearance must be ≥ 50 mL/min to be eligible.

c) Except subjects with known Gilbert's syndrome.

d) ECHO scans must be used throughout the study

10. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and agree to use effective contraception, as defined in Section 7.4.3.1 from 7 days prior to enrollment, throughout the treatment period, and for 4 months after the last dose of study treatment.

11. [redacted]

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 except for Cohort D where subjects can be symptomatic.
2. Prior treatment with a BRAF inhibitor or a MEK inhibitor.
3. Known ocular or primary mucosal melanoma
4. Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, within the last 3 weeks, or chemotherapy without delayed toxicity within the last 2 weeks preceding the first dose of the combination. Prior systemic treatment in the adjuvant setting is allowed (same timelines as above). (Note: Ipilimumab treatment must end at least 8 weeks prior to enrollment.)
5. Treatment with stereotactic radiosurgery within 14 days prior to start of study treatment, or treatment with whole-brain radiation within 28 days prior to study treatment.
6. Any presence of leptomeningeal disease or any parenchymal brain metastasis >4.0 cm in diameter.
7. Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is longer, prior to dosing
8. Current or expected use of a prohibited medication as described in Section 6.2
9. History of malignancy with confirmed activating RAS mutation at any time. *Note*: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.
10. History of malignancy other than disease under study within 3 years, of study enrolment with exceptions below.

    Exception: Subjects with a history of completely resected non-melanoma skin cancer, or subjects with indolent second malignancies are eligible.

11. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that, in the opinion of the investigator, could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.
12. A history of), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection

(subjects with laboratory evidence of cleared HBV and/or HCV will be permitted.

13. A history or evidence of cardiovascular risk including any of the following:

    a) Current LVEF <LLN

    b) A QT interval corrected for heart rate using the Bazett's formula (QTcB; ≥480 msec; See Appendix 4)

    c) A history or evidence of current clinically significant uncontrolled arrhythmias;

    Clarification: Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible

    d) A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment.

    e) A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines. See Appendix 5

    f) Treatment refractory hypertension defined as a blood pressure of systolic >140mmHg and/ or diastolic > 90 mmHg which cannot be controlled by anti-hypertensive therapy

    g) Patients with intra-cardiac defibrillators

    h) Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (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.

14. A history or current evidence of retinal vein occlusion (RVO)

15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/ or dimethyl sulfoxide (DMSO).

16. Pregnant or nursing females.

17. History of interstitial lung disease or pneumonitis

18. **Subjects registered in France and Germany:** French/German Subjects please refer to Appendix 9 for country specific guidance.

4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.2.1. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment 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 5.9.1 and Appendix 6. Note: continuation of either the combination or either of the single agent **study treatments beyond radiographic disease progression** (as defined by RECIST 1.1) may be possible if the investigator determines that subject has clear evidence of clinical benefit from study treatment, continuing study drug(s) may be in the best interest for the subject and the subject is willing to continue on study drug(s). In this case, consultation between the investigator and the Novartis Global Clinical Lead is mandatory and the patient must sign a separate informed consent form. If continuing the subject on study treatment is agreed then all study procedures, including tumour assessments, must be followed as scheduled (Table 19). In addition, after each tumour assessment, the investigators must confirm with the Novartis Global Clinical Lead that the subject is still benefitting from study treatment and therefore can continue receiving study treatment.

In addition, study treatment may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Request of the subject or his/her proxy
- Investigator's discretion
- Subject is lost to follow-up
- Study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF). Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

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

Note: If one study treatment is withheld or discontinued the other treatment may continue to be administered if appropriate. Subjects who discontinue one therapy but remain on the other will be considered to be on study treatment and should be assessed as indicated in the Time and Events (Table 19). Permanent discontinuation below references requires discontinuation of both study treatments.

All subjects who permanently discontinue all study treatment without disease progression will be followed for progression according to the Time and Events (Table 19).

All subjects who permanently discontinue study treatment will have monthly skin assessments, survival follow up and new anti-cancer therapy (including radiotherapy and surgery follow up) through month 6 after treatment discontinuation. If they start new anti-cancer therapy or at the end of the 6 month follow up visit, they will be followed every 12 weeks for survival follow up and new anti-cancer therapy (including radiotherapy and surgery) until death, have withdrawn consent or are lost to follow-up, or study closure. Study closure is defined by where all subjects still in follow up have had at least 3 years follow-up from the date of first dose of study treatment, whichever is earlier. Refer to specific guidelines in the Time and Events Table (Table 19).

4.2.2. Subject Completion and Withdrawal

A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period or has had at least 3 years follow-up from the date of first dose of study treatment at the end of the trial. The cause of death will be documented 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 closed or terminated.

5. STUDY TREATMENTS

5.1. Investigational Product

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

No special preparation of study medication is required. Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Material Safety Data Sheets (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

5.1.1. Dabrafenib

Dabrafenib study medication will be provided as 50 mg and 75 mg capsules. Each capsule will contain 50 mg or 75 mg of free base [redacted]

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

5.1.2. Trametinib

Trametinib study medication 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 [redacted]

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

5.2. Dosage and Administration

5.2.1. Dabrafenib and Trametinib Combination

- Dabrafenib, 150 mg, BID;
- Trametinib, 2.0 mg, once daily.

When administered in combination with trametinib, take the once-daily dose of trametinib at approximately the same time each day with either the morning dose or the evening dose of dabrafenib. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 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 dose as originally scheduled.

If administration of trametinib is interrupted or permanently discontinued, administration of dabrafenib may be continued. If administration of dabrafenib is interrupted or permanently discontinued, administration of trametinib may continue.

If a subject misses a dose of dabrafenib, the subject may take the dose immediately if the next dose is scheduled for at least 6 hours later. If the next scheduled dose of dabrafenib is due in less than 6 hours, the subject should skip the dose and resume dabrafenib dosing at the next scheduled dose. If a subject misses a dose of trametinib, the subject may take the dose immediately if the next dose is scheduled for at least 12 hours later.

1. See Section 5.8 for dose modification guidelines on dabrafenib and trametinib.

5.3. Handling and Storage of Study Treatment

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. Study medication is to be stored at the temperature specified on the label. Maintenance of a temperature log (manual or automated) is required. Access to and administration of dabrafenib and trametinib will be limited to the investigator and authorized site staff.

Procedures for final disposition of unused study treatments will be provided in the Study Procedures Manual (SPM).

5.4. Treatment Assignment

Subjects will be entered into the appropriate cohort based on the mutation and disease status. Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Each site will be given a subject number range. This can be obtained from your site monitor.

Upon obtaining consent from the subject for the study the subject will be registered into interactive voice response system (IVRS), by the investigator or authorized site staff to register and record subject activity. Study-specific instructional worksheets will be provided for the use of IVRS.

Once the target number of each cohort has been enrolled, that cohort will be closed to further enrolment and IVRS will no longer allow a subject to be entered.

5.5. Blinding

This is an open-labeled study.

5.6. 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 Novartis, 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.

5.7. Treatment Compliance

Subjects will be instructed to return treatment bottles at each visit. Compliance with study treatment will be assessed by querying the subject and through pill count at each visit. Compliance will be documented in the source documents and the 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. The investigator will make every effort to bring non-compliant subjects into compliance.

5.8. Dose Modification Guidelines

The severity of AEs will be graded using the CTCAE, version 4.0 www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. 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 and new primary RAS-mutation positive non- cutaneous malignancies(likely related to dabrafenib); and decreased LVEF, RVO (retinal vein occlusion), RPED, and pneumonitis (likely related to trametinib), the guidance suggests that both therapies be reduced, interrupted or discontinued 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 forClinically Significant	X	X	5.8.2
Guidelines for Specific Adverse EventsCardiovascular Adverse Events[a]			
LVEF		X	5.8.3.1
Hypertension	X	X	5.8.3.2
Prolonged QTc	X	X	5.8.3.3
Skin –Related Adverse Events (Except cuSCC)[b] or new primary melanomas			
Rash	X	X	5.8.4.1
Hand-Foot Skin Reaction	X	X	5.8.4.2
cuSCC	X	X	5.8.4.3
Other Adverse Events			
Pyrexia	X		5.8.5.1
Diarrhea	X	X	5.8.5.2
Renal Insufficiency	X	X	5.8.5.3
Visual Changes		X	5.8.5.4
Pneumonitis		X	5.8.5.5
Liver Chemistry StoppingCriteria	X	X	5.9.1

a. For subjects enrolled in France please see Appendix 9 and Appendix 11 for additional dose modification guidelines

b. Refer to Section 5.8.4.3 for management of cuSCC

5.8.1. Dose Levels of dabrafenib and trametinib

The dose levels for this study are provided in Table 4.

Table 4 Dose Level Reduction Guidelines

Dose Level	DabrafenibDose/Schedule	TrametinibDose/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

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.

If the subject requires both a dose reduction below 75 mg BID for dabrafenib and a dose reduction below 1 mg once daily for trametinib, the subject must discontinue the combination study treatment.

If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued but these 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 Novartis Global Clinical Lead is required to restart study treatment after ≥21 days of interruption.

5.8.2. General Guidelines for Clinically Significant Toxicities on the dabrafenib and trametinib combination treatment arm

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 study specific dose modification guidelines as in Table 3 are provided in Table 5 below. These guidelines are intended primarily for toxicities not easily managed with routine supportive care. For example, alopecia is not an indication for dose modification, nor is grade 2 nausea and vomiting that can be easily managed with anti-emetics.

These are general guidelines and investigators should always use clinical judgment in determining dose adjustments for any individual patient. Some toxicities may require hospitalization for stabilization, additional work-up, and consultation with a specialist before treatment can be restarted. Specific adverse events and recommended management include:

- **Pancreatitis** – In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

- **Uveitis:** 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.

- **Hyperglycemia**: Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in subjects with pre- existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

Table 5 Dose Modification Guidelines for Events Considered Related to Study Treatment (Dabrafenib and Trametinib Combination Treatment)

CTCAE Grade	Action and Dose Modification[a,b]
Grade 1 or Grade 2 tolerable	Continue study treatment at same dose level (no dose modification) and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	
1st, 2nd	Interrupt study treatment until toxicity resolves to ≤ grade 1 then restart at next lower dose level
3rd	Discontinue treatment.
Grade 4	
1st occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level or discontinue at discretion of investigator
2nd occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 or baseline then restart at two dose levels lower than the starting dose or discontinue at discretion of investigator and after discussion with the GLobal Clinical Lead.
3rd occurrence	Discontinue treatment

a. Treatment should be discontinued if more than 2 dose reductions are required

b. Approval from the Novartis Global Clinical Lead is required to restart study treatment after ≥21 days

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed 150 mg twice daily and the trametinib should not exceed 2 mg once daily.

5.8.3. Guidelines for Cardiovascular Adverse Events on the dabrafenib and trametinib combination treatment arm

Cardiovascular adverse events have been seen in subjects receiving either dabrafenib, trametinib or both in combination (see the trametinib, dabrafenib and combination IBs for additional information); [GlaxoSmithKline Document Number HM2009/00151/02 2011; GlaxoSmithKline Document Number CM2010/00010/02 2011 and GlaxoSmithKline Document Number 2011N126811_00.2012]

5.8.3.1. 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 19). All ECHOs will be collected; instructions are provided in AgMedNet Imaging Acquisition Guidelines. 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

Dose Modification Guidelines and Stopping Criteria for LVEF.

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 trametinib and repeat ECHO within 2 weeks[a,b] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) o Consult with the Novartis Global Clinical Lead and request approval for restart. o If approved, restart treatment with trametinib reduced by one dose level. o Repeat ECHO at 2 , 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not recover** within 4 weeks o Consult with cardiologist. o **Permanently discontinue trametinib.** o **Report as SAE.** o Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
Symptomatic[b,c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib.** • **Interrupt dabrafenib.**[d] • **Report as SAE.** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[b,d]

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; 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. If recurrent episodes of LVEF reduction occur in subjects receiving dabrafenib monotherapy, consult Global Clinical Lead.
c. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with Novartis Global Clinical Lead.

5.8.3.2. Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib.

Recommendations for blood pressure monitoring and management are provided in Section 5.8.3.2.1 and Section 5.8.3.2.2.

5.8.3.2.1. 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 subject's 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 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.

5.8.3.2.2. 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 in Table 7:

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**
• 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**
Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• **Permanently discontinue study treatment** • Continue follow-up per protocol.

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

5.8.3.3. 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 QTcB-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If event resolves, restart study treatment at lower dose level or current dose level[b] • If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist. • If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist.

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 Novartis Global Clinical Lead agree that the subject will benefit from further treatment.

French Only See Appendix 9, for Valvular Toxicity criteria

5.8.4. Guidelines for Skin-related Adverse Events on the dabrafenib and trametinib combination treatment arm

Cutaneous adverse events have been observed in subjects receiving dabrafenib, trametinib or both therapies in combination (see the Investigator Brochures for more information); [GlaxoSmithKline Document Number HM2009/00151/02 2011; GlaxoSmithKline Document Number CM2010/00010/02 2011 and GlaxoSmithKline Document Number 2011N126811_00.2012]. Recommendations for supportive care and guidelines for dose modifications are provided (Section 5.8.4.1, Section 5.8.4.2 and Section 5.8.4.3). 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 Novartis Global Clinical Lead may be required. In addition, the Sponsor may require biopsies of any new skin lesions especially those suspicious of cuSCC and keratoacanthomas (KA) for further study.

5.8.4.1. 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].

Table 9 Guidelines for Supportive Care of Rash

Type of Care	Action
Prevention/Prophylaxis Start from Day 1[a]	• 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
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. o Use mild-strength topical steroid (hydrocortisone 1% cream) or o Topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID)
Symptomatic Care	• 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

BID = twice daily; SPF = skin 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 adjustment for rash considered to be related to study treatment are provided in Table 10

Table 10 Management and Dose Modification Guidelines for Rash

CTCAE	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[b]**
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** o If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level o If norecovery 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**

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 Novartis Global Clinical Lead 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

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

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

Measures for PPES should include:

- Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles

- Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40 % cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5%

cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.

- Dose modification may also be required.

5.8.4.3. Guidelines for cuSCC and treatment emergent melanomas

Cutaneous squamous cell carcinomas and keratoacanthomas (KA) have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB); [GlaxoSmithKline Document Number 2011N126811_00.2012]. 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. Pathology report should be placed in subject chart.

New Primary Melanoma: New primary melanomas have been reported in patients treated with dabrafenib. These were identified primarily within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.

New primary cancers and treatment-emergent malignancies, with the exception of basal cell carcinoma (BCC) should be reported as a SAE. BCC should be reported as an AE or SAE based on the discretion of the investigator. A biopsy of the new malignancy should be taken, where possible, and results submitted to Novartis for further analyses. Testing of these biopsies may include RAS mutation testing and analysis of proteins related to the action of dabrafenib. Genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens may be performed, and would be restricted to the analysis of pathway mutations known to be associated with, and relevant to, BRAF-mutant tumors or pathway activation.
Evaluate for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of study treatment, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

5.8.5. Guidelines for Other Adverse Events of Special Interest on the dabrafenib and trametinib combination treatment arm

5.8.5.1. Guidelines for Pyrexia

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy, and is increased in incidence and severity in subjects receiving dabrafenib in combination with trametinib (see dabrafenib and dabrafenib and trametinib combination IBs); [GlaxoSmithKline Document Number CM2010/00010/02 2011 and GlaxoSmithKline Document Number 2011N126811_00.2012]. In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or

weakness.

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 anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia (see Section 5.8.5.3).
Guidelines regarding management and dose modifications for pyrexia considered to be related to study treatment are provided in Table 11

Table 11 Management and Dose Modification Guidelines for Pyrexiaa,[b]

Adverse Event	Adverse Event Management	Action and Dose Modification
Pyrexia[a]	AllEvents[b]: • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d] 1st Event[b]: • Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration or hypotension[e] 2nd Event[f] • Within 3 days of onset of pyrexia o Optimize anti-pyretic therapy o Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[f]	1st Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** 2nd Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]**

Adverse Event	Adverse Event Management	Action and Dose Modification
	SubsequentEvents: • Within 3 days of onset of pyrexia: ○ Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f] ○ If corticosteroids have been tapered and pyrexia recurs, restart steroids ○ If corticosteroids cannot be tapered consult Global Clinical Lead	SubsequentEvents: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level**[g] • If dabrafenib must be reduced to <75mg BID, permanently **discontinue dabrafenib. Trametinib may be continued.**

a. Pyrexia is defined as a body temperature equal to or above 38.5 Celsius or 101.3ºFahrenheit.
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
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (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. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia.
f. 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.
g. 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.

5.8.5.2. 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 12.

Table 12 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.**

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 Global Clinical Lead and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction

5.8.5.3. 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 13.

Table 13 Management and Dose Modification Guidelines for Renal **Insufficiency**

Serum CreatinineLevel	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 Novartis Global Clinical Lead. If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation. • 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: o Renal insufficiency persists despite volume repletion. o 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]

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 Section 5.8.5.1.

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 Novartis Global Clinical Lead is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

5.8.5.4. 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 [Refer to Section 7.4.5]. 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 14.

Table 14 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[bc]	• 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. • IfRPEDsuspectedordiagnosed: see RPED dose modification Table 15 below; **report as SAE if diagnosed.** • IfRVOdiagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2[c] and Grade 3[c]	• 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. • IfRPEDdiagnosed, see RPED dose modification Table 15 below; **report as SAE.** • IfRVOdiagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 4[c]	• 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.**

Abbreviations: RPED = retinal pigment epithelial detachment; 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.
c) Blood sample for PK analysis should be drawn as close as possible to the time of the event.

Table 15 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

a) Refers to CTCAE Version 4.0 'Retinopathy'

5.8.5.5. Guidelines for Pneumonitis

Pneumonitis has been observed in subjects receiving trametinib, dabrafenib, and in dabrafenib in combination with 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 trametinibat 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 trametinib until recovery to grade ≤1 • Restart with trametinib be 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 trametinib
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 trametinib until recovery to grade ≤1 • After consultation with medical monitor, trametinib may be restarted reduced by one dose level • If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib treatment
Grade 4	• Same as grade 3	• Permanently discontinue trametinib

BAL= broncioalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

5.9. Monitoring, Interruption, and Stopping Criteria for Hepatobiliary Events

5.9.1. Liver Chemistry Stopping Criteria

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

Liver chemistry stopping criteria 1-5 are defined as:

1. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured)

   NOTE: If serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥ 3xULN and bilirubin ≥ 2xULN. 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.

2. ALT ≥ 8xULN

3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

4. ALT ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia.

5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for >2 weeks.

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

- **Immediately discontinue subject from** study treatment
- Report the event to Novartis **within 24 hours** of learning its occurrence
- Complete the liver event CRF and 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.**

- NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. 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 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
- Follow up for overall survival is required following discontinuation from study treatment.
- Do not rechallenge with study treatment.

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 5.9.1.1), 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.

For subjects meeting any of the liver stopping 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 5.9.1.1)
- 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.

5.9.1.1. 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 10 days 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, pyrexia, rash or eosinophilia as relevant on the AE form. Please note that treatment with trametinib often associates with rash which is usually acneiform and affects the scalp, face, neck, chest, and upper back. Discuss with Novartis Global Clinical Lead as needed.
- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.
- Record alcohol use on the liver event alcohol intake 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, and 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 PCR of hepatitis D RNA virus (where needed) – as outlined in: www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.

5.9.1.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3xULN **but** <8xULN which exhibit a decrease to 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 Novartis Global Clinical Lead 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 values
- 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 6 for an algorithm of liver chemistry monitoring, stopping, and follow-up criteria.

5.9.1.3. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Treatment Appendix 7

Approval by Novartis for study treatment restart can be considered where:

The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.

If the restart/rechallenge is approved by Novartis in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

The subject must also provide signed informed consent specifically for the study treatment restart/rechallenge. Documentation of informed consent must be recorded in the study chart.

Study treatment must be administered at the dose specified by Novartis.

Subjects approved by Novartis for restart/rechallenge of study treatment must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

5.9.1.4. Drug Restart Following Transient Resolving Liver Events Not Related to Study Treatment

Approval by Novartis for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.
- If restart of study treatment is approved by Novartis in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by Novartis.
- Subjects approved by Novartis for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated, and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study treatment must be stopped.

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 with the exception of new anti-cancer therapy, if taken after study treatment discontinuation; these will be documented until study completion/withdrawal or death. 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 however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

While patients are on study treatment, **palliative** radiation therapy is permitted for non-target lesions that are either new or present at baseline.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib be held for seven days before and two days after XRT in subjects receiving dabrafenib monotherapy or in combination with trametinib. These recommendations can be modified based on the physician's assessment of the risk of

radiation skin injury.

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 dosing and for the duration of the study will not be allowed. The Novartis Global Clinical Lead can approve the use of a prohibited medication if it is required for a single use (such as for a procedure) while treatment with study drug is interrupted.

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: Patients 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 Novartis Global Clinical Lead is required in these situations. The list may be modified based on emerging data. Refer to the SPM for the most current list.

Investigators may be requested to perform additional safety tests during the course of the

Table 17 Prohibited Medications: Drugs that are Strong Inhibitors or Inducers of CYP3A and CYP2C8

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 trametinib or they may alter dabrafenib or trametinib concentrations:

- Drugs that are mild/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, and 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 medicationsA partial list of these medications is provided in Table 18. The list may be modified based on emerging data. Refer to the SPM for the most current list.
- Therapeutic level dosing of warfarin can be used with approval by the Novartis Global Clinical Lead and close monitoring of PT/INR by the site. Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib-mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued,

Investigators may be requested to perform additional safety tests during the course of the warfarin exposure may be increased. Thus, warfarin dosing may need to be adjusted based on PT/INR during and after treatment with dabrafenib. 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.

- Prophylactic tamoxifen may be used with the approval of the Novartis Global Clinical Lead. Tamoxifen is a substrate for CYP2C9 and CYP3A4. Co-administration of dabrafenib with tamoxifen may result in loss of efficacy of tamoxifen.

Table 18 Medications to be used with Caution

USE WITH CAUTION: Concentrations of these drugs may be increased or decreased by dabrafenib	
Class/TherapeuticArea	**Mild/Moderate CYP3A and CYP2C8**
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/TherapeuticArea	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19 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

Investigators may be requested to perform additional safety tests during the course of the

Class/TherapeuticArea	CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19 Substrates that May be Affected by Induction
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, digoxin, 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 as exposure to dabrafenib may be decreased	
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 Novartis Global Clinical Lead for clarification.

6.4. Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (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 Novartis Global Clinical Lead immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. Novartis does not recommend specific treatment. The investigator will use clinical judgment to treat any overdose. Haemodialysis is not expected to enhance the elimination of either dabrafenib or trametinib as both are highly bound to plasma proteins.

Decisions regarding dose modifications or interruptions should be made by the investigator in consultation with the Novartis Global Clinical Lead based on the clinical evaluation of the subject.

A plasma sample for PK analysis may be requested by the Novartis Global Clinical Lead on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 10 days from the date of the last dose of on-study dosing.

Investigators may be requested to perform additional safety tests during the course of the

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.

Procedures conducted as part of the subject's routine clinical management (e.g., imaging) and obtained prior to signing of informed consent may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe specified in the protocol. Central laboratory results for BRAF testing, coagulation, hematology, clinical chemistry, and serum pregnancy are required for eligibility.

Refer to the Time and Events (Table 19) for the timing of all assessments. Assessments must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. Details on efficacy and safety assessments are presented in Section 7.2 and Section 7.4, respectively. [redacted]

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) outlines study assessments and their timing.

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40 then monthly Until Treatment Disc	Treatment Disc[26]	Follow up[9] [27]	Conclusion
Informed consent	X														
Tumour tissue sample for BRAF V600 mutation[3]	X														
Intracranial target and non –target lesion assessment and response[21] [27]	X		X	X		X		X		X		X	X		
Extracranial target and non-target lesion assessment and response[22] [27]	X		X	X		X		X		X		X	X		
Inclusion / exclusion criteria[4]	X														
Register subject	X														
Chemistry and Haematology[5]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test[6]	X														
Coagulation	X														
Physical examination	X												X		
Height[7]	X														
Weight, Temp, BP, Resp and HR[8]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographic data	X														
Disease characteristics[9]	X														
Prior anti-cancer therapy, radiotherapy and surgical procedures	X														
Past and current medical conditions, family history	X														
Alcohol consumption	X														
Past and current tobacco consumption	X														
Cytokine[12]	X		X												
Neurological assessment[13]	X		X	X		X		X		X		X	X		

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40 then monthly Until Treatment Disc	Treatment Disc[26]	Follow up[9, 27]	Conclusion
Ophthalmic Examination[14]	X		X					X							
Dermatologic skin assessment[15]	X		X	X	X	X	X	X	X	X	X	X	X		
Dispense oral study treatment and assess treatment compliance[16]		X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[17]	X		X	X	X			X			X		X		
ECHO[18]	X		X		X			X			X		X		
Concomitant medications[25]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood products and blood supportive care products	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up monthly dermatologic skin assessment contact, anti-cancer therapy[20]														X	
Survival Follow-up, anti-cancer therapy[24]														X	
Subject completion or withdrawal															X
Death record (if applicable)															X

[redacted]; MRI = magnetic resonance imaging; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; ECHO = echocardiogram; Unshc = unscheduled; Disc = discontinuation; Fwp = follow-up; Conc = conclusion

1. For Week 1 visit and thereafter, all visits will have a window of ± 3 days and scans will have ± 7 days for flexible scheduling.All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments.

2. Screening procedures may be performed 14 days prior to first dose of study drug, except for tumour assessments which may be performed 28 days prior to first dose of study

drug, and echocardiograms and ECGs which may be performed 35 days prior to the first dose of study drug. AllsSubjects who have undergone local BRAF testing and who are BRAF V600 D/E/K/R mutation positive, may begin screening procedures.For ALL cohorts, sites still need to send in tissue sample to the central laboratory for retrospective testing. Beginning with Day 1 visit, all visits have a ± 3 day visit window and scans will have ± 7 days for flexible scheduling.

3. BRAF tumour tissue at screening will be centrally tested all subjects regardless of cohort via Central Laboratory. Subjects who qualify enrollment , must send tumour tissue sample to the central laboratory for retrospective confirmation and additional biomarker testing within 21 days of visit. Archival tissue samples are sufficient for molecular testing, but fresh tumour biopsies are also acceptable.
4. Only subjects who meet all inclusion and exclusion criteria will be eligible to enter into the study. No waivers can be granted.
5. Chemistry and haematology evaluations are performed by the central laboratory. Subjects will be dosed based on the central laboratory results. Screening laboratory assessments performed within 14 days of first dose of study drug do not need to be repeated.
6. 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.
7. Height Measurements should be in metric scale and required only at screening.
8. Weight, body temperature, blood pressure, heart rate, and respirations are to be recorded at each visit.
9. Disease characteristics: Record data in eCRF on initial diagnosis: Tumour Classification (cutaneous, etc), date of intracranial and date of extracranial initial diagnosis, stage at initial diagnosis, TNM staging at initial diagnosis, histology at initial diagnosis; Record data on Last Recurrence: date of last recurrence of intracranial and extracranial disease; Record data at Screening: Date of Stage at Screening, Stage at Screening, TNM staging at Screening.
10. [redacted] Any tissue remaining after the screening BRAF tumour testing for the central and retrospective confirmation (Cohorts A, B, C, D) will be used for biomarker testing.
11. [redacted]
12 Cytokines: A blood sample for potential analysis of cytokines is mandatory at Screening and at week 4. Subsequent cytokine samples should also be collected if indicated. (See Section 5.8.5.1 Management of Guidelines for Pyrexia).
13. Neurological assessments will remain at every 12 weeks starting at Week 40 even though the subjects are required to have monthly visits.
14. Ophthalmology Exam: An ophthalmic examination will be performed prior to first dose (baseline) and week 4, week 24 and annually thereafter unless clinically indicated sooner.Additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.4.5 for details
15. Dermatologic skin assessments should be performed by the same Investigator or dermatologist at each visit to ensure consistency of assessments; Use of a dermatologist is

preferred but not mandatory. Dermatologic skins assessments are required monthly while on study treatment and monthly for a 6-month time frame after discontinuation of study treatment as per the European label. As part of the skin assessments, Full-body photography of subjects at screening is recommended with photographs of any new or changing lesions recommended at subsequent visits.

16. Dispensation of Study Treatment: Dispense a 4-6 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays and/or dose escalations.

17. ECG assessments must be performed within 35 days prior to first dose. Thereafter, ECG assessments will be conducted at weeks 4, 8 and 12 and then every 12 weeks up to andincluding discontinuation visit. 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. Measurements and calculations that must be collected are as follows: Date and time of ECG, heart rate, PR Interval, QRS duration, QRS Axis, Uncorrected QT interval, Corrected QT interval (QTc), Method of QTc calculation (i.e. Bazett)

18. Echocardiogram screening assessments (moving videography) must be performed within 35 days prior to first dose and at weeks 4,12 and then every 12 weeks up to and including discontinuation visit. An echocardiogram will need to be performed at study discontinuation unless one has been performed within the last 8 weeks. Please see Section 7.4.9 for LVEF guidelines for study drug management and requirements for ECHO Scans.

19. Adverse events and Serious Adverse Events will be recorded form the time of first dose of study treatment is administered until 30 days after discontinuation of study treatment. All SAEs assessed as related to study participation (e.g. related to study procedures) should be collected from time of informed consent. Please refer to section 7.4.2.6 for reporting timelines.

20. **Skin Exam Follow-up contact**: Every month up to and including month 6 following study treatment discontinuation (or until new anti-cancer therapy initiated),, all subjects who permanently discontinue study treatment will be followed for survival, dermatologic skin assessments and new anti-cancer therapies (including radiotherapy and surgery). The date of the visit must be recorded.

21. Intracranial Tumour assessment is conducted with contrast-enhanced MRI and applied using modified RECIST 1.1 criteria. Target and non-target lesions must be identified at time of screening scan and the same lesions must be re-assessed at each restaging scan. Brain scans should occur at 4 weeks, 8 weeks, and then every 8 weeks thereafter until week 40. At week 40, scans may occur every 12 weeks, unless response confirmation is indicted. Complete response/partial response confirmation assessments must take place at least 4 weeks after the initial response. If the last radiographic assessment for intracranial disease was more than 8 weeks prior to discontinuation from study and progressive disease has not been documented, disease assessment should be obtained at the time of study discontinuation.

22. Extracranial tumour assessment is conducted using RECIST 1.1 criteria. Target and non-target lesions must be identified at time of screening scan and the same lesions must be re-assessed at each restaging scan. Scans should occur at 4 weeks, 8 weeks and then every 8 weeks thereafter until week 40. At week 40, scans may occur every 12 weeks, unless response confirmation is indicated. Complete response /partial response confirmation assessments must take place at least 4 weeks after the initial response. If the last radiographic assessment for extracranial disease was more than 8 weeks prior to discontinuation from study and progressive disease has not been documented, disease assessment should be obtained at the time of study discontinuation.

23. [redacted]

24. **Survival Follow-up contact**: All subjects who permanently discontinue study treatment will be followed for survival follow up and new anti-cancer therapy, every 12 weeks (±7

days) until death, subject withdrawal or study closure. Follow up contact may include clinic visits, telephone contacts or email communications. The date of contact must be recorded.

25. Document all medications taken from the time of screening until 30 days after the last dose of study treatment with the exception of new anti-cancer therapy, if taken after study treatment discontinuation; these will be documented until study completion/withdrawal or death. Any concomitant medication(s), including dietary supplements, taken during thestudy will be recorded in the eCRF

26. The **treatment discontinuation visit** should be performed within 30 days of the subject's last dose. If a subject discontinues study treatment at a scheduled visit, the assessments performed at that visit can be used to fulfill the treatment discontinuation visit requirements. Laboratory assessments and other required assessments do not need to be repeated at the discontinuation visit if they were performed within 14 and 30 days, respectively, of the discontinuation visit. If the last disease assessment was >8 weeks prior to study withdrawal and disease progression had not been documented, a disease assessment should be obtained.

27. **Progressive Disease Follow Up (if applicable)**: For those subjects who permanently discontinue study treatment without progressive disease will have radiographic disease assessments performed on the same assessment schedule noted in the Time and Events (Table 19) every 8 weeks until Week 40 and then every 12 weeks thereafter until disease progression, start of new anti-cancer therapy or death. The date of the visit must be recorded.

***** Special Note*** Dose Modification Guidelines may require blood samples that are not indicated in this time and event section Table 19. If a patient has a dose modification, refer to the specific Dose Modification Guideline section of the protocol for further recommendations and requirements of blood samples.**

7.1. Critical Baseline Assessments

Efficacy assessments conducted at baseline are described in Section 7.2.2, tumour biomarker analysis are described in Section 7.6. Safety assessments conducted at baseline and during treatment are described in Section 7.4. Cardiovascular medical history/risk factors will be assessed at baseline.

7.1.1. Baseline Documentation of Intracranial Target and Non-Target Lesions

- All baseline lesion assessments must be performed 28 days prior to the first dose of study treatment.
- Measurable and non-measurable intracranial (i.e. brain parenchyma) lesions (refer to Section 7.3.1 for study definition of measurable intracranial lesions) up to a maximum of 5 lesions should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (by imaging techniques).

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

  Note: Measurable intracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.
- All other intracranial lesions should be identified as non-target and should alsobe recorded at baseline. Measurements of non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.1.2. Baseline Documentation of Extracranial Target and Non-Target Lesions

- All baseline lesion assessments must be performed 28 days prior to the first dose of study treatment.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm 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.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved extracranial organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for

accurate repeated measurements (either by imaging techniques or clinically).

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

Note: Measurable extracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- 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.

- 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

For this study, efficacy comprises intracranial, extracranial and overall response and disease control, duration of all responses, PFS, and OS. Intracranial, extracranial and overall response assessments conducted at baseline and during the study are described in Section 7.2. Intracranial, extracranial, and overall response will be assessed by RECIST 1.1 with modifications.

7.2.1. Efficacy Endpoints

The primary efficacy endpoint of this study is the intracranial response rate (IR) in BRAF V600E mutation positive subjects (Cohort A). The IR is defined as the percentage of subjects whose intracranial response is a confirmed Complete Response (CR) or Partial response (PR) assessed by investigator using modified RECIST 1.1 criteria.

7.2.1.1. Secondary Endpoints

The following endpoints will be assessed as secondary endpoints in all cohorts (unless stated otherwise)

- IR in Cohort B, C and D
- Intracranial disease control (IDC)
- extracranial response rate (ERR)
- overall response rate (ORR)
- duration of intracranial, extracranial and overall response (DIR, DER and DOR respectively)
- progression-free survival (PFS)

- overall survival (OS) and long-term (particularly 3-year) OS
- Safety of dabrafenib and trametinib combination therapy

[redacted]

7.2.2. Efficacy Assessment

Disease progression and response evaluations for ***intracranial*** and ***extracranial*** disease will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [Eisenhauer, 2009]; Minor modifications will be applied to the assessment of intracranial lesions:

- **General**: target lesions should be representative of the subject's baseline tumour burden and should be selected based on their size (i.e. lesions with the longest diameter) and their suitability for accurate repeat assessment.
- **Intracranial lesions**: (the modifications to RECIST 1.1. impact the number and the minimal size of the target lesions selected at baseline) up to five lesions should be selected as target lesions; all brain lesions in excess of these five target lesions have to be regarded as non-target lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension with the longest diameter ≥ 5 mm when evaluated with contrast-enhanced MRI.

  Contrast-enhanced MRI is the only imaging modality accepted for the assessment of intracranial lesions.
- **Extracranial lesions**: up to two lesions per organ representative of all involved organs should be selected as target lesions; the total number of target lesions should not exceed five and all lesions in excess of these five target lesions have to be regarded as non-target lesions.

See the Time and Events (Table 19) for the schedule of intracranial and overall efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions. For post baseline assessments, a window of ±3 days is permitted to allow for flexible scheduling.

The following assessments are required at baseline:

- Contrast enhanced brain MRI
- CT for chest/abdomen/pelvis or MRI for abdomen/pelvis
- Clinical assessment for palpable and/or cutaneous lesions using callipers or photography.

As outlined in (Table 19) at specific post baseline assessment time points, repeat

evaluations of the target- and non-target lesions identified by the baseline MRI / CT scans and clinical assessments (calliper, photography) are required.

Confirmation of intracranial, extracranial and overall CR and PR is required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (i.e., regularly scheduled study visit evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments). If the criteria for a CR or PR are not confirmed, then stable disease (SD) can be considered the best response if it has been demonstrated for a minimum of 8 weeks.

7.2.2.1. Assessment Guidelines

For intracranial lesion assessments:

- Contrast-enhanced MRI must be used throughout the study. Contrast-enhanced MRI is the only imaging modality accepted for the assessment of intracranial lesions.
- The technical specification of the MRI scanning sequences should be optimised for the evaluation of brain lesions which 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].
- As a modification to RECIST 1.1, target lesions as small as 5mm may be selected, however the scanning should be in accordance with RECIST 1.1: contiguous slices of maximum thickness corresponding to half the size of the lesion. [Eisenhauer, 2009] All measurements must be taken and recorded in millimetres (mm), using a ruler or callipers.
- Refer to Image Acquisition Guidelines (Brain MRI) for slice thickness requirements that should be performed in accordance with RECIST 1.1 criteria.

For extracranial lesion assessments:

- Contrast-enhanced CT (preferred) or MRI is recommended. 5 mm contiguous slices are recommended. The minimum size of a measurable extracranial 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 optimised 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].
- Clinical examination: Skin nodules or palpable lesions will only be considered measurable when they are superficial. In the case of skin lesions, documentation by colour photography (cameras will be provided by the sponsor from central vendor) is necessary. For both skin nodules and palpable lesions, size measurements using a ruler/calliper are required. [Eisenhauer, 2009].

- X-ray should not be used for target lesion measurements owing to poor lesion definition.
- 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 is generally not suitable for ongoing assessments of disease. However 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. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- 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 CRF.

7.2.2.2. Follow-Up Assessments for Subjects Permanently Discontinued from Study Treatment

All subjects who permanently discontinue study treatment will have monthly skin assessments, survival follow up and new anti-cancer therapy (including radiotherapy and surgery follow up) through month 6 after treatment discontinuation. If they start new anti-cancer therapy or at the end of the 6 month follow up visit, they will be followed every 12 weeks for survival follow up and new anti-cancer therapy (including radiotherapy and surgery) until death or study completion. In addition, those subjects who permanently discontinue study treatment without progressive disease will have radiographic disease assessments performed on the same assessment schedule noted in the Time and Events (Table 19) every 8 weeks until Week 40 and then every 12 weeks thereafter until disease progression, start of new anti-cancer therapy or death.

7.2.2.3. Assessment of Subject Completion

If the last radiographic assessment for intracranial disease, extracranial disease or both was more than 8 weeks prior to discontinuation from study and progressive disease has not been documented, the appropriate disease assessment should be obtained at the time of study discontinuation.

7.3. Guidelines for Evaluation of Disease

7.3.1. Measurable and Non-Measurable Definitions for Intracranial Disease

Measurable intracranial lesion: A lesion that can be accurately measured in at least one dimension with the longest diameter ≥ 5 mm when evaluated with contrast-enhanced MRI.

Non-measurable intracranial lesion: All other lesions including lesions too small to be considered measurable (longest diameter < 5 mm).

Measurable intracranial disease: The presence of at least one measurable lesion.

Non-Measurable only intracranial disease: The presence of only non-measurable lesions which would exclude the subject from participation in this study.

7.3.1.1. Measurable and Non-Measurable Definitions for Extracranial Disease

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

- ≥ 10 mm with MRI or CT with a recommended contiguous slice thickness of 5 mm. i.e. minimum size of measurable baseline lesion should be twice the slice thickness
- ≥ 10 mm calliper/ruler measurement or medical photography.

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

Non-Measurable only extracranial disease: The presence of only non-measurable lesions.

7.3.2. Response Criteria

7.3.2.1. Intracranial Response (IR) - Evaluation of Intracranial Target Lesions

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

- Complete Response (CR): Disappearance of all target lesions.
- 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 Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- If an intracranial target 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.

7.3.2.2. Intracranial Response (IR) - Evaluation of Intracranial Non-Target Lesions

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

- Complete Response (CR): The disappearance of all non-target lesions.
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) identified as a site of disease.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No intracranial non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- Intracranial non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

7.3.2.3. Extracranial Response (ER) - 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.
- 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 Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- If an extracranial target 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.

7.3.2.4. Extracranial Response (ER) - Evaluation of Extracranial Non-Target Lesions

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

- Complete Response (CR): The disappearance of all non-target lesions.
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) identified as a site of disease.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No extracranial non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- Extracranial non-target lesions which are not assessed at a particular timepoint based on the assessment schedule should be excluded from the response determination (that is., the non-target response does not have to be "Not Evaluable" if the non-target lesions were not scheduled for assessment at a particular timepoint).

7.3.2.5. Overall Response - Evaluation of Target Lesions

Overall target lesion response is based on all (that is, intracranial and extracranial) target lesions, up to 10 total. The sum of longest diameters of all target lesions will be used to determine overall response. Definitions for assessment of response for target lesion(s) based on modified RECIST 1.1 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 thesmallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.

- Not Applicable (NA): No extracranial 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 not assessed, sum of the diameters cannot 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 target 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 target 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.

7.3.2.6. Overall Response - Evaluation of Non-Target Lesions

Overall non-target lesion response is based on all (that is, intracranial and 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): **No intracranial or extracranial non-target** lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five 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 tumour burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease considerations should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions which are not assessed at a particular timepoint based on the assessment schedule should be excluded from the response determination (i.e., non-target response does not have to be "Not Evaluable").

7.3.2.7. New Lesions

New intracranial or extracranial 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.

7.3.2.8. Evaluation of Intracranial Response

Table 20 presents the intracranial response at an individual time point for all possible combinations of tumour responses in target and non-target intracranial lesions with or without the appearance of new intracranial lesions for subjects with measurable (as defined in Section 7.3.1) intracranial disease at baseline.

Table 20 Evaluation of Intracranial Response

Target Lesions	Non-Target Lesions	New Lesions	Intracranial Response
CR	C	No	CR
CR	Non-CR/Non-PD or	No	PR
PR	Non-PD or NA or	No	PR
SD	Non-PD or NA or	No	SD
NE	Non-PD or NA or	No	NE
PD	A	Yes or No	PD
Any	P	Yes or No	PD
Any	A	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.

7.3.2.9. Evaluation of Extracranial Response

Table 21 presents the extracranial response at an individual time point for all possible combinations of tumour responses in target and non-target extracranial lesions with or without the appearance of new extracranial lesions for subjects with measurable (as defined in Section 7.3.1) extracranial disease at baseline.

Table 21 Evaluation of Extracranial Response

Target Lesions	Non-Target Lesions	New Lesions	Extracranial Response
CR	C	N	CR
CR	Non-CR/Non-PD or	N	PR
PR	Non-PD or NA or	N	PR
SD	Non-PD or NA or	N	SD
NE	Non-PD or NA or	N	NE
PD	A	Yes or No	PD
Any	P	Yes or No	PD
Any	A	Ye	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 that may require discontinuation of study 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 if study treatment is discontinued.
- 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.

7.3.2.10. Evaluation of Overall Response

Table 22 presents the overall response at an individual time point for all possible

combinations of tumour responses in all intracranial and extracranial target and non-target lesions with or without the appearance of new lesions.

Table 22 Evaluation of Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	C	No	CR
CR	Non-CR/Non-PD or	No	PR
PR	Non-PD or NA or	No	PR
SD	Non-PD or NA or	No	SD
NE	Non-PD or NA or	No	NE
PD	A	Yes or No	PD
Any	P	Yes or No	PD
Any	A	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 that may require discontinuation of study 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 if study treatment is discontinued.
- 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.

7.3.2.11. Evaluation of Best Intracranial, Extracranial and Overall Response

The best intracranial, extracranial, and overall response is the best response recorded from the start of the treatment until intracranial, extracranial, and overall disease progression and will be determined programmatically by Novartis based on the investigators assessment of intracranial, extracranial, and overall response at each time point.

- To be assigned a status of intracranial, extracranial, overall stable disease (SD) follow-up disease assessment must have met the SD criteria at least once after first dose of study treatment at a minimum interval of 8 weeks.
- If the minimum time for SD is not met, best response will depend on the 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.

Confirmation Criteria:

- To be assigned a status of intracranial, extracranial, or overall PR or CR, a confirmatory disease assessment should be performed not less than 4 weeks after the

criteria for response are first met.

7.4. Safety

7.4.1. Safety Endpoints

The secondary objectives of the study include characterizing the safety of dabrafenib and trametinib combination therapy. As a consequence, clinical assessments including vital signs and physical examinations, 12-lead ECG, ECHO, chemistry and haematology laboratory values, and AEs will be monitored and evaluated.

7.4.2. 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 as outlined in Section 7.4.2.1 and Section 7.4.2.2 respectively.

7.4.2.1. Definition of an AE

Any untoward medical occurrence in a patient 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 (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Any new primary cancer must be reported as an SAE.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity 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* will not 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 fulfill 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 leads 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

7.4.2.2. Definition of a SAE

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

- Results in death
- 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.

- 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 out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills 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.
- 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.

- Is a congenital anomaly/birth defect.
- Medical or scientific judgement 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.
- Protocol-specific SAEs:
    - All events of possible drug-induced liver injury with hyperbilirubinae defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients 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.
    - Any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and new primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.
    - Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance (Section 5.8.3.1).
    - Retinal pigment epithelial detachment (RPED) or retinal vein occlusion (RVO)

7.4.2.3. 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 felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs, in accordance with the definitions provided.

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.

7.4.2.4. *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. If however, 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 disease progression, then this must be reported as an SAE.

7.4.2.5. *Time Period and Frequency for 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.

All SAEs and adverse events (AEs) will be collected from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment regardless of initiation of a new anti-cancer therapy or transfer to hospice.

From the time a subject consents to participate in and completes the study (See Section 4.2), all SAEs assessed as **related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to Novartis as indicated in Table 23.

After study treatment discontinuation, 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 from the last dose of study treatment, the investigator may report any AE that he/she believes is **possibly related** to study treatment.

7.4.2.6. *Prompt Reporting of Serious Adverse Events and Other Events to Novartis*

Serious adverse events (SAEs), pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to Novartis as described in Table 23 once the investigator determines that the event meets the protocol-definition for that event.

Table 23 Time Frames for Reporting SAEs and Other Events

	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
Pregnancy	24 hours	Pregnancy notificatio	2 weeks	Pregnancy follow-up form
Cardiovascular or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Liver Chemistry Abnormalities:				
ALT ≥ 3 x ULN **PLUS** total bilirubin ≥ 2 x ULN (> 35% direct) or ALT ≥ 3 x ULN and INR > 1.5, if INR measured[a]	24 hours[b]	SAE data collection tool, liver event eCRF form, and liver imaging and/or biopsy	24 hours	Updated SAE data collection tool and updated liver event eCRF form[c]
ALT ≥ 8 x ULN; ALT ≥ 3 x ULN with hepatitis or rash or ≥ 3 x ULN but < 5 x ULN that persists ≥ 4 weeks	24 hours[b]	Liver event eCRF form[c]	24 hours	Updated liver event eCRF form[c]
ALT ≥ 5 x ULN **PLUS** total bilirubin < 2 x ULN	24 hours[b]	Liver event eCRF form does not need completing unless elevations persist for 2	24 hours	
ALT ≥ 5 x ULN **PLUS** total bilirubin < 2 x ULN that persists	24 hours[b]	Liver event eCRF form[c]	24 hours	Updated liver event eCRF form[c]
ALT ≥ 3 x ULN but < 5 x ULN **PLUS** total bilirubin < 2 x ULN	24 hours[b]	Liver event eCRF form does not need completing unless elevations persist for 4 weeks or subject cannot be		

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; eCRF = electronic case report form; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

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

In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.

Liver chemistry stopping, follow-up, and monitoring criteria are provided in Appendix 7. Methods for detecting, recording, evaluating, and following-up on AEs and SAEs and procedures for completing and transmitting SAE reports to Novartis are provided in the SPM.

7.4.2.7. Regulatory reporting requirements for SAEs

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

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

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

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

7.4.3. Pregnancy

7.4.3.1. Pregnancy Testing 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 tubal occlusion, 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 <40 pg/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.

Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and agree to use effective contraception, Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below throughout the treatment period and until 4 months after the last dose of study treatment.

Novartis 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.
- Male partner sterilization prior to the female subject's entry, and this male is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 7 days prior to enrollment, throughout the treatment period, and for at least 4 months after the last dose of study treatment. Abstinence is only acceptable when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods, etc) and withdrawal are not acceptable methods of contraception.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

Note: 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 prior to 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.

If a subject becomes pregnant during the treatment period of the study, the study treatments should be stopped immediately.

Note: French/German subjects: no contraception for men is required

7.4.3.2. 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 Novartis within 24 hours 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 study treatment, must be promptly reported to Novartis.

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 Novartis as described above.

7.4.4. Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule (Table 19). If any local laboratory assessments are undertaken during the course of the trial and they result in a change in patient management (for example SAE or AE or dose modification) the assessment data must be recorded in the patients CRF.

Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples and a list of reference ranges for all safety parameters will be provided by the central laboratory in a separate instruction manual.

Laboratory assessments must be processed through [redacted] Central Laboratories. If an investigator feels that that safety of the patient is jeopardized by waiting for central labs to return, local labs may be drawn in addition to the central lab for treatment purposes. If any additional laboratory assessments are performed at the institution's local laboratory, refer to the SPM for appropriate processing and handling of samples to avoid duplication and/or additional blood draws.

If local laboratory assessments document a need for dose modification/interruption, an AE or an SAE, these assessments should be entered into the eCRF per the eCRF completion guidelines.

Clinical chemistry and haematology parameters to be tested are listed in Table 24. Female subjects will have a serum pregnancy test at Screening; urine pregnancy testing may be done during study treatment, if necessary.

Table 24 Clinical Chemistry and Hematology Parameters

Clinical Chemistry Parameters
Albumin
Alkaline Phosphatase
Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT)
Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT)
Gamma-Glutamyl Transpeptidase (GGT)
Blood Urea Nitrogen (BUN) or urea
Calcium Creatinine[c]
Glucose (random)
Lactate Dehydrogenase (LDH)
Magnesium
Phosphate
Potassium
Sodium
Total Bilirubin[b]
Total Protein
Hematology Parameters
White Blood Cell (WBC) Count (absolute)
Absolute neutrophil (ANC) count
Hemoglobin
Hemoglobin A1C
Hematocrit
International Normalized Ratio (INR; at Screening only)[a]
Platelet Count
Prothrombin Time (PT; at Screening only)[a]
Partial Thromboplastin Time (PTT; at Screening only)[a]
Automated WBC Differential (expressed as %):
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils
Other tests

Amylase and lipase [monitor via local laboratory where appropriate to evaluate certain AEs (i.e., abdominal pain, pancreatitis, etc.)]
serum β-hCG (human chorionic gonadotrophin)
For subjects with a history of chronic HBV and/or HCV, the following tests will be performed at Screening: • Viral hepatitis serology; • Hepatitis B surface antigen and Hepatitis B core antibody (IgM); and/or • Hepatitis C RNA

a. Coagulation panel to be done at Screening only.
b. Bilirubin fractionation is recommended if total bilirubin is > 2 x the upper limit of normal (ULN).
c. If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockcroft-Gault formula [Appendix 3].

7.4.5. Ophthalmic Examination

Subjects are required to have a standard ophthalmic examination conducted by an ophthalmologist prior to first dose (baseline), week 4(Month 1), week 24 (Month 6) and annually thereafter unless clinically indicated sooner. Additional ophthalmic examinations will be performed only as symptomatically warranted.

The exam will include visual acuity (best corrected), tonometry (intraocular pressure measurement), visual field examination, slit lamp biomicroscopy of the anterior segment (with special attention to inflammation) and the posterior segment, and indirect fundoscopic examination with special attention to possible retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected or noted. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

7.4.6. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at Screening). Body temperature, weight and height measurements should be recorded in the metric scale.

See Section 5.8.3.2.1 for details on monitoring of hypertension.

7.4.7. Physical Examinations

Complete physical examination is indicated at screening and discontinuation and will include assessments of eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease, and of the head, neck, ears, nose, mouth, throat, thyroid, lymph nodes, extremities, and a full skin exam to assess cutaneous malignancies and proliferative skin diseases. Dermatologic skin exams may be referred to a Dermatologist, if needed.

If possible, the same physician should perform each examination for the duration of the study to ensure consistency between evaluations (i.e., if the subject is referred to a Dermatologist for the Screening examination, the Dermatologist should do all follow-up dermatologic skin assessments).

Neurological exams should be performed by the Investigator as per the schedule in (Table 19). Alternatively, subjects may be referred to a Neurologist, 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

Neurological Symptoms may include the following (but are not limited to):

- 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

7.4.8. Electrocardiograms (ECG)

Twelve (12)-lead ECGs will be obtained using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, RR and QTcB intervals.

At each assessment, a single 12-lead ECG will be performed by qualified site personnel after the subject has rested in a semi-recumbent or supine position for at least 5 minutes.

Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the Sponsor if necessary. See Section 5.8.3.3 for dose modifications guidelines if QTc prolongation occurs.

7.4.9. Echocardiograms (ECHO)

Echocardiograms (ECHO) will be performed to assess cardiac ejection fraction. The echocardiographer's evaluation should include an evaluation for left ventricular ejection fraction. Copies of all ECHO scans will be centrally collected for review. Collection details will be AgMedNet Imaging Acquisition Guidelines.

[redacted]

[redacted]

[redacted]

7.6.2. BRAF mutation assay

Subjects in ALL cohorts may be enrolled based on certified assay local test results. [redacted]

The tissue requirements for the BRAF mutation assay evaluating patient eligibility for the study may be provided in the SPM.

Additional biomarkers related to the activity of dabrafenib and trametinib may also be analyzed as described in Section 7.6.

[redacted]

8. DATA MANAGEMENT

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets that support the protocol objectives.

For this study, subject data will be entered into the electronic case report forms (eCRFs), transmitted electronically to Novartis (or designee), and be combined with data from other sources in a validated data system.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures with the objective of resolving errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. All AEs and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom medication dictionary.

The eCRFs (including queries and audit trails) will be retained by Novartis, and copies will be sent to the investigator to maintain as the investigator copy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses

The primary efficacy objective of this study is to assess the intracranial response (IR) rate in BRAF V600E mutation positive subjects assessed by Investigators using modified RECIST 1.1 criteria for Cohort A:

- Cohort A: 75 Subjects who are treatment-naive for brain metastases,

asymptomatic and stable on corticosteroids.

The study is designed to provide evidence to support the null hypothesis, H_0: IRR $\leq$ 35% or to reject it in favor of the alternative hypothesis, H_A: IRR $\geq$ 50% for BRAF V600E mutation-positive subjects in Cohort A.

The null hypothesis is based on results of BRF113929 (BREAK-MB), a study of dabrafenib in two cohorts of patients with histologically confirmed metastatic melanoma to the brain [Long, 2012]. The IR in patients with no prior local treatment for brain metastases was 39%; in patients with prior local treatment, the IR was 31%.

While the BREAK-MB trial demonstrated activity in patients with active brain metastases, all of the patients in that trial were asymptomatic from CNS disease. Vemurafenib, another elective inhibitor of oncogenic BRAF kinase that specifically targets cancer cells harboring mutated BRAFV600, was recently studied in a cohort of 24 patients with symptomatic brain metastases. Median PFS in the brain was 4.3 months and for other sites was 4.6 months. In addition, an improvement in performance status (decrease from baseline of at least 1 point of ECOG score) was seen in 83.3% of patients, and 66.7% reported a reduction of ≥30% (compared with baseline dose) or complete discontinuation of corticosteroids.

This current trial is expected to build upon the current body of evidence of targeted therapy in melanoma brain metastases through an evaluation of the combination of dabrafenib and trametinib in patients with V600-mutation positive melanoma brain metastases.

The alternative hypothesis was selected as the IR that would be clinically relevant for this combination therapy. The study is designed to have 82% statistical power to detect an IR of 50% in V600E mutation-positive subjects who receive dabrafenib in combination with trametinib in Cohort A.

This hypothesis will be tested using a one-sided test for superiority with α=0.05. There will be no other testing; therefore, there will be no adjustment of the Type I error for multiple testing.

9.2. Study Design Considerations

9.2.1. Sample Size Assumptions

The sample size is based on the hypothesized improvement in intracranial response over study GSK BRF113929 (BREAK-MB) in Cohort A. 35% intracranial response (IR) is not clinically significant over existing therapies. An intracranial response (IR) of 50% is of clinical significance.

For the primary endpoint cohort (A), 75 BRAF V600E mutation positive subjects will be enrolled. At the time of the primary efficacy analysis, at least 33 subjects with an IR (44%) are required to establish that the evidence does not support the null hypothesis.

The sample size is based on a one-sided superiority trial of binomial proportions with an overall Type I error rate 0.05 incorporating an interim analysis with alpha-spending function proposed by Lan; 1983 with Pocock Boundary. The null hypothesis in Cohort A

will be tested assuming IR of 35% against an IR of 50% using a one-sided test for superiority with a=0.05 and power=82%. Sample Size Sensitivity

Table 25 shows statistical power for the test of the null hypothesis in Cohort A under the assumed IR of 35% and for scenarios where the alternative response rate is lower and higher, assuming 75 BRAF V600E mutation positive subjects.

Table 25 Statistical Power Scenarios with 75 BRAF V600E Mutation Positive **Subjects in Cohort A**

IR	Statistical Power
40%	22.9%
45%	53.8%
50%	82.1%
55%	96.2%

9.2.2. Sample Size Re-estimation

No formal sample size re-estimation is planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All subjects who receive at least one dose of study medication will comprise the All Treated Subjects (ATS) population.

The V600E population will comprise all BRAF V600E mutation positive subjects who receive at least one dose of study treatment.

The V600D/K/R population will comprise all BRAF V600D/K/R mutation positive subjects who receive at least one dose of study treatment.

9.3.2. Analysis Data Sets

The primary datasets for efficacy will comprise efficacy data from subjects in the V600E population from Cohort A. The V600D/K/R population will also be used to report on secondary efficacy endpoints by cohorts.

The data sets for assessing all safety endpoints will include all safety data collected on subjects in the ATS population.

9.3.3. Treatment Comparisons

Treatment comparisons are not applicable for this study. The primary objective will be supported by testing the null hypothesis in Cohort. A. The four cohorts will not be compared statistically for any endpoint.

.3.4. Interim Analysis

There is a formal interim analysis for futility only with a statistical decision rule in this trial. For Cohort A, an interim analysis will take place after 22 subjects have been treated and had the opportunity for at least two disease assessments. The responses used in this interim analysis do not have to be confirmed. At least 8 of the 22 subjects must have an IR (intracranial CR or PR) for the trial to continue. If 7 or fewer subjects have an IR, this is evidence that the null hypothesis is true. If accrual is not complete at the time of the interim analysis, it will continue during this analysis.

An IDMC will review accumulating safety and efficacy data, including the results of the interim review of safety and efficacy and make recommendations to continue, modify, or terminate the study if there are concerns regarding safety. The IDMC will review the study results at least once for efficacy and futility. Additional routine reviews of safety data will be scheduled as needed. The IDMC responsibilities and review schedules are outlined in the IDMC Charter.

9.3.5. Key Elements of Analysis Plan

Data will be listed and summarized according to the Novartis' 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 accrual will be spread thinly across centres and summaries of data by centre would be unlikely to be informative, data from all participating centres will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from the study will be included in analyses, regardless of duration of treatment.

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 time-to-event 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 for missing time-to-event data.

Demographic and baseline characteristics will be summarized according to current Novartis 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.

For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented progression or death, progression free-survival 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, progression-free survival will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

There will be no adjustments of the Type I error rate for multiplicity.

9.3.5.1. Efficacy Analyses

9.3.5.1.1. Primary Analysis

The IR is defined as the percentage of subjects who have a best confirmed intracranial complete or partial response by investigator assessment. Subjects who have an intracranial 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. The primary efficacy analysis will be performed when all subjects in cohort A have had the opportunity for ***three (3)*** post baseline disease assessments. At least 33 of 75 V600E subjects (44%) must show an intracranial response for the null hypothesis to be rejected. The IR, along with exact two-sided 95% confidence interval, will be reported. Investigator-assessed IR will be considered the primary analysis.

Secondary Analyses

Secondary efficacy endpoints are listed in [Table 1] **and Section 2**. Each will be analyzed separately as outlined in this table.

The **overall response rate (ORR)**, defined as the percentage of subjects with a confirmed overall CR or PR by investigator assessment using the RECIST 1.1 criteria. To determine the overall response, all target and non-target lesions will be assessed using modified RECIST 1.1 criteria. Subjects who have an overall 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. Overall response will be determined using RECIST 1.1. Rules for assigning each subject's visit-level best overall response are given in Section 7.3.2.10. A two-sided 95% confidence interval will be reported along with the point estimate.

The **duration of response** for intracranial, extracranial, and overall response will be summarized descriptively using Kaplan-Meier quartiles, along with two-sided 95% confidence intervals. Only the subset of subjects who show a complete or partial tumour response will be included in these analyses. Censoring rules for duration of response will use the rules for PFS. Caution should be exercised while interpreting the results due to possible competing risks.

Progression free survival (PFS), defined as the time from the first dose of dabrafenib and trametinib to the earliest of death or progression, will be summarized using Kaplan-Meier quartile estimates along with two-sided 95% confidence intervals. If a subject receives subsequent anti-cancer therapy prior to the date of documented progression or death, progression free-survival 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, progression-free survival will be censored at the date of the last adequate assessment.

Overall survival (OS): OS, defined as the time 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. Also of interest will be the tail of the OS curve, with the 3-year OS estimate of particular interest.

All responses are investigator-assessed. If necessary, independent central review will be performed under charter if there is a requirement.

9.3.5.2. Safety Analyses

The ATS population will be used for the analysis of safety data. All safety measures will be analyzed separately for each cohort and also aggregately if appropriate. Safety analyses may also be reported for the V600E and V600D/K/R analysis populations for each cohort. Complete details of the safety analyses will be provided in the RAP.

This study, or a single cohort thereof, may be stopped at any time if excessive toxicities with the study treatment are observed.

9.3.5.2.1. Extent of Exposure

The number of subjects administered study medication will be summarized according to the duration of therapy. Summaries of dose and dose intensity will be provided as appropriate for dabrafenib and trametinib.

9.3.5.2.2. Adverse Events

Adverse events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4.0) [NCI, 2009].

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 of the following AEs of special interest will be summarized separately: non-melanoma skin lesions, pyrexia, cardiac events, anaemia, and neutropenia. In particular, the rate of non-melanoma skin lesions will be calculated as the percentage of subjects with the appearance of any non-melanoma skin lesions after the start of treatment. Exact two-sided 95% confidence intervals for the rate of non-melanoma skin lesions in each arm will also be presented. Details will be given in the RAP.

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

9.3.5.2.3. Clinical Laboratory Evaluations

Haematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade (version 4.0). 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 (version 4.0) criteria. 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; no visit windows will be applied. Unscheduled data will be included in "post-baseline" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study medication. Further details will be provided in the RAP.

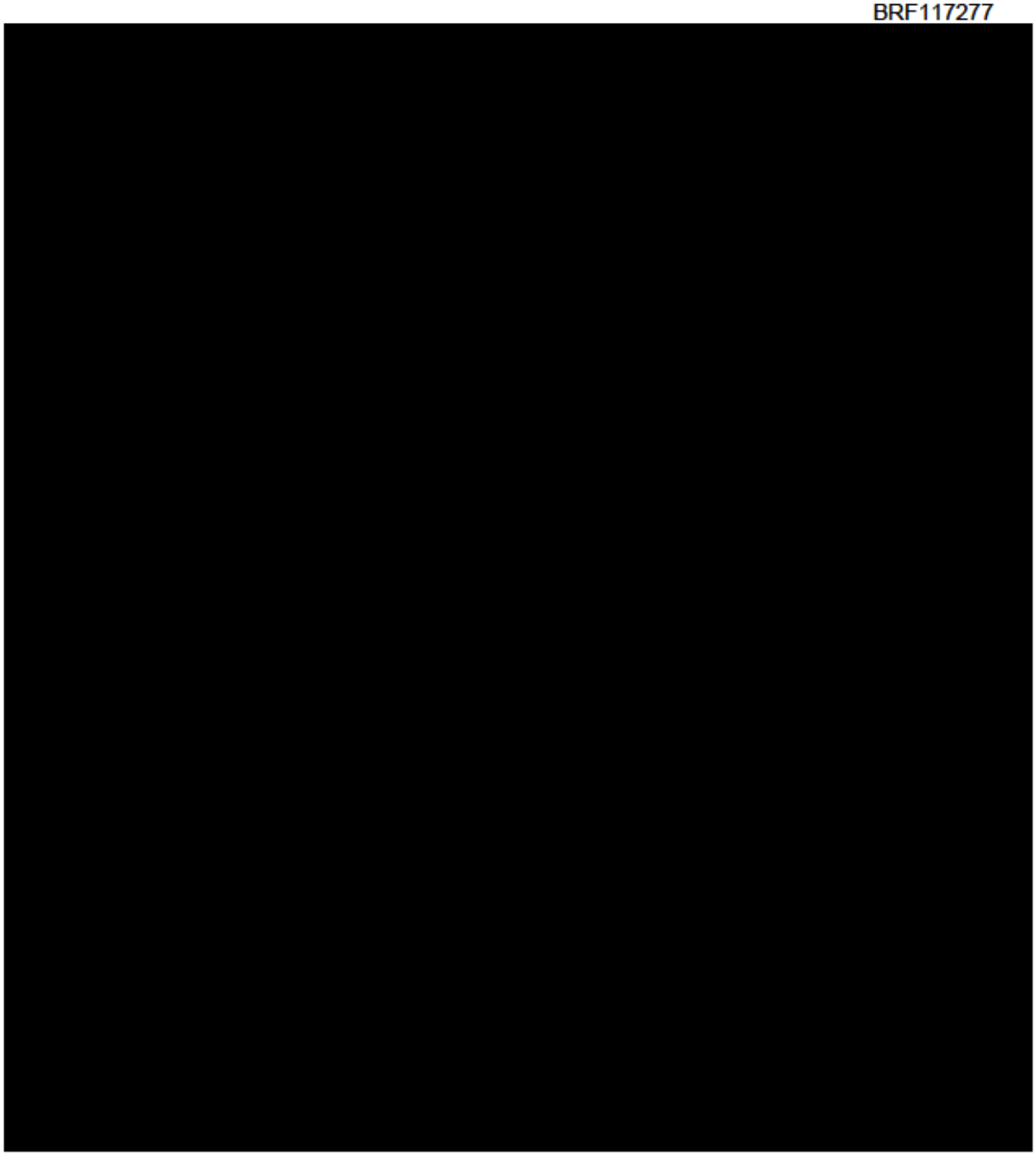
9.3.5.2.4. Other Safety Measures

The results of scheduled assessments of 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; no visit windows will be applied. All data will be listed. Further details will be provided in the RAP.

9.3.5.2.5. Measure of Agreement between In Vitro Diagnostic (IVD) Screening Assay and Response Genetics, Inc. (RGI) Screening Assay for Determining BRAF V600E or V600K Mutation-Positive Subjects

A secondary objective of the study is the development and validation of a BRAF in vitro diagnostic (IVD) assay. The clinical assay validation will determine the extent of agreement between the IVD assay to detect BRAF mutations and the Response Genetics, Inc. (RGI) assay to detect BRAF mutations. Efficacy results of subjects determined to be BRAF mutation-positive by the IVD assay will be described to illustrate comparability to the results from all subjects enrolled in the trial (that is, those determined to be BRAF mutant by the RGI assay). Appropriate statistical methods [US FDA, 2007] will be used; these methods will be outlined further in the RAP. All available tissue samples will be used in the assay validation. Measures of positive percent agreement and negative percent agreement will be reported, as well as the two-sided 95% confidence intervals.

[redacted]



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, Novartis 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 including those required under a US IND.

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

The study will be conducted in accordance with GCP, all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Novartis 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 [redacted] 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 Novartis procedures, Novartis personnel (or designated Clinical Research Organisation [CRO]) will contact the site 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 Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

Novartis (or designated CRO) personnel will monitor the study 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, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis 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 closed when all cohort A subjects still in follow up have had the opportunity for at least 3 years follow-up from the date of first dose of study treatment or 70% of cohort A patients have died or are lost to follow up, whichever is earlier
Upon completion or termination of the study, the Novartis personnel (or designated CRO) monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and Novartis Standard Operating Procedures.

Novartis 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 non-compliance. If Novartis determines that such action is required, Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Novartis 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**, Novartis will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. Novartis 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 Novartis 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.

The investigator must notify Novartis 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.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Novartis provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

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 Novartis site or other mutually-agreeable location.

Novartis 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.

Novartis aims to post a results summary to the Novartis Clinical Trial Results website www.novartisclinicaltrials.com and other publicly available registers no later than 12 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. Novartis also aims to publish the full study protocol on the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) 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 Novartis Clinical Trial Results website (www.novartisclinicaltrials.com)to supplement the results summary.

10.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

11. REFERENCES

Agarwala SS, Kirkwood JM, Gore M *et al*. Temozolomide for the Treatment of Brain Metastases Associated With Metastatic Melanoma: A Phase II Study. *Journal of Clinical Oncology* 2004; 22(11): 2101-2107.

Alcalá AM, Flaherty, KT. BRAF inhibitors for the treatment of metastatic melanoma: clinical trials and mechanisms of resistance. Clin Cancer Res 2012; 18(1):33-39.

Balagula Y, Huston KB, Busam KJ, et al. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs 2010; 29: 1114-1121

Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson Jr JA, McCallum R, Mitchel EP, O'Dorisio TM, Vokes EE, & Wadler S. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea. *Journal of Clinical Oncology*. 2004;22:2918-2926.

Brooks SM, Werk EE, Acherman SJ, Sullivan I, Thrasher K. Adverse Effects of Phenobarbital on Corticosteroid Metabolism in Patients with Bronchial Asthma. *New England Journal of Medicine* 1972; 286:1125-8.

Carnahan J, Beltran PJ, Babij C, et al. Selective and potent Raf inhibitors paradoxically stimulate normal cell proliferation and tumour growth. Mol Cancer Ther 2010; 9(8):2399-2410.

Carroll KJ. Back to basics: explaining sample size in outcome trials, are statisticians doing a thorough job? Pharm Stat 2009; 8(4):333-345.

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E Mutation. N Engl J Med 2011; 364:2507-16.

Corcoran RB, Dias-Santagata D, Bergethon K, Iafrate AJ, Settleman J, Engleman JA. BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation. Sci Signal 2010; 3(149):ra84.

Cranmer D, Jeter JM, Morgan SS *et al*. Whole-Brain Radiation Therapy in Melanoma: An Open Question. *The Lancet Oncology* 2010; 11(1):13.

Davies H, Bignell, G.R., Cox, C., Stephens, P., Edkins, S., *et al*. Mutations of the BRAF Gene in Human Cancer. *Nature* 2002; 417:949-954.

Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer 2011;117:1687-96.

Dummer R, Rinderknecht J, Goldinger S.M., Wagner I, Mitchell L, Veronese M.L., Nick S, P. Hilfiker P and Gobbi S; Meeting Abstract 8548 ASCO 2013;An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases.

Eggermont AM, Robert C. New drugs in melanoma: it's a whole new world. Eur J Cancer 2011; 47: 2150-2157

Eisen T, Ahmad T, Flaherty KT, Gore M, Kaye S et al. Sorafenib in Advanced Melanoma: A Phase II Randomised Discontinuation Trial Analysis. *British Journal of Cancer* 2006; 95(5): 581–586.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New Response Evaluation Criteria in Solid Tumours: Revised RECIST guidelines (version 1.1). *European Journal of Cancer*. 2009; 45: 228-247.

Emery CM, Vijayendran KG, Zipser MC, et al. MEK1 mutations confer resistance to MEK and B-RAF inhibition. Proc Natl Acad Sci U S A 2009; 106(48):20411-20416.

Falchook G, Infante JR, Fecher LA, et al. The oral MEK1/2 inhibitor GSK1120212 demonstrates early efficacy signals. Annals of Oncology 2010; 21 (8): 4950.

Fife KM, Colman MH, Stevens GN, Firth IC, Moon D *et al*. Determinants of Outcome in Melanoma Patients with Cerebral Metastases. *Journal of Clinical Oncology* 2004; 22: 1293-1300.

Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 2010; 363(9):809-819.

Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov LV, Hassel JC, Rutkowski P, Mohr P, Dummer R,Trefzer U, Larkin J, Utikal J,Dreno B, Nyakas M, Middleton MR, Becker JC, Casey M, Sherman JL, Wu FS,Ouellet D, Martin A,Patel K, Schadendorf D, METRIC Study Group; N Engl J Med 2012; 367:107-114July 12, 2012DOI: 10.1056/NEJMoa1203421

GlaxoSmithKline Document Number 2011N126811_00: GSK1120212 + GSK2118436 (trametinib and dabrafenib), Investigator's Brochure. 15-FEB-2012.

GlaxoSmithKline Document Number 2011N126811_01 GSK1120212 + GSK2118436. Investigator's Brochure Version 2. Report Date 17-MAY-2013.

GlaxoSmithKline Document Number CM2010/00010/02: GSK2118436 (dabrafenib) Investigator's Brochure. 20-May-2011.

GlaxoSmithKline Document Number CM2010/00010/03 Study ID GSK2118436 Investigator's Brochure. . Report Date 03-May-2013.

GlaxoSmithKline Document Number HM2009/00151/02: GSK1120212 (trametinib) Investigator's Brochure. 23-Jun-2011.

GlaxoSmithKline Document Number RM2009/000064/02 Study ID GSK2118436. Investigator Brochure. Report Date 27-May-2010.

Gorden A, Osman I, Gai W, et al. Analysis of BRAF and N-RAS mutations in metastatic melanoma tissues. Cancer Res. 2003; 63: 3955-3957.

Gordon MS, Infante JR, Messersmith W, et al. The oral MEK1/MEK2 inhibitor, GSK1120212, effectively inhibits the MAPK pathway: pharmacokinetic, pharmacodynamic, and clinical response relationship. 22ND EORTC-NCI-AACR Symposium: Molecular Targets and Cancer Therapeutics 2010, abstract 373.

Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, Rutkowski P, Blank CU, Miller Jr WH, Kaempgen E, Martín-Algarra S, Karaszewska B, Mauch C, Chiarion-Sileni V, Martin A, Swann S, Haney P, Mirakhur B, Guckert ME, Goodman V, Chapman PB, Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial, The Lancet, 28 July–3 August 2012, Pages 358-365, ISSN 0140-6736

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzales R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ; Improved Survival with Ipilimumab in Patients with Metastatic Melanoma; N Engl J Med. 2010 Aug 19;363(8):711-23

Hong DS, Vence L, FalchookG, er al. BRAF(V600) Inhibitor GSK2118436 Targeted Inhibition of Mutant BRAF in Cancer Patients Does Not Impair Overall Immune Competency. Clin Cancer Res April 15, 2012 18; 2326

Houben R, Becker JC, Kappel A, et al. Constitutive activation of the Ras-Raf signalling pathway in metastatic melanoma is associated with poor prognosis. J Carcinog. 2004; 3:6.

Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. Melanoma Res 2001; 11(1):75-81.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.

Kim K, Lewis K, Pavlick A, et al., A phase II study of the MEK1/MEK2 inhibitor GKS1120212 in metastatic BRAF-V600E or K mutant cutaneous melanoma patients previously treated with or without a BRAF inhibitor. Pigment Cell Res. 2011;24:1021.

Kind P. The EuroQoL Questionnaire: An Index of Health-Related Quality of Life, Quality of Life and Pharmacoeconomics in Clinical trials, Second Edition, 1996; pp 191-200.

Kirschner M, Helmke B, Starz H, et al. Preponderance of the oncogenic V599E and V599K mutations in the B-raf kinase domain is enhanced in melanoma lymph node metastases. Melanoma Res. 2005; 15: 427-434.

Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008; 26(4):527-534.

Kumar R, Angelini S, Czene K, et al. BRAF mutations in metastatic melanoma: a possible association with clinical outcome. Clin Cancer Res. 2003; 9: 3362-3368.

Lacouture ME, Anadkat MJ, Bensadoun RJ, et al, Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011; 19:1079-1095.

Lacouture ME, Shenhong W, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. The Oncologist 2008; 13: 1001-1011.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70(3):659-663.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Libra M, Malaponte G, Navolanic PM, et al. Analysis of BRAF mutation in primary and metastatic melanoma. Cell Cycle 2005; 4: 1382-1384.

Linos E, Swetter SM, Cockburn MG, et al. Increasing burden of melanoma in the United States. J Invest Dermatol. 2009; 129 (7): 1666-1674.

Lipworth AD, Robert C, Zhu AX. Hand-Foot Syndrome (Hand-Foot Skin Reaction, Palmar-Plantar Erythrodysesthesia); Focus on Sorafenib and Sunitinib. *Oncology*. 2009; 77:257-71.

Long GV, Sosman JA, Daud AI, et al: Phase II three-arm randomised study of the BRAF inhibitor dabrafenib alone vs combination with MEK1/2 inhibitor trametinib in patients with BRAF V600 mutation-positive metastatic melanoma. 2012 ESMO Congress. Abstract LBA27. Presented September 29, 2012

Majer M., Samlowski W.E. Management of Metastatic Melanoma Patients with Brain Metastases. *Current Oncology Reports* 2007 9(5):411-416.

Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459-65.

McLellan B, Kerr H. Cutaneous toxicities of the multikinase inhibitors sorafenib and sunitinib. Dermatologic Therapy 2011; 24: 396-400.

McWilliams RR, Rao RD, Buckner JC, Link MJ, Markovic S, *et al*. Melanoma-Induced Brain Metastases. *Expert Reviews in Anticancer Therapy*. 2008; 8(5): 743-55.

NCI. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. DHHS, NCI, NIH, Bethesda, MD; 2009.

Nissan MH, Solit DB, The "SWOT" of BRAF inhibition in melanoma: BRAF inhibitors, MEK inhibitors or both? Curr Oncol Rep 2011; 13: 479-487.

O'Brien PC, Fleming TR. Multiple Testing Procedures for Clinical Triasls. Biometrics. 1979; 35:549-556.

Oken M.M, Creech, R.H, Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology.* 1982; 5:649-655.

Omholt K, Platz A, Kanter L, et al. NRAS and BRAF mutations arise early during melanoma pathogenesis and are preserved throughout tumour progression. Clin Cancer Res. 2003; 9: 6483-6488.

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001; 33(5):337-343.

Ries LAG, Melbert D, Krapcho M et al (eds). SEER cancer statistics review1975-2005: National Cancer Institute, Bethesda MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

Robert C, Arnault JP, Mateus C. RAF inhibition and induction of squamous cell carcinoma. Curr Opin Oncol 2011; 23 (2): 177-182.

Robert C, Thomas L, Bondarenko I et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma 2011. N Eng J Med; 364: 2517-26.

Samlowski WE, Watson GA, Wang M, Rao G, Klimo P *et al*. Multimodality Treatment of Melanoma Brain metastases Incorporating Stereotactic Radiosurgery (SRS). *Cancer* 2007; 109(9): 1855-62.

Sampson JH, Carter JHJr, Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg. 1998; 88: 11-20.

Sondak VK, Flaherty LE. Improved outcomes for patients with metastatic melanoma. Nat Rev Clin Oncol 2011; 8: 513-515.

Staudt M, Lasithiotakis K, Leiter U, Meier F, Eigentler T, *et al*. Determinants of Survival in Patients with Brain Metastases from Cutaneous Melanoma. *British Journal Cancer* 2010; 102(8): 1213-8.

Trefzer U, Minor D, Ribas A et al. BREAK-2: a Phase IIA trial of the selective BRAF kinase inhibitor GSK2118436 in patients with BRAF mutation-positive (V600E/K) metastatic melanoma. Pigment Cell Res. 2011;24:1020.

U.S. Food and Drug Administration (US FDA). *Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.* FDA, Silver Spring, MD; 2007. www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm. Accessed 9 September 2010.

Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, *et al*. Mechanism of Activation of the RAF-ERK Signaling Pathway by Oncogenic Mutations of B-RAF. *Cell.* 2004; 116: 85-867.

Weber J, K. Flaherty, J. Infante, G. Falchook, R. Kefford, A. Daud, O. Hamid, R. Gonzalez, R. Kudchadkar, D. Lawrence, H.A. Burris III, G.V. Long, A. Algazi, K. Lewis, K.B. Kim, I. Puzanov, P. Sun, S. Little, K. Patel, J. Sosman; Updated safety and efficacy results from a Phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK ½ inhibitor trametinib (GSK1120212) in patients with BRAFi-naïve metastatic melanoma, Journal of Clinical Oncology 30, 2012 (suppl; abstr 8510)

Wellbrock C., Karasarides M., Marais R. The RAF Proteins Take Centre Stage. *Nature Reviews in Molecular Cell Biology.* 2004; 5:875-885

12. APPENDICES

12.1. Appendix 1: Melanoma of the Skin Staging

American Joint Committee on Cancer

Melanoma of the Skin Staging

7th EDITION

Definitions

Primary Tumor (T)

- TX Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)
- T0 No evidence of primary tumor
- Tis Melanoma in situ
- T1 Melanomas 1.0 mm or less in thickness
- T2 Melanomas 1.01–2.0 mm
- T3 Melanomas 2.01–4.0 mm
- T4 Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and number of mitoses per mm², as shown below:

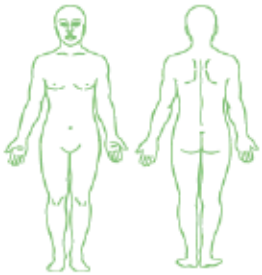
T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS/MITOSES
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

- NX Patients in whom the regional nodes cannot be assessed (for example, previously removed for another reason)
- N0 No regional metastases detected
- N1-3 Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

NOTE: N1–3 and a–c subcategories assigned as shown below:

N CLASSIFICATION	NO. OF METASTATIC NODES	NODAL METASTATIC MASS
N1	1 node	a: micrometastasis[1] b: macrometastasis[2]
N2	2–3 nodes	a: micrometastasis[1] b: macrometastasis[2] c: in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	



Distant Metastasis (M)

- M0 No detectable evidence of distant metastases
- M1a Metastases to skin, subcutaneous, or distant lymph nodes
- M1b Metastases to lung
- M1c Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	SERUM LDH
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]				Pathologic Staging[4]		
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

ajcc®

American Cancer Society®

Financial support for AJCC 7th Edition Staging Posters provided by the American Cancer Society

Notes

[1] Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

[2] Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

[3] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Reference: American Joint Committee on Cancer. (2009). 7th Edition of AJCC Melanoma Staging System. Retrieved 19 April 2012 from www.cancerstaging.org/staging/posters/melanoma8.5x11.pdf.

12.2. Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6):649-655.

12.3. Appendix 3: Cockcroft-Gault Formula

To determine eligibility for the study, investigators should calculate a subject's creatinine clearance by the Cockcroft-Gault formula as follows [Cockcroft, 1976]:

$$\text{CrCl for males (mL/min)} = \frac{(140-\text{age[years]})\times(\text{weight[kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

$$\text{CrCL for females (mL/min)} = \frac{0.85\times(140-\text{age[years]})\times(\text{weight[kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

For SI units:

$$\text{CrCl for males (mL/min)} = \frac{(140-\text{age[years]})\times(\text{weight[kg]})\times 1.23}{(\text{serum creatinine [}\mu\text{mol/L]})}$$

$$\text{CrCL for females (mL/min)} = \frac{(140-\text{age[years]})\times(\text{weight[kg]})\times 1.05}{(\text{serum creatinine [}\mu\text{mol/L]})}$$

CrCl = creatinine clearance; SI = Système International d'Unités.

Reference:

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.

12.4. Appendix 4: QT interval on electrocardiogram corrected using the Bazett's formula (QTcB)

Bazett's formula used to correct QT interval for heart rate is:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QTcB is the QT interval corrected for heart rate, RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, *measured in seconds*, often derived from the heart rate (HR) as 60/HR, and QT is the QT interval *measured in milliseconds*.

Reference:

Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; 7: 353-370.

12.5. Appendix 5: New York Heart Association (NYHA) Guidelines

The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure [The Criteria Committee of the New York Heart Association, 1994]. It places subjects in 1 of 4 categories based on the level of limitation experienced during physical activity:

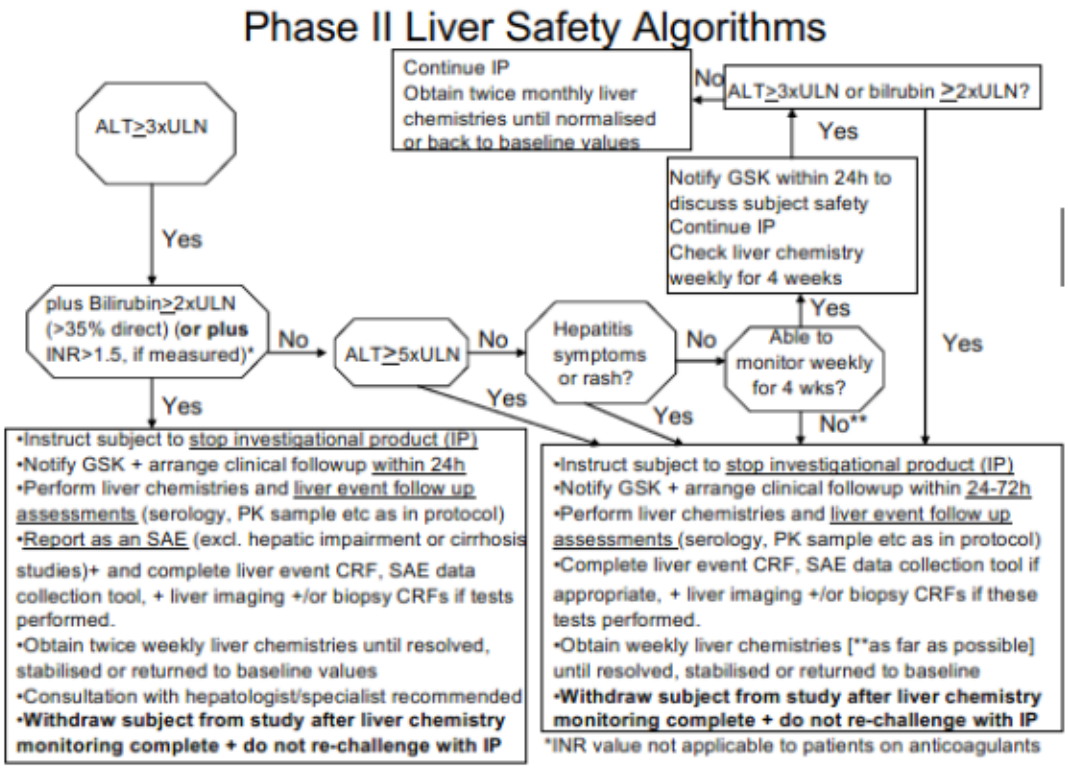
Functional Capacity	Objective Assessment
Class I: Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A:** No objective evidence of cardiovascular disease.
Class II: Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B:** Objective evidence of minimal cardiovascular disease.
Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C:** Objective evidence of moderately severe cardiovascular disease.
Class IV: Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D:** Objective evidence ofsevere cardiovascular disease.

Reference:

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown, & Co; 1994:253-256.

12.6. Appendix 6: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Phase II Liver Safety Algorithms



12.7. Appendix 7: Liver Safety Drug Restart or Rechallenge Guidelines

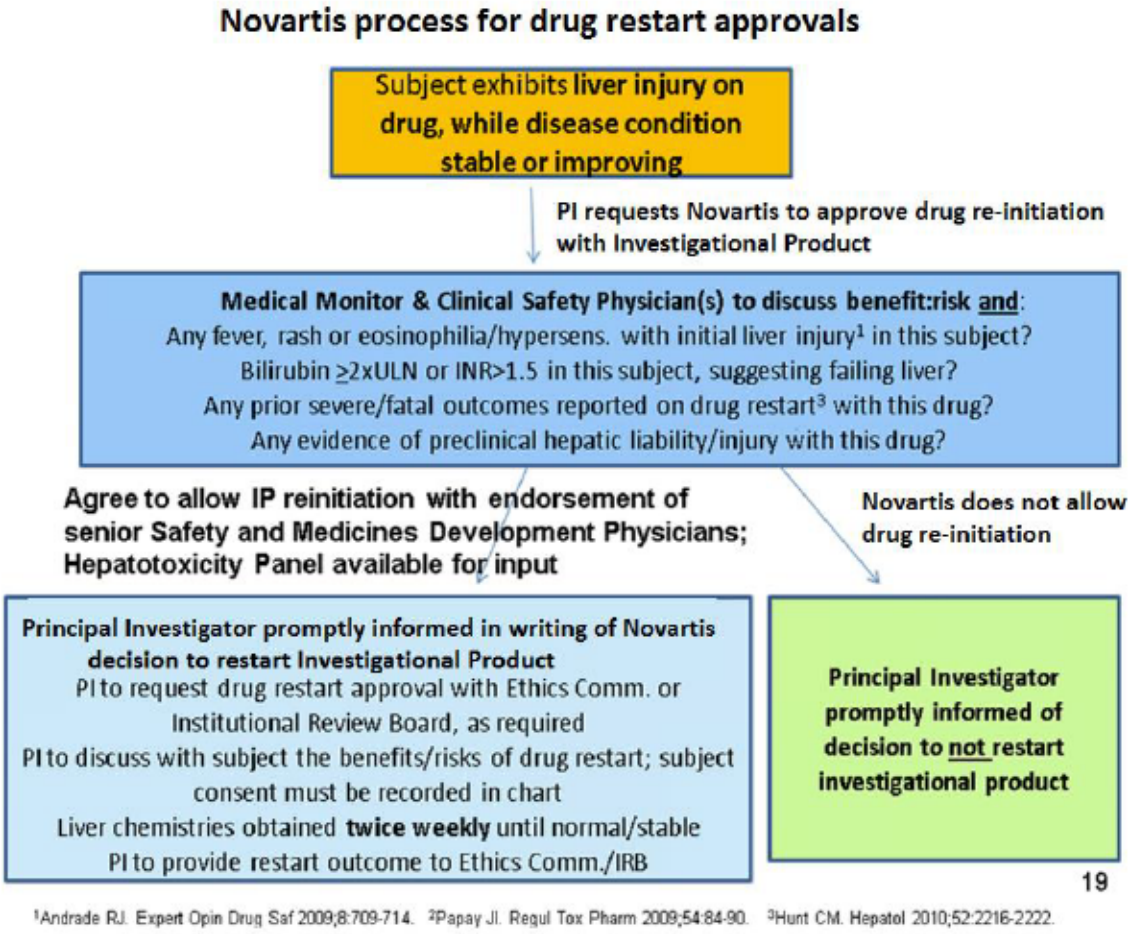
1. Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternative medicine available. It applies to Phase I-IV studies (excluding healthy volunteer studies; example of phase I studies are oncology studies).

2. In Phase III-IV, drug restart may be considered for liver safety events with a clear underlying cause (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis, or hypersensitivity (fever, rash or eosinophilia) and drug not associated with HLA genetic marker of liver injury) when liver chemistries have improved to normal or are within 1.5x baseline and ALT<3xULN.

Liver Events Possibly Related to IP - Drug Restart/Rechallenge Following Possible Drug-induced Liver Injury Challenge Guidelines

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies**[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin ≥2xULN or INR>1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge[2,3] or evidence of drug-related preclinical liability / mitochondrial impairment[3]

Novartis Decision Process for Drug Restart Approval or Disapproval (*also see* Figure 1)



Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment

- Novartis Global Clinical Lead & Clinical Safety Physician to review the subject's restart/rechallenge risk factors & complete checklist (Table 26).

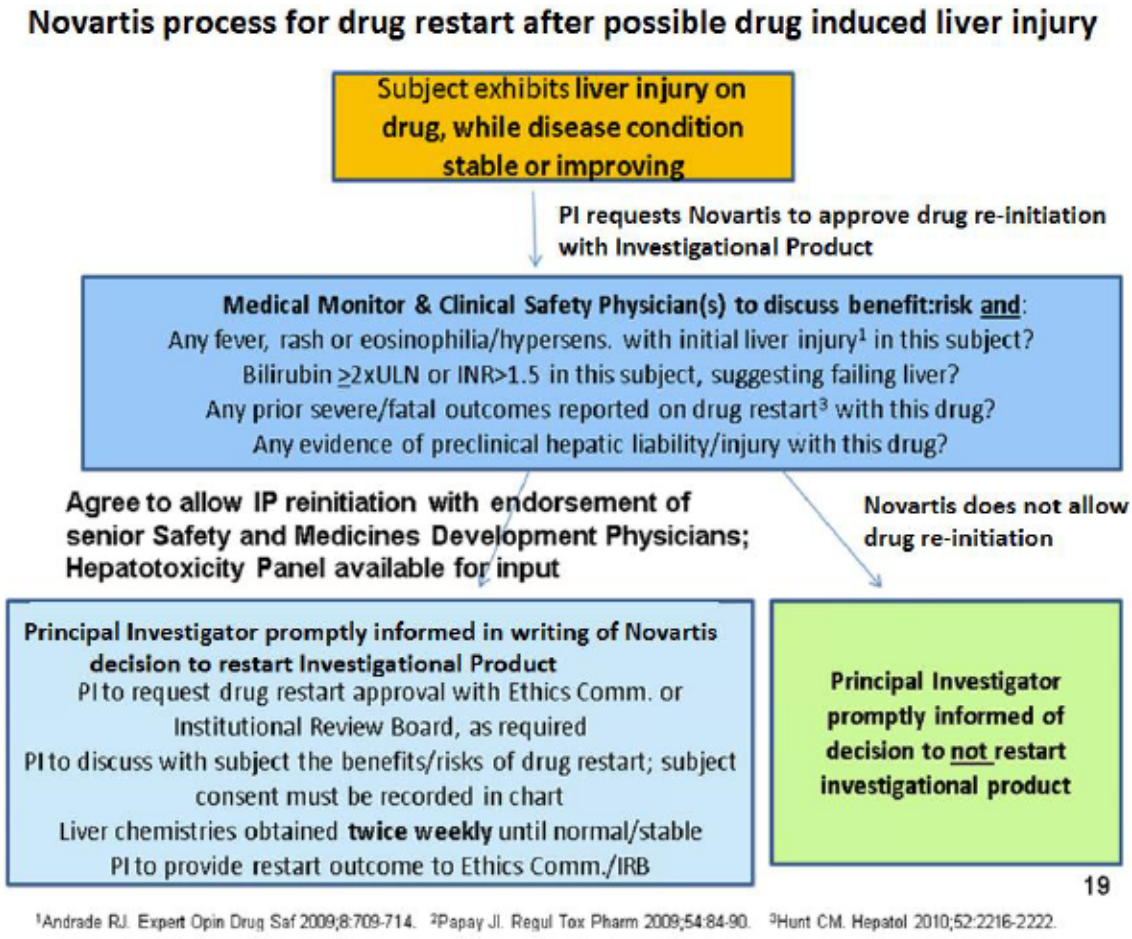
Table 26 Checklist for drug rechallenge for critical medicine

(Following drug-induced liver injury, drug rechallenge is associated with 13%mortality across all drugs in prospective studies)		
	Yes	**No**
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy. Provide brief explanation**:		
Relative benefit-risk favorable for drug restart/rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
– fever, rash, eosinophilia, or hypersensitivity		
– or bilirubin ≥2xULN (direct bilirubin >35% of total)		
• Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR ≥1.5		
• Severe or fatal restart/rechallenge has earlier been observedwith IP **If yes, please provide brief explanation**:		
• IP associated with known preclinical hepatic liability/ injury		

Principal Investigator (PI) Actions:

- The PI must obtain Ethics Committee or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the possible benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.
- The drug must be reinitiated at Novartis approved dose(s).
- Liver chemistries should be followed twice weekly until stable.
- The Ethics Committee or Institutional Review Board must be informed of the subject's outcome, as required.
- Novartis to be notified of any adverse events, as per Section 7.4.2.

Figure 2 Novartis process for drug restart after possible drug-induced liver injury



References:

- Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
- Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222
- Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

Drug Restart Guidelines

Novartis Decision Process for Drug Restart Approval or Disapproval (also see Figure 2)

- Principal Investigator (PI) requests consideration of drug reinitiation for a subject stable or improving on investigational product (IP), who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and resolves.
- GSK Medical Monitor & Clinical Safety Physician to review the subject's diagnosis, restart risk factors & complete checklist (Table 27).

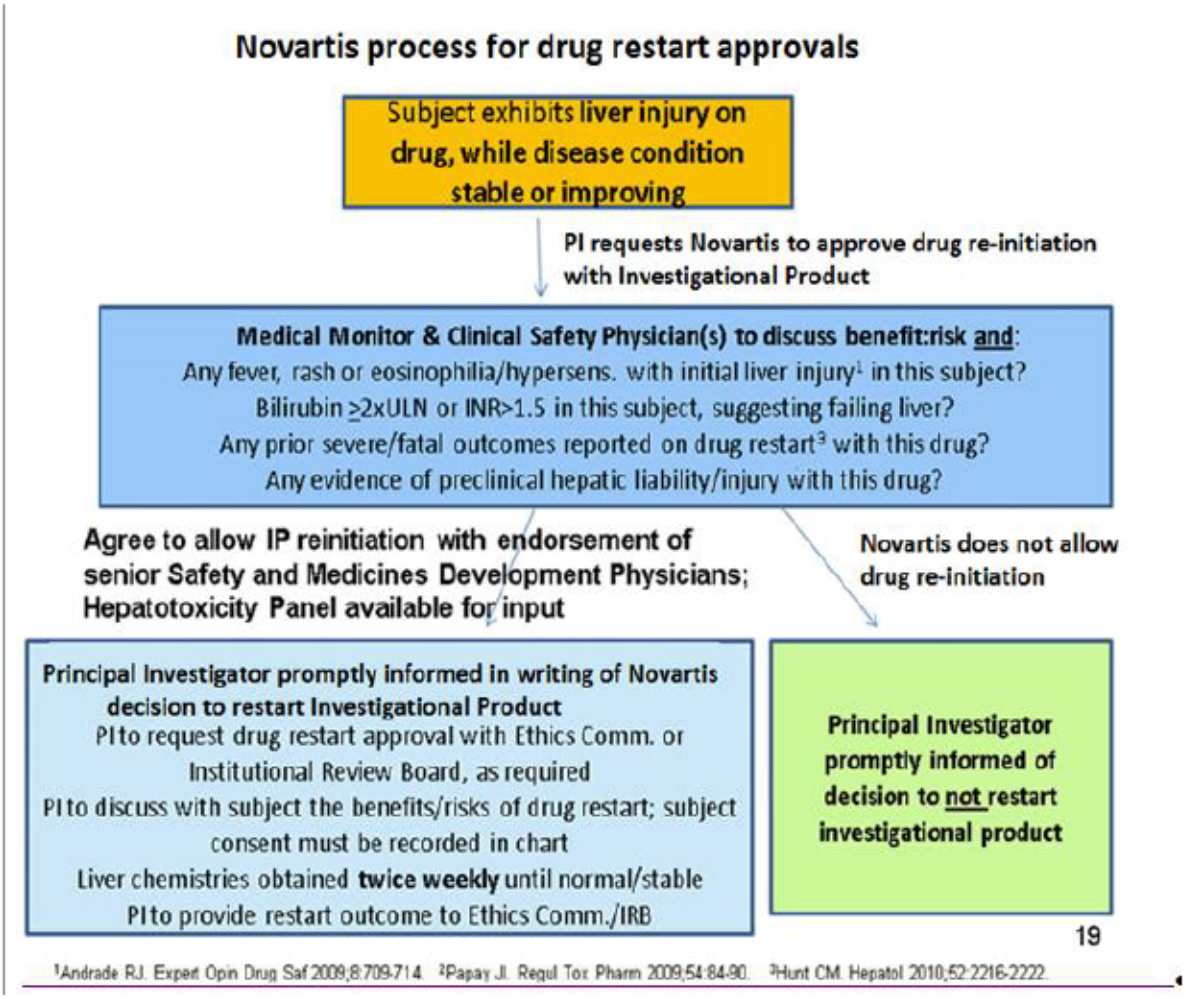
Table 27 Checklist for Phase III drug restart

after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, CHF, acute viral hepatitis), liver chemistries improving to normal or ≤1.5x baseline and ALT<3xULN.		
	Yes	**No**
Is subject stable or improving on the investigational product (IP)?		
Donotrestart if the **following risk factors at initial liver injury**:		
• Fever, rash, eosinophilia, or hypersensitivity		
• Drug-induced liver injury		
• Alcoholic hepatitis (AST>ALT, typically <10xULN)		
• IP associated with liver injury and an HLA genetic marker (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		

Principal Investigator (PI) Actions

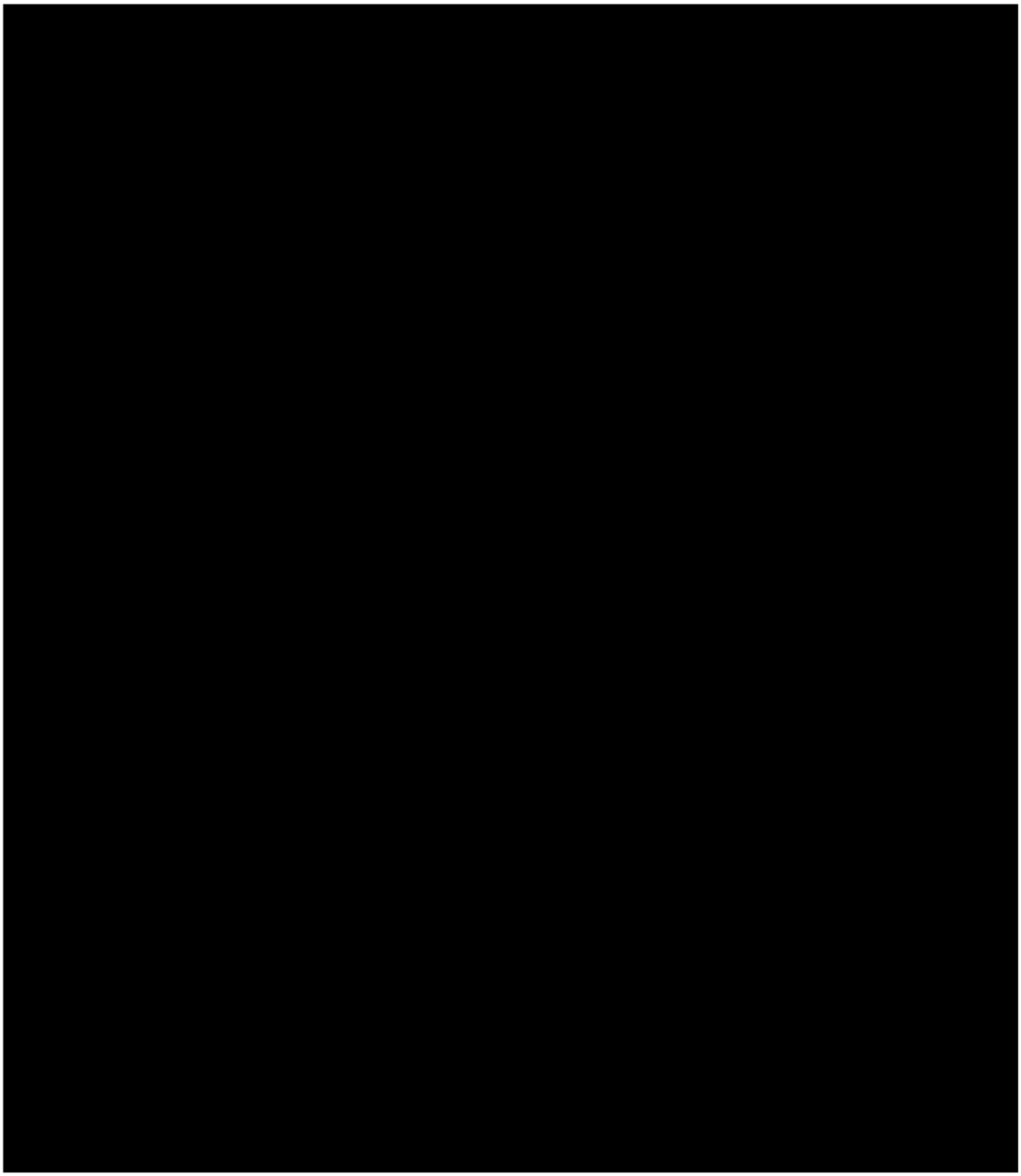
- The PI must obtain Ethics Comm. or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.
- Liver chemistries should be followed weekly until stable.
- The Ethics Committee or Institutional Review Board must be informed of the patient's outcome, as required.
- Novartis to be notified of any adverse or serious adverse events, as per Section 7.4.2.6 and Section 7.4.2.7.

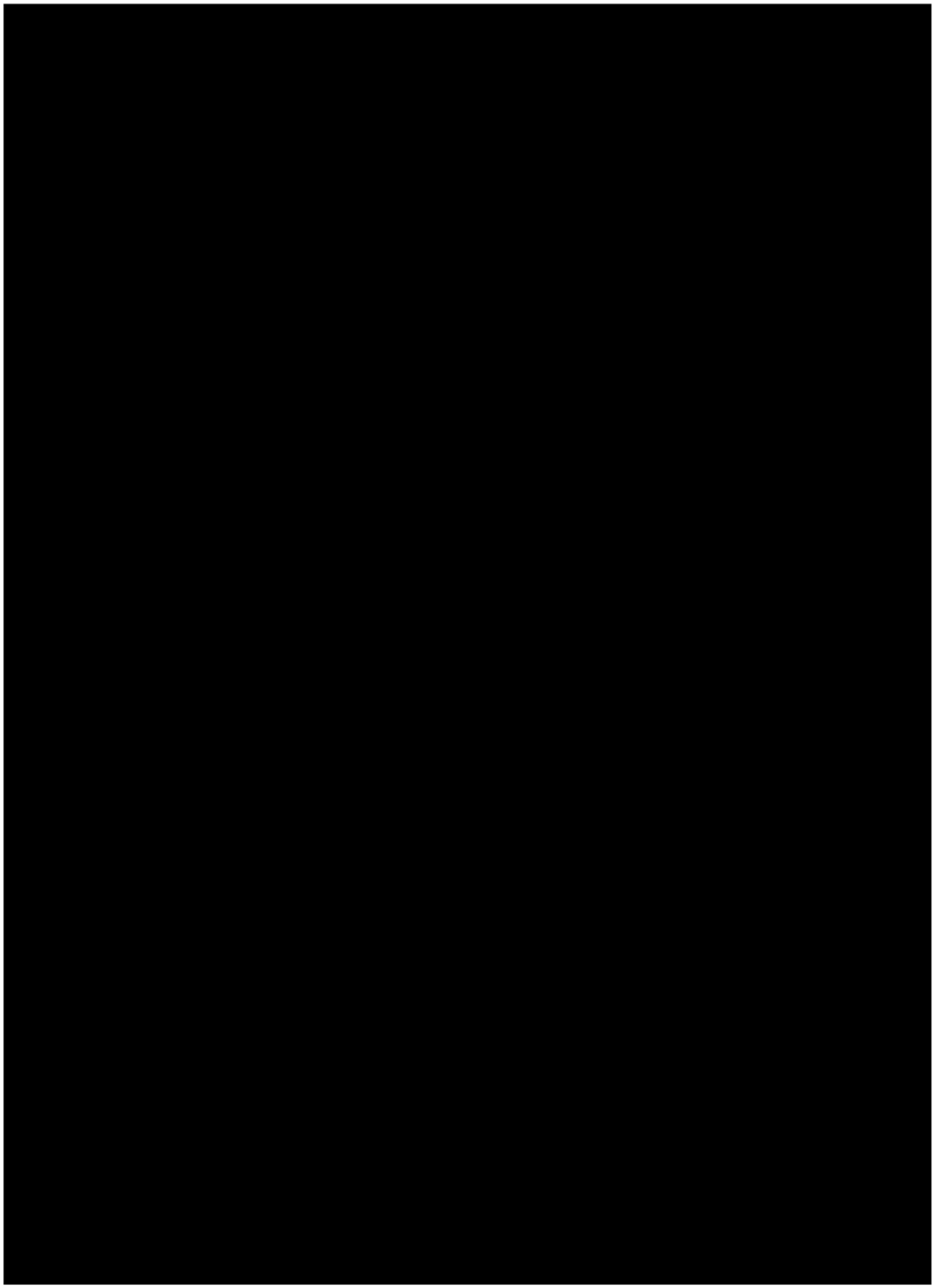
Figure 3 Novartis process for drug restart approvals

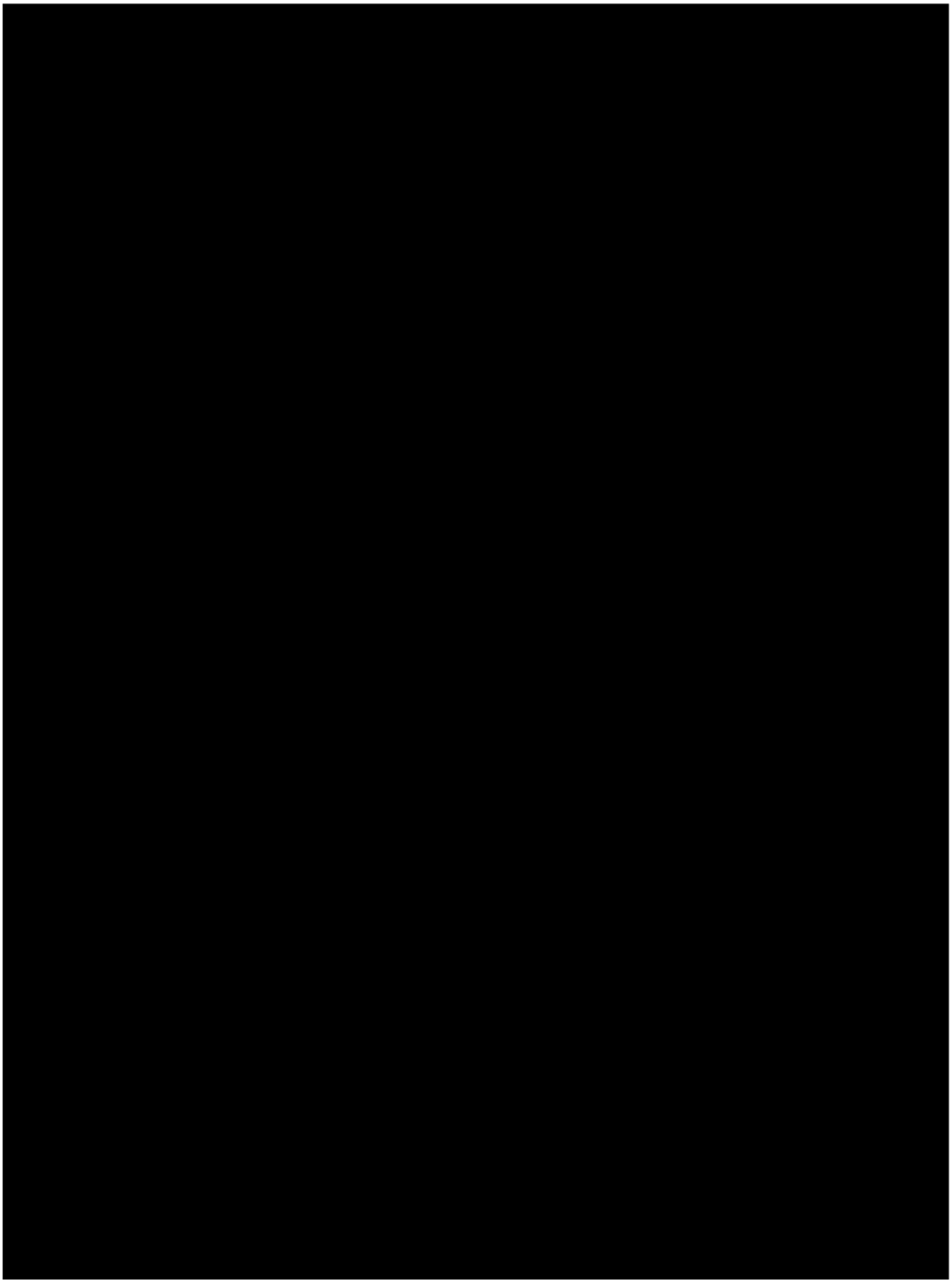


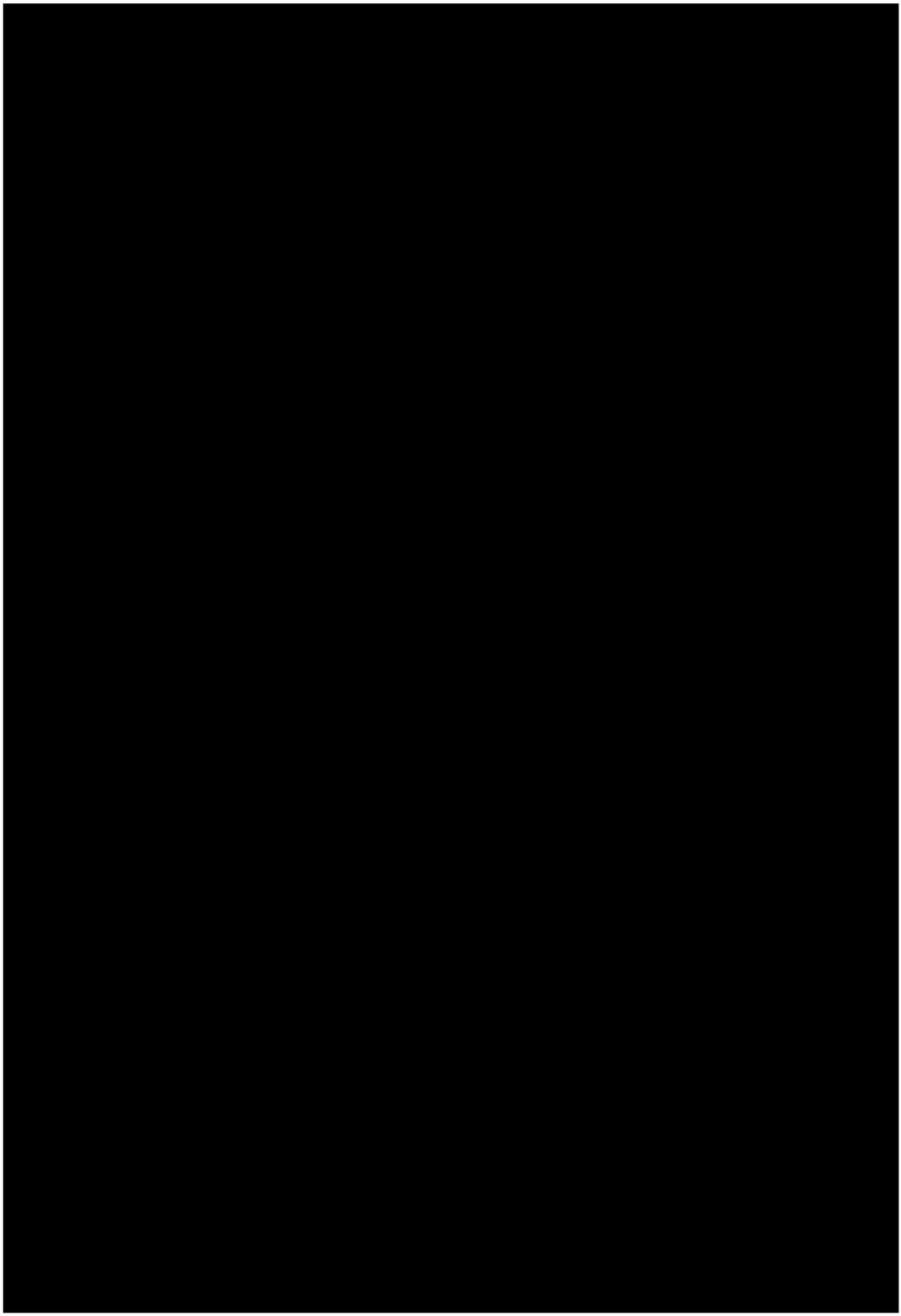
References:

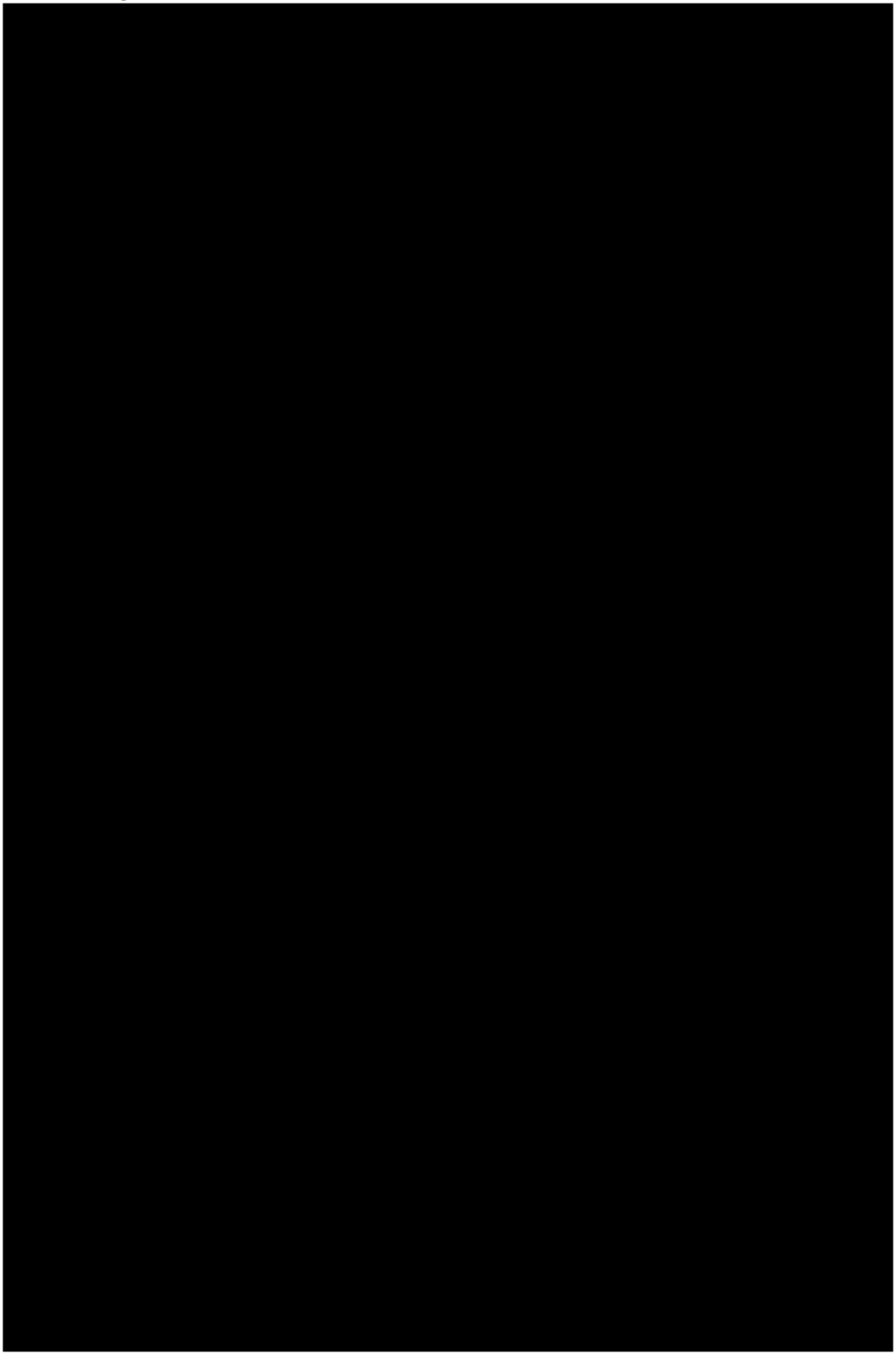
- Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
- Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.
- Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.











[redacted]

12.9.1 Exclusion Criteria

- Subjects with history of HIV are excluded from this the study. (Section 4.1.3)
- Subjects under guardianship / under supervision (another person is responsible, decide for the patient) or deprived of liberty (in prison for example) will be excluded from this study.
- Subjects presenting uncorrected electrolyte abnormalities (including magnesium) cannot be allowed.
- Subjects taking medications known to induce QT prolongation are excluded from this study.

12.9.2 Valvular toxicity citeria

Guidelines for Valvular Toxicity for Subjects Enrolled in France

- Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0) should temporarily discontinue dabrafenib and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.
    - If the valve recovers to baseline any time during the next 4 weeks, after consultation and approval of the Novartis Global Clinical Lead, the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
    - If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue dabrafenib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.
- Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) valvular toxicity must discontinue dabrafenib. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart dabrafenib at a reduced dose after consultation and approval of the Novartis Global Clinical Lead. For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

ECHO must be performed at baseline and at follow-up visit(s). Copies of all ECHO(s) and cardiology consultations performed on subjects who experience a valvular toxicity will be required by Novartis for review.

12.9.2 Non-cutaneous secondary/recurrent malignancy

Prior to initiation of study treatment subjects should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen Computed Tomography (CT) scan. During treatment subjects should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations are recommended before the start of and at the end of treatment or when considered clinically indicated. Complete blood cell counts should be performed as clinically indicated. Following discontinuation of dabrafenib monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy, whichever comes first. Any non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE and treated according to standard clinical practice.

12.10. Appendix 10: Protocol Changes for Amendment 01

Amendment Number 01

This amendment is applicable to all investigational study sites in all countries.
Administrative changes including updated Sponsor Contact information.

Secondary Objectives

Previous:

#7. overall survival (OS)

Revised:

#7. overall survival (OS) and long-term (particularly 5-year) OS

Reasonforchange: Addition of long term overall survival.

Study Design

Previous:

Survival and new anti-cancer therapy follow-up will continue until 70% of the total enrolled population has died or been lost to follow-up. At such time the study will be closed. Subjects who meet the inclusion/exclusion criteria for the roll over study will have the option to roll over into GSK114144 roll-over study.

Revised:
After treatment discontinuation, subjects will be followed for skin assessments, survival, safety, and disease progression as applicable. Survival and new anti-cancer therapy follow-up will continue until either all subjects are dead or lost to follow-up, or all subjects still in follow-up have had at least 5 years of follow-up, whichever is earlier. At such time the study will be closed.

Reasonforchange:
Survival follow-up period has been extended in order to collect additional long-term overall survival data.

Section 1.1 Background

Addition:
Dabrafenib, another small molecule BRAF-inhibitor received FDA-approval in May 2013 and EMA approval in August 2013.

Reasonforchange:
Updated information available

Section 1.1 Background

Addition:
In Jan 2014 the combination of dabrafenib and trametinib received FDA approval, and in February 2014 the combination received approval in Australia.

Reasonforchange: Approval in United States and Australia

Table 1 Study Objectives and Endpoints

Previous:
To assess C Cohorts A, B, C and D for overall survival (OS)

Revised:
To assess C Cohorts A, B, C and D for overall survival (OS) and long-term (particularly 5-year) OS

Reasonforchange:
Addition of long term overall survival.

STUDY DESIGN

Previous:Cohort A, B, C:
Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least **3 weeks** prior to first dose of study treatment. (Refer to Section 6.3 Cautionary Medications).

Revised: Cohort A, B, C:
Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least **1 month** prior to first dose of study treatment. (Refer to Section 6.3 Cautionary Medications).

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

STUDY DESIGN

Previous:
Protocol-specified guidelines for dose adjustments, interruptions and discontinuation due to adverse events are provided below. After discontinuation of study treatment, subjects will remain in the study for follow-up assessments including monthly skin assessments up to 6 months and updates on anti-cancer treatment until death. Subjects who have not died, but are no longer being followed for disease progression or survival are considered

to have withdrawn from the study. The study will be completed when either all subjects are dead or lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up, whichever is earlier.

Revised:
Protocol-specified guidelines for dose adjustments, and discontinuation due to adverse events are provided below. After discontinuation of study treatment, subjects will remain in the study for follow-up assessments including monthly skin assessments up to 6 months and updates on anti-cancer treatment until death. Subjects who have not died, but are no longer being followed for disease progression or survival are considered to have withdrawn from the study. The study will be completed when either all subjects are dead or lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up from the date of first dose of study treatment, whichever is earlier.
Reasonforchange:
Survival follow-up period has been extended in order to collect additional long-term overall survival data.

4.1.2 Inclusion Criteria

Previous:Criteria#5:

Prior TMX for brain metastases and adjuvant IFN are acceptable and does not count toward the two previous systemic treatment regimens.

Revised:
Prior temozolomide for brain metastases and adjuvant interferon are acceptable and does not count toward the two previous systemic treatment regimens.

Reasonforchange:
Clarification of TMX and IFN

Previous:Criteria#6:,
Must be able to undergo MRI and have at least one measurable intracranial lesion for which all of the following criteria have to be met:

- For target lesions with diameter of > 0.5cm but ≤ 1 cm documented measurement by a neuroradiologist.
- For all lesions with a diameter of ≥ 3cm but ≤ 4 cm documented measurement by a neurologist.

Revised:
Must be able to undergo MRI and have at least one measurable intracranial lesion for which all of the following criteria have to be met:

- For target lesions with diameter of > 0.5cm but ≤ 1 cm documented measurement by a neuroradiologist/appropriately qualified radiologist /**neurosurgeon** is required.
- For all lesions with a diameter of ≥ 3cm but ≤ 4 cm documented measurement by a neuroradiologist / appropriately qualified radiologist /**neurosurgeon** is required.

Reasonforchange:
Typographical correction of neurologist to neuroradiologist and the addition of appropriately qualified radiologist /neurosurgeon based upon country requirements.

4.1.2 Inclusion Criteria

Previous:

Table 2 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
ANC	$\geq 1.2 \times 10^9$/L
Hemoglobin	≥ 9 g/dL
Platelet count	$\geq 100 \times 10^9$/L
PT/INR[a] and PTT	≤ 1.5 x ULN
Hepatic	
Albumin	≥ 2.5 g/dL
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

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. Creatinine clearance must be ≥ 50 mL/min to be eligible. See Appendix 3.
c. ECHO scans must be used throughout the study

Revised:

Table 2 Definitions for Adequate Baseline Organ Function

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

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 enrollment.
b) If serum creatinine is > 1.5 mg/dL, calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 3). Creatinine clearance must be ≥ 50 mL/min to be eligible.
c) Except subjects with known Gilbert's syndrome.
d) ECHO scans must be used throughout the study

Reasonforchange:

Albumin removed, PT/INR[a] and PTT was updated from ≤ 1.5 x ULN to ≤ 1.3 x ULN to align with the updated asset standard language for the dabrafenib and trametinib combination.

4.1.2 Inclusion Criteria

Previous:

Women of childbearing potential must have a negative serum pregnancy test within 14 days of first dose of study treatment and agree to use effective contraception throughout the treatment period and for 4 months after the last dose of study treatment.

NOTE: Oral contraceptives are not reliable due to potential drug- drug interaction with dabrafenib

Revised:

Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and agree to use effective contraception, as defined in Section 7.4.3.1 from 14 days prior to enrollment, throughout the treatment period, and for 4 months after the last dose of study treatment.

Reasonforchange:

Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

4.1.3 Exclusion Criteria

Previous:

2. Prior treatment with any BRAF inhibitor (including but not limited to dabrafenib, vemurafenib, LGX818, or any BRAF mutant selective agent) or any MEK inhibitor (including but not limited to trametinib, AZD6244, and RDEA119).

4. Anti-cancer therapy (chemotherapy with delayed toxicity, extensive radiation therapy, immunotherapy, biologic therapy, or major surgery) or investigational anti-cancer therapy within 3 weeks, or chemotherapy without delayed toxicity within the 2 weeks of starting study treatment. (Note: Ipilimumab treatment must end at least 8 weeks prior to dosing.

8. History of another malignancy.

Exception: Subjects who have been disease-free for 3 years (i.e. subjects with second malignancies that are indolent or definitively treated at least 3 years) or subjects with a history of completely resected non-melanoma skin cancer.

Revised:

2. Prior treatment with a BRAF inhibitor or a MEK inhibitor.
3. Known ocular or primary mucosal melanoma
4. Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, within the last 3 weeks, or chemotherapy without delayed toxicity within the last 2 weeks preceding the first dose of the combination. Prior systemic treatment in the adjuvant setting is allowed (same timelines as above). (Note: Ipilimumab treatment must end at least 8 weeks prior to enrollment.)
9. History of malignancy with confirmed activating RAS mutation at any time.

Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

Reasonforchange: Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Removalof:
Acute infection requiring intravenous antibiotics.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Previous:
A history or current evidence/risk of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED) including:

- Presence of predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or
- Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or RPED such as:
    i. Evidence of new optic disc cupping;
    ii. Evidence of new visual field defects on automated perimetry;
    iii. Intraocular pressure >21 mm Hg as measured by tonography.

Revised:
A history or current evidence of retinal vein occlusion (RVO)

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

4.2.1 Permanent Discontinuation from Study Treatment

Previous:
Survival and new anti-cancer therapy follow-up will continue until either all subjects are dead, withdrawn consent or lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up, whichever is earlier. At such time the study will be closed.

Revised:
Survival and new anti-cancer therapy follow-up will continue until either all subjects are dead, withdrawn consent or lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up from the date of first dose of study treatment, whichever is earlier.. At such time the study will be closed.

Reasonforchange:
Clarification that 5 years follow up is from the date of first dose of study treatment.

4.2.1. Subject Completion and Withdrawal

Previous:
A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period or has had at least 5 years follow-up from the end of the trial. The cause of death will be documented in the eCRF.

Revised:
A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period or has had at least 5 years follow-up from the date of first dose of study treatment at the end of the trial. The cause of death will be documented in the eCRF.

Reasonforchange:
Clarification that 5 years follow up is from the date of first dose of study treatment.

5.2.1 Dabrafenib and Trametinib Combination

Previous:
Both study treatments should be administered **in the morning** at approximately the same time every day. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal. If administration of trametinib is interrupted or permanently discontinued, administration of dabrafenib may be continued. If administration of dabrafenib is interrupted, or permanently discontinued, administration of trametinib may continue.

Revised:
When administered in combination, take the once-daily dose of trametinib at approximately the same time each day with either the morning dose or the evening dose of dabrafenib. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

5.2.1 Dabrafenib and Trametinib Combination

Previous:
Subjects should abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pommelos within 7 days prior to dosing until treatment discontinuation, as these have been shown to inhibit CYP3A4 activity.

Revised:
Removed

Reasonforchange:
This restriction is no longer required.

5.8 Dose Modification Guidelines

Previous:
With the exceptions of pyrexia (likely related to dabrafenib); and decreased LVEF, RVO (retinal vein occlusion), and RPED (likely related to trametinib), the guidance suggests that both therapies be reduced, interrupted or discontinued simultaneously in response to toxicities that are considered by the investigator to be treatment related.

Revised:
With the exceptions of pyrexia and new primary RAS-mutation positive non-cutaneous malignancies(likely related to dabrafenib); and decreased LVEF, RVO (retinal vein occlusion), RPED, and pneumonitis (likely related to trametinib), the guidance suggests that both therapies be reduced, interrupted or discontinued simultaneously in response to toxicities that are considered by the investigator to be treatment related.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Table 3 Categories of Dose Modification Guidelines

Previous:

Adverse Event	Dabrafenib	Trametinib
Visual Changes (RV0)		X
Pneumonitis	X	X

Revised:

Adverse Event	Dabrafenib	Trametinib
Visual Changes		X
Pneumonitis		X

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Table 5 Dose Modification Guidelines for Events Considered Related to Study Treatment (Dabrafenib and Trametinib Combination Treatment)

Previous:

Dose Modification Guidelines for Events Considered Related to Study Treatment (Dabrafenib and Trametinib Combination Treatment)

CTCAE	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

CTCAE	Action and Dose Modification
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[a] medical monitor.

Revised:

Dose Modification Guidelines for Events Considered Related to Study Treatment (Dabrafenib and Trametinib Combination Treatment).

CTCAE	Action and Dose Modificationa,b
Grade 1 or Grade 2	**Continue study treatment at same dose level (no dose modification) and monitor as clinically indicated.**
Grade 2 (Intolerable) or Grade 3	
1st, 2nd or 3rd occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 then restart at next lower dose level
4th or greater occurrence	Discontinue treatment.
Grade 4	
1st occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level or discontinue at discretion of investigator
2nd occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 or baseline then restart at two dose levels lower than the starting dose or discontinue at discretion of investigator and after discussion with the medical monitor.
3rd occurrence	Discontinue treatment

Treatment should be discontinued if more than 3 dose reductions are required
Approval from the GSK Medical Monitor is required to restart study treatment after ≥21 days.

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed 150 mg twice daily and the trametinib should not exceed 2 mg once daily.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Table 6 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Previous:
Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Dose Modification Guidelines and Stopping Criteria for LVEF

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 trametinib and dabrafenib 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 treatment with trametinib or placebo reduced dose by one dose level.
		• Restart dabrafenib at previous dose level[b]
		• 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[d].

Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib.** • **Discontinue dabrafenib** • **Report as SAE** • **Consult with cardiologist**

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) If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult medical monitor.
c) Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
d) Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.
e) Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.

Revised:

Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Dose Modification Guidelines and Stopping Criteria for LVEF

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 trametinib and repeat ECHO within 2 weeksa,b • 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 • If approved, restart treatment with trametinib reduced by one dose level • Repeat ECHO at 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** • **Report as SAE** • Repeat ECHO after 2, 4, 8, 12, and16 • weeks or until resolution
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib** • **Interrupt dabrafenib.**[d] • **Report as SAE** • **Consult with cardiologist**

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) If recurrent episodes of LVEF reduction occur in subjects receiving dabrafenib monotherapy, consult medical monitor.
d) Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
c) Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Table 8 Withholding and Stopping Criteria for QTcB-Prolongation

Previous:
Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline • 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.

Revised:
Withholding and Stopping Criteria for QTcB-Prolongation

QTc-	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If event resolves, restart study treatment at current dose level[b] **• If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist.** • **If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist.**

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.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

5.8.4.3. Guidelines for cuSCC and new cases of secondary melanomas

Previous:
Cutaneous squamous cell carcinomas have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB); [GlaxoSmithKline Document Number 2011N126811_00.2012]. 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 cuSCC tumour tissue for analysis and as directed in the SPM.

Revised:
12.9.1.1 Guidelines for cuSCC and treatment emergent melanomas

Cutaneous squamous cell carcinomas have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB); [GlaxoSmithKline Document Number 2011N126811_00, 2012]. 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. Pathology report should be placed in subject chart

New Primary Melanoma: New primary melanomas have been reported in patients treated with dabrafenib. These were identified primarily within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.New primary cancers and treatment-emergent malignancies, with the exception of basal cell carcinoma (BCC) should be reported as a SAE. BCC should be reported as an AE or SAE based on the discretion of the investigator. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses. Testing of these biopsies may include RAS mutation testing and analysis of proteins related to the action of dabrafenib. Genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens may be performed, and would be restricted to the analysis of pathway mutations known to be associated with, and relevant to, BRAF-mutant tumors or pathway activation.

Evaluate for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of study treatment, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination

5.8.5.1. Guidelines for Pyrexia

Previous:
Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy or in combination with trametinib (see dabrafenib and dabrafenib and trametinib combination IBs); [GlaxoSmithKline Document Number CM2010/00010/02 2011 and GlaxoSmithKline Document Number 2011N126811_00.2012]. In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE as per Section 7.4.2.6.
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 - ibuprofen (preferred) or acetaminophen/paracetamol 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 5.8.5.3).

Guidelines regarding management and dose modifications for pyrexia considered to be related to study treatment are provided in Table 11.

Table 11 Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification
Pyrexia	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 (**acetaminophen is recommended as first line anti-pyretic before moving into ibuprofen**) clinically indicated and continue prophylactic treatment[f]	1st Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**

Adverse Event	Adverse Event Management	Action and Dose Modification
[a]	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	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 <50 mg BID, permanently **discontinue dabrafenib. Trametinib may be continued**

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
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (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 sample for cytokine analysis should be taken immediately at the first occurrence of fever (i.e. when the subject visits the clinic) and after the fever has disappeared (i.e. during the next routine visit), samples must be sent to the central laboratory.
f. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. 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.

Revised:
Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy, and is increased in incidence and severity in subjects receiving dabrafenib in combination with trametinib (see dabrafenib and dabrafenib and trametinib combination IBs); [GlaxoSmithKline Document Number CM2010/00010/02 2011 and GlaxoSmithKline Document Number 2011N126811_00.2012]. In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

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 anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia (see Section 5.8.5.3).

Guidelines regarding management and dose modifications for pyrexia considered to be related to study treatment are provided in Table 11.

Table 11 Management and Dose Modification Guidelines for Pyrexia[a,b]

Adverse Event	Adverse Event Management	Action and Dose Modification
Pyrexia[a]	<u>All Events:</u> • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d] <u>ent[b]:</u> • Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration or hypotension[e] <u>2nd Event[f]</u> • 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] <u>Subsequent Events</u>: • Within 3 days of onset of pyrexia: ○ Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f] ○ If corticosteroids have been tapered and pyrexia recurs, restart steroids ○ If corticosteroids cannot be tapered consult medical monitor	<u>1st Event:</u> • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level ○ If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** <u>2nd Event:</u> • **Interrupt dabrafend** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level ○ If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** <u>Subsequent Events:</u> • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[g]** • If dabrafenib must be reduced to <50 mg BID, permanently **Discontinue dabrafenib.Trametinib may be continued**

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
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (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. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
f. 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.
g. 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.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

5.8.5.4. Guidelines for Visual Changes

Previous:
Episodes of visual changes have been observed in subjects receiving dabrafenib, trametinib or the combination of both therapies. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Special attention should be given to retinal (e.g., CSR) or retinal vein abnormalities (e.g., RVO). For events of visual changes regardless of severity, 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 considered to be related to study treatment are provided in Table 34

Table 14 Management and Dose Modification Guidelines for Visual Changes

CTC AE	Adverse Event Management	Action and Dose Modification
Grade 1	• Consult ophthalmologist within 7 days of onset • Exclude CSR or RVO • Consult retinal specialist in case of CSR or RVO • Report RVO as SAE • Continue follow up examination(s) by retinal specialist for CSR and RVO	• Continue study treatment at the same dose level until ophthalmologic examination can be conducted[b] • If ophthalmologic examination cannot be performed within 7 days of onset, interrupt study treatment until CSR and RVO can be excluded and symptoms resolve • Restart trametinib at same dose level • CSR: Interrupt trametinib until symptoms resolve and exam by retinal specialist shows resolution • Restart with trametinib reduced by one dose level • RVO: **Permanently discontinue trametinib**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Exclude CSR and RVO • Consult retinal specialist in case of RVO or CSR for follow-up exam • Report RVO as SAE • Continue follow up examination(s) by retinal specialist for CSR and RVO	• Interrupt trametinib until signs and symptoms have resolved to baseline • Restart with trametinib reduced by one dose level • CSR: Interrupt trametinib until symptoms resolve and exam by retinal specialist shows resolution Restart trametinib **reduced by one dose level** • RVO: **Permanently discontinue trametinib**
Grade 4	• Consult ophthalmologist immediately • Exclude CSR and RVO • Report RVO as SAE • Continue follow up examination(s) by retinal specialist for CSR and RVO	• **Permanently discontinue trametinib**

CSR = central serous retinopaty; 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.

Revised:

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 14.

Table 14 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• 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 15 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**

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
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.**

Abbreviations: RPED = retinal pigment epithelial detachment; 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.

Table 15 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

Refers to CTCAE Version 4.0 'Retinopathy'

Language for Ophthalmologic Exam description

Ophthalmologic Exam

At certain time points in the trial and if visual changes develop, an eye exam is indicated. (Refer to Section 5.8.5.4 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.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Table 37 Management and Dose Modification Guidelines for Pneumonitis

5.8.5.5. Guidelines for Pneumonitis

Addition:

Pneumonitis has been observed in subjects receiving dabrafenib and 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
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
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 trametinib 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

CTCAE Grade	Adverse Event Management	Action and Dose Modification
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 trametinib 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 trametinib**

BAL= broncioalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

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) If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult medical monitor.
c) Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
d) Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.
e) Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.

Reasonforchange: Omitted from protocol V00

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 with the exception of new anti-cancer therapy, if taken after study treatment discontinuation; these will be documented until study completion/withdrawal or death. 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, the dates of administration and reason for medications will be recorded. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

Patients 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.

While patients are on study treatment, palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline. The total dose may not exceed 30 Gy.

Revised:
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 however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin. While patients are on study treatment, palliative radiation therapy is permitted for non target lesions that are either new or present at baseline.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib be held for seven days before and two days after XRT in subjects receiving dabrafenib monotherapy or in combination with trametinib. These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury.

Reason for change:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.
The total dose may not exceed 30 Gy.

Revised:
Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib be held for seven days before and two days after XRT in subjects receiving dabrafenib monotherapy or in combination with trametinib. These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury.

Reason for change:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Previous:

Table 18 Medications to be used with Caution

USE WITH CAUTION: Concentrations of these drugs may be increased or decreased by dabrafenib	
Class/Therapeutic Area	**Mild/Moderate CYP3A and CYP2C8**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant, cimetidine, montelukast
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, or CYP2C19 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
USE WITH CAUTION: Concentrations of these drugs may be increased or decreased by dabrafenib	
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, cerivastatin

Class/Therapeutic Area	Mild/Moderate CYP3A and CYP2C8
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,
Selective Aldosterone Blockers	Eplerenone

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.

Revised:

Table 18 Medications to be used with Caution

USE WITH CAUTION: Concentrations of these drugs may be increased or decreased by dabrafenib	
Class/Therapeutic Area	**Mild/Moderate CYP3A and CYP2C8**
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, or CYP2C19 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
Class/Therapeutic	**Mild/Moderate CYP3A and CYP2C8**
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, digoxin, 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 as exposure to	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole,

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.

Reason for change:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Table 19 Time and Events Table

Previous:

Study Assessments[1]	Screen[-2]	Week 1[-2]	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	and then Monthly Until	Unsch	Disc	Fwp[19]	Conc
Informed consent	X															
Tumour tissue sample for BRAF V600 mutation[3]	X															
Intracranial target and non –target lesion assessment and response[21]	X		X	X		X		X		X		X		X		
Extracranial target and non-target lesion assessment and response[22]	X		X	X		X		X		X		X		X		
Inclusion / exclusion criteria[4]	X															
Register subject	X															
Chemistry and Haematology[5]	X	X	X	X	X	X	X	X	X	X	X	X		X		
Serum pregnancy test[6]	X															
Coagulation	X															
Physical examination	X													X		
Height[7]	X															
Weight, Temp, BP, Resp and HR[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographic data	X															
Disease characteristics[9]	X															
Prior anti-cancer therapy, radiotherapy and surgical procedures	X															
Past and current medical conditions, family history	X															
Alcohol consumption	X															

Study Assessments[1]	Screen[-2]	Week 1[-2]	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	and then Monthly Until	Unsch	Disc	Fwp[19]	Conc
Past and current tobacco consumption	X															
[redacted]																
Cytokine[12]	X		X													
Neurological assessment[13]	X		X	X		X		X		X		X		X		
Ophthalmic Examination[14]	X		X													
Dermatologic skin assessment[15]	X		X	X	X	X	X	X	X	X	X	X		X	X	
Dispense oral study treatment and assess compliance[16]		X	X	X	X	X	X	X	X	X	X	X				
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[17]	X		X	X	X			X			X			X		
ECHO[18]	X		X		X									X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood products and blood supportive care products	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up contact, anti-cancer therapy[20]															X	
Subject completion																X
Death record																X

Revised:

Time and Events Table

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	then Monthly	Unscheduled	Discontinued	Follow up[9]	Conclusion
Informed consent	X															
Tumour tissue sample for BRAF V600 mutation[3]	X															
Intracranial target and non –target lesion assessment and response[21]	X		X	X		X		X		X		X		X		
Extracranial target and non-target lesion assessment and response[22]	X		X	X		X		X		X		X		X		
[redacted]																
Inclusion / exclusion criteria[4]	X															
Register subject	X															
Chemistry and Haematology[5]	X	X	X	X	X	X	X	X	X	X	X	X		X		
Serum pregnancy test[6]	X															
Coagulation	X															
Physical examination	X													X		
Height[7]	X															
Weight, Temp, BP, Resp and HR[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographic data	X															
Disease characteristics[9]	X															
Prior anti-cancer therapy, radiotherapy and surgical procedures	X															
Past and current medical conditions, family history	X															
Alcohol consumption	X															

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	then Monthly	Unscheduled	Discontinued	Follow up[9]	Conclusion
Past and current tobacco consumption	X															
[redacted]																
Cytokine[12]	X		X													
Neurological assessment[13]	X		X	X		X		X		X		X		X		
Ophthalmic Examination[14]	X		X													
Dermatologic skin assessment[15]	X		X	X	X	X	X	X	X	X	X	X		X	X	
Dispense oral study treatment and assess compliance[16]		X	X	X	X	X	X	X	X	X	X	X				
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[17]	X		X	X	X			X			X			X		
ECHO[18]	X		X		X			X			X			X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood products and blood supportive care products	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up contact, anti-cancer therapy[20]															X	
Subject completion																X
Death record																X

Reason for change:
Week 1 was updated to Day 1; Footnotes updates; Subjects who have undergone local BRAF testing and who are BRAF V600 E ~~or V600K~~ mutation positive- V600K was removed as this was a typographical error; clarification that patients must wait for BRAF mutation status confirmation from central testing before first dose for cohort A; Ophthalmology Exam: An ophthalmic examination was updated from will be performed at Screening to prior to first dose; First dose of study medication must be within 72 hours of randomization was deleted; Follow-up contact: All subjects who permanently discontinue study treatment will be followed for survival, dermatologic skin assessments and new anti-cancer therapies (including radiotherapy and surgery) every month for 6 months after study treatment discontinuation – (or until a new cancer treatment is initiated) was added for clarification; ECHO exams in the table were corrected to screening, weeks 4,12 and then every 12 weeks including discontinuation visit .

Table 19 Footnotes
Previousfootnote#2:
Screening procedures may be performed 14 days prior to first dose of study drug, except for tumour assessments which may be performed 28 days prior to first dose of study drug, and echocardiograms and ECGs which may be performed 35 days prior to the first dose of study drug. Subjects who have undergone local BRAF testing and who are BRAF V600 E or V600K mutation positive, may begin screening procedures but sites still need to send in tissue sample to the central laboratory for central testing for cohort assignment. Beginning with Week 1 visit, all assessment visits have a ± 7 day visit window for flexible scheduling.

Revisedfootnote#2:
Screening procedures may be performed 14 days prior to first dose of study drug, except for tumour assessments which may be performed 28 days prior to first dose of study drug, and echocardiograms and ECGs which may be performed 35 days prior to the first dose of study drug. Subjects who have undergone local BRAF testing and who are BRAF V600 E ~~or V600K~~ mutation positive, may begin screening procedures however, must wait for BRAF mutation status confirmation from central testing before first dose for cohort A. For Cohorts B, C, and D sites still need to send in tissue sample to the central laboratory for retrospective testing. Beginning with Day 1 visit, all visits have a ± 3 day visit window and scans will have ± 7 days for flexible scheduling.

ReasonforChange:
Typographical errors

Table 19 Footnote
Previousfootnote#14:
Ophthalmology Exam: An ophthalmic examination will be performed at Screening and week 4; after week 4, additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.4.5 for details.
Revisedfootnote#14:

25. Ophthalmology Exam: An ophthalmic examination will be performed prior to first dose and week 4; after week 4, additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.4.5 for details

ReasonforChange:
Updated timing of exam from preformed at screening to prior to forst dose to allow more flexible scheduling.

Table 19 Footnote
Previousfootnote#16:
Dispensation of Study Treatment: Dispense a 4-6 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays and/or dose escalations. First dose of study medication must be within 72 hours of randomization.

Revisedfootnote#16:
Dispensation of Study Treatment: Dispense a 4-6 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays and/or dose escalations. ~~First dose of study medication must be within 72 hours of randomization.~~

ReasonforChange:
This restriction is no longer required.

Table 19 Footnote
Previousfootnote#20:
Follow-up contact: All subjects who permanently discontinue study treatment will be followed for survival, dermatologic skin assessments and new anti-cancer therapies (including radiotherapy and surgery) every month for 6 months after study treatment discontinuation.

Revisedfootnote#16:
Follow-up contact: All subjects who permanently discontinue study treatment will be followed for survival, dermatologic skin assessments and new anti-cancer therapies (including radiotherapy and surgery) every month for 6 months after study treatment discontinuation or until a new cancer treatment is initiated

ReasonforChange:
Clarification of follow up untildiscontinuation or new cancer treatment initiated

7.2.1.1. Secondary Endpoints

Previous:
overall survival (OS)

Revised:
overall survival (OS) and long-term (particularly 5-year) OS

Reason for change:
Addition of long term overall survival.

7.4.2.2 Definition of a SAE

Previous:

- Laboratory abnormalities as referenced in Section 7.4.2.3.
- LVEF that meets stopping criteria Section 5.8.3.1.
- CSR or RVO
- Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills

Revised:

- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance (Section 5.8.3.1)
- ~~Laboratory abnormalities as referenced in Section 7.4.2.3.~~
- LVEF that meets stopping criteria Section 5.8.3.1.
- ~~CSR or RVO~~
- ~~Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills~~

Reason for change:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

7.4.4.1. Pregnancy Testing and Prevention

Addition:
Note: French/German subjects: no contraception for men is required

Reason for change:
Alignment with European label

Clinical Chemistry Parameters
Albumin
Alkaline Phosphatase
Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT)
Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT)
Gamma-Glutamyl Transpeptidase (GGT)
Bicarbonate
Blood Urea Nitrogen (BUN) or urea
Calcium Chloride
Creatinine[c]
Glucose (random)
Lactate Dehydrogenase (LDH)
Magnesium
Phosphate
Potassium
Sodium
Total Bilirubin[b]
Total Protein

Revised:

Clinical Chemistry Parameters
Albumin
Alkaline Phosphatase
Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT)
Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT)
Gamma-Glutamyl Transpeptidase (GGT)
Blood Urea Nitrogen (BUN) or urea
Calcium
Creatinine[c]
Glucose (random)
Lactate Dehydrogenase (LDH)
Magnesium
Phosphate
Potassium
Sodium
Total Bilirubin[b]
Total Protein

Reason for change:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

Subjects are required to have a standard ophthalmic examination performed by an ophthalmologist at baseline, at week 4 and as clinically warranted per protocol's guidance.

Revised:
Subjects are required to have a standard ophthalmic examination performed by an ophthalmologist at prior to first dose, at week 4 and as clinically warranted per protocol's guidance.

Reasonforchange:
Updated to align with the updated asset standard language for the dabrafenib and trametinib combination.

9.3.3. Treatment Comparisons

Previous:
There are no treatment comparisons. The primary objective will be supported by testing the null.). The three cohorts will not be compared statistically for any endpoint.

Revised:
There are no treatment comparisons. The primary objective will be supported by testing the null hypothesis in Cohort A The three cohorts will not be compared statistically for any endpoint.

Reason for change:
Clarification of cohort A

Addition of Appendix 9 for French and German country specific requirements

12.9 Appendix 9: Country Specific Requirements

[redacted]

12.9 Exclusion Criteria

- Subjects with history of HIV are excluded from this the study. (Section 4.1.3)
- Subjects under guardianship / under supervision (another person is responsible, decide for the patient) or deprived of liberty (in prison for example) will be excluded from this study.
- Subjects that present with electrolyte abnormalities are excluded from this study.
- Subjects taking medications known to induce QT prolongation are excluded from this study.

12.9. Valvular toxicity citeria

Guidelines for Valvular Toxicity for Subjects Enrolled in France

- Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0) should temporarily discontinue dabrafenib and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.
    - If the valve recovers to baseline any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
    - If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue dabrafenib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Table 29 Withholding and Stopping Criteria for QTcB-Prolongation

Previous:

QTc-	Action and Dose Modification
• QTcB ≥501 msec	4) **Interrupt** all study treatments until QTcB prolongation resolves to grade 1 or baseline 5) **Test** serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. 6) Review concomitant medication usage for agents that prolong QTc. 7) If event resolves, restart study treatment at current dose level[b] 8) If event does not resolve, permanently discontinue study treatments. 9) Consider evaluation with cardiologist. 10) If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist.
• QTcB ≥501 msec	**11) Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline** **12) Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits.** **13) Review concomitant medication usage for agents that prolong QTc.** **14) If event resolves, restart study treatment at lower dose level or current.dose level[b]** **15) If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist.** **16) If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist.**

Revised:

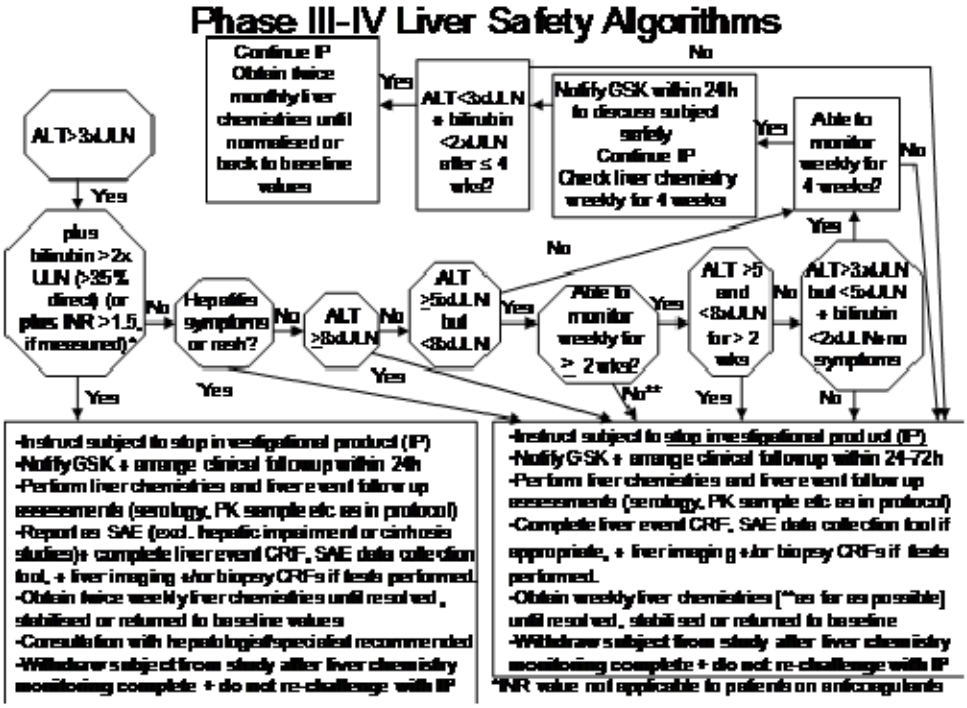
Reason for change: To be in line with label

Table 30 Management and Dose Modification Guidelines for Pneumonitis

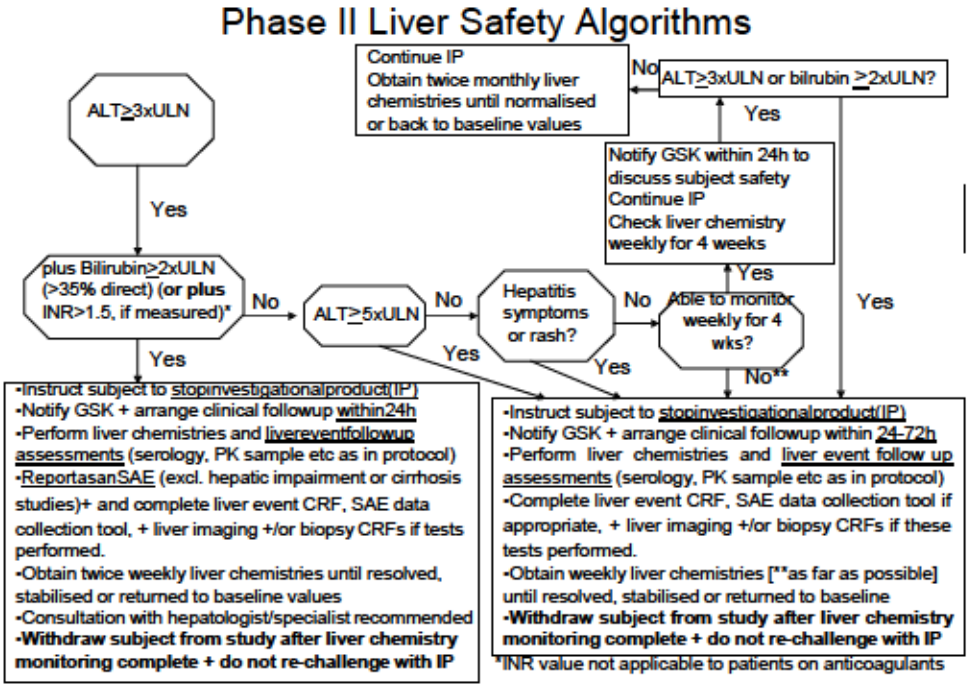
Removal of footnotes as they did not pertain to the pneumonitis guidelines

Appendix 6: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Previous:



Revised:



Reason for change:
Appendix 6 – removal of Phase III to IV algorithm and placement of phase II algorithm.

- Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) valvular toxicity must discontinue dabrafenib. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart dabrafenib at a reduced dose after consultation and approval of the GSK medical monitor. For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

ECHO must be performed at baseline and at follow-up visit(s). Copies of all ECHO(s) and cardiology consultations performed on subjects who experience a valvular toxicity will be required by GSK for review.

12.9 Non-cutaneous secondary/recurrent malignancy

Prior to initiation of study treatment subjects should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen Computed Tomography (CT) scan. During treatment subjects should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations are recommended before the start of and at the end of treatment or when considered clinically indicated. Complete blood cell counts should be performed as clinically indicated. Following discontinuation of dabrafenib monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy, whichever comes first. Any non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE and treated according to standard clinical practice. Reason for change:
Country-specific updates as requested by the French regulatory agency.

12.11. Appendix 11: Protocol Changes for Amendment 02

Amendment Number 02

This amendment is applicable to all investigational study sites in **France only**.
Administrative changes including updated Sponsor Contact information.

Previous:

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 trametinibat 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 trametinib until recovery to grade ≤1 • Restart with trametinibreduced 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 trametinib
Grade 3	• CT scan (high- resolution with lung windows) • Clinical evaluation and laboratory work- up for infection • Consul 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 trametinib until recovery to grade ≤1 • After consultation with medical monitor, trametinibmay be restarted reduced by one dose level. • • If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib treatment
Grade 4	• Same as grade 3	• Permanently discontinue trametinib

BAL= broncioalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

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) If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult medical monitor.
c) Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
d) Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.
e) Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.

Revised:
Removal of footnotes.

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 recommende. • Consultation of pulmonologist recommended.	• Continue trametinibat 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 trametinib until recovery to grade ≤1 • Restart with trametinib be 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 trametinib
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 trametinib until recovery to grade ≤1 • After consultation with medical monitor, trametinib may be restarted reduced by one dose level • If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib treatment
Grade 4	• Same as grade 3	• Permanently discontinue trametinib

Reason for change:
Removal of footnotes as they did not pertain to the pneumonitis guidelines.

Table 29 Withholding and Stopping Criteria for QTcB-Prolongation

Previous:

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline. • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If event resolves, restart study treatment at current dose level[b] • If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist. • If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist.

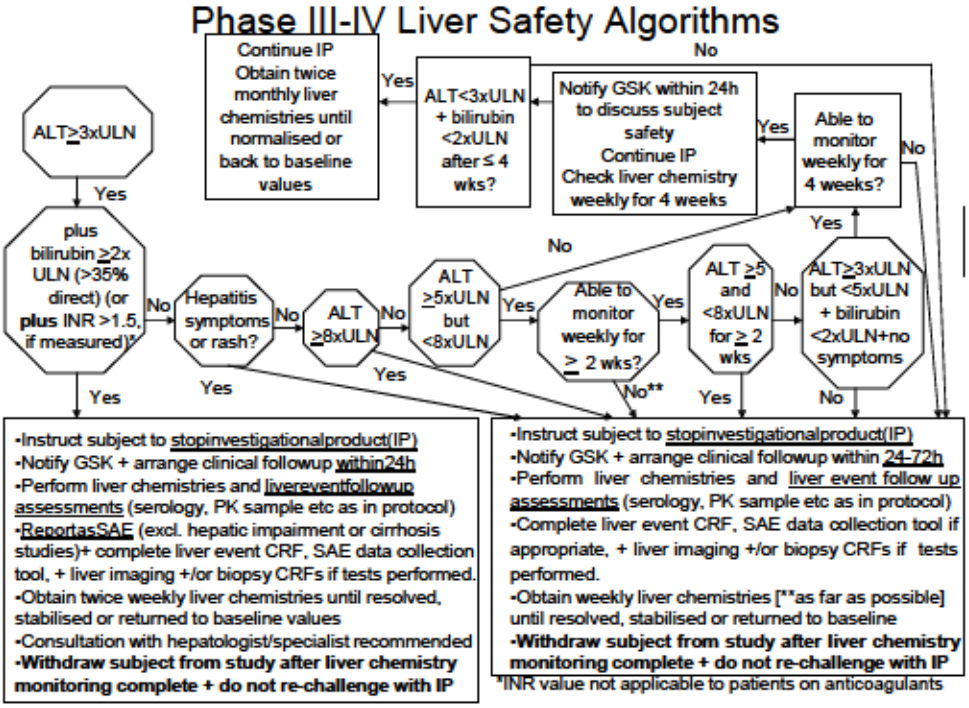
Revised:

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If event resolves, restart study treatment at lower dose level or current dose level[b] • If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist. • If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist.

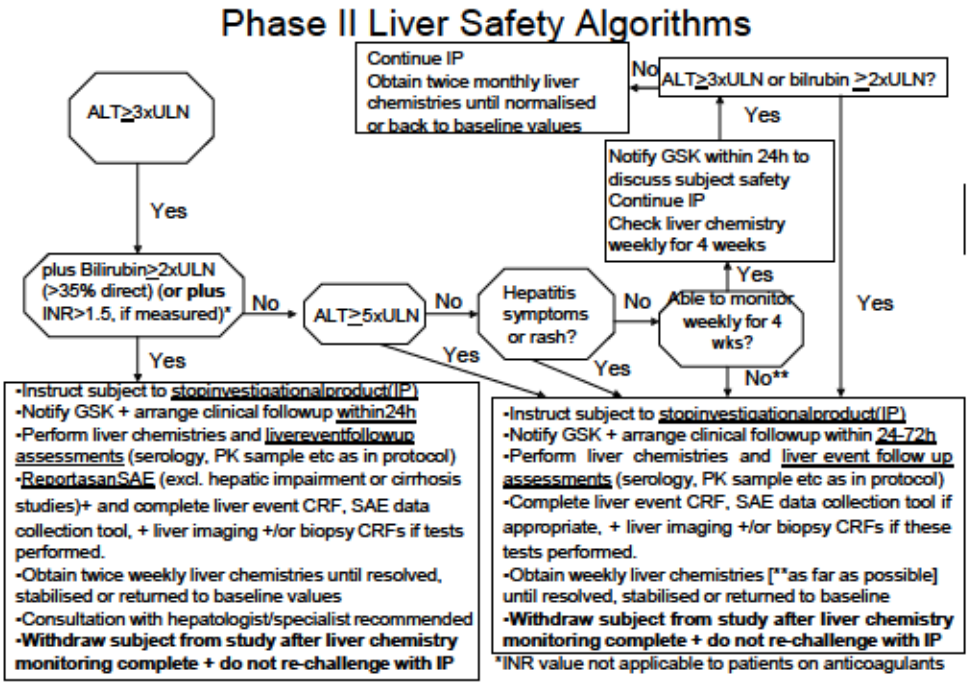
Reason for change:
To be in line with label.

Appendix 6: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Previous:



Revised:


Phase II Liver Safety Algorithms
ALT≥3xULN
Yes
plus Bilirubin≥2xULN (>35% direct) (or plus INR>1.5, if measured)*
No
ALT≥5xULN
No
Hepatitis symptoms or rash?
No
Able to monitor weekly for 4 wks?
No**
Yes
Yes
Yes
Yes
Yes
Continue IP
Obtain twice monthly liver chemistries until normalised or back to baseline values
No
ALT≥3xULN or bilrubin ≥2xULN?
Yes
Notify GSK within 24h to discuss subject safety
Continue IP
Check liver chemistry weekly for 4 weeks
•Instruct subject to stopinvestigationalproduct(IP)
•Notify GSK + arrange clinical followup within24h
•Perform liver chemistries and livereventfollowup assessments (serology, PK sample etc as in protocol)
•ReportasanSAE (excl. hepatic impairment or cirrhosis studies)+ and complete liver event CRF, SAE data collection tool, + liver imaging +/or biopsy CRFs if tests performed.
•Obtain twice weekly liver chemistries until resolved, stabilised or returned to baseline values
•Consultation with hepatologist/specialist recommended
•Withdraw subject from study after liver chemistry monitoring complete + do not re-challenge with IP
•Instruct subject to stopinvestigationalproduct(IP)
•Notify GSK + arrange clinical followup within 24-72h
•Perform liver chemistries and liver event follow up assessments (serology, PK sample etc as in protocol)
•Complete liver event CRF, SAE data collection tool if appropriate, + liver imaging +/or biopsy CRFs if these tests performed.
•Obtain weekly liver chemistries [**as far as possible] until resolved, stabilised or returned to baseline
•Withdraw subject from study after liver chemistry monitoring complete + do not re-challenge with IP
*INR value not applicable to patients on anticoagulants

Reason for change:
Appendix 6 – removal of Phase III to IV algorithm and placement of phase II algorithm.

12.12. Appendix 12: Protocol Changes for Amendment 03

Amendment Number 03

This amendment is applicable to all investigational study sites in all countries.

1) Revised list of authors

2) Clarification Protocol Amendment 2 is a country-specific amendment as requested by the French regulatory agency.

3) Minor administrative changes and correction to typographical errors throughout the document.

4) Table of Contents Updated with Section 1.3, Appendix 11 and 12 references.

5) Section 1.3 header added for clarity between study and dose rationale.

6) Study design revised for clarity around treatment discontinuation and follow up of subjects.

7) Exclusion HIV removed per March 2014 updates to Inc/Exc (combination).

8) Permanent discontinuation from study treatment revised for clarity around treatment discontinuation and follow up of subjects.

9) Dosage and administration section revised based on combination dosage and administration March 2014.

10) Table 3 added footnotes for consistency across MEK/BRAF protocols.

11) Dose Level Reduction Guidelines revised for consistency across MEK/BRAF protocols.

12) Table 6 superscript b and c added to symptomatic LVEF for consistency across MEK/BRAF protocols.

13) Table 7 well controlled BP revised for consistency across MEK/BRAF protocols.

14) Section 5.8.4 added 'keratoacanthoma for consistency across MEK/BRAF protocols.

15) Section 5.8.4.3 added 'keratoacanthoma for consistency across MEK/BRAF protocols.

16) Table 11 revised dabrafenib dose reduction for consistency across MEK/BRAF protocols.

17) Section 5.8.5.4 added reference Section 7.5.5.

18) Table 14 added footnote for PK reference.

19) Table 16 added footnotes for consistency across MEK/BRAF protocols.

20) Section 6.1 revised for clarity to time requirements for concomitant medications.

21) Table 17 header revised for clarity on prohibited medications.

22) Table 19 revised for clarity on required assessments.

23) Section 7.3.2.1 revised for consistency between updated Image Acquisition Guidelines for Brain MRI.

24) Section 7.3.2.2 revised for clarity around treatment discontinuation and follow up of subjects.

25) Section 7.5.3.1 revised serium pregnancy test to 7 days prior to enrolment in accordance with Oct 2014 safety guidance.

26) Section 7.5.5 revised with new ophthalmic criteria from July 2014 trametinib safety guidance.

27) Section 9.2.1 revised with description on how sample size of 75 was calculated.

28) Section 9.3.3 Treatment comparison clarified as NA for this study.

29) Table 25 revised for clarity between row 1 and row 2 in a superiority binomial trial.

30) Section 9.3.5.1.1 Secondary Analyses added line for clarification to interpretation.

31) Appendix 11 added to reflect amendment 02 changes.

32) Appendix 12 added to reflect amendment 03 changes.

12.13. Appendix 13: Protocol Changes for Amendment 04

This amendment is applicable to all investigational study sites in all countries:

1. Updating contact details of Medical Monitor.
2. Table 1 Study Objectives – 1. Primary endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and 2 secondary endpoint number 9 OS changed from 5 to 3 year.
3. Section 3 Study design – cohort A patient population updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts). And definition of study closure updated from "where all subjects still in follow up have had at least 5 years follow up…" to "where all subjects still in follow up have had at least 3 years follow up…"
4. Section 3.1 Discussion of Design – primary efficacy objective endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts)
5. Section 4.1.2 Inclusion Criteria 4 updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and Inclusion criteria 10 - period for contraception amended from 14 days prior to baseline to 7 days to be consistent with all other sections of protocol and current IB 7 safety update.
6. Section 4.2.1 reference to 5 year survival changed to 3.
7. Section 4.2.2 reference to 5 year survival changed to 3.
8. Section 5.2,1 Duplicated sentence deleted.
9. Section 5.8.1 Amended from dose reductions below 50 to dose reductions below 75 mg BID.
10. Table 5 "or greater occurrence" deleted.
11. Table 19 Time and Events Table – footnotes 2 and 3 amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts).
12. Section 7.2.1.1 secondary endpoint reference to 5 year survival changed to 3.
13. 7.4.3.1 Pregnancy Testing and Prevention – section updated period for contraception amended from 14 days prior to baseline to 7 days to be consistent with all other sections of protocol and current IB 7 safety update.
14. 7.6.2 BRAF mutation assay section amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts).
15. Section 9.3.5.1.1 Primary Analysis reference to 5 year survival changed to 3.
16. Section 10.5 Study and Site Closure reference to 5 year survival changed to 3.
17. Appendix 13 added to reflect amendment 04 changes.

12.14. Appendix 13: Protocol Changes for Amendment 05 (dated 13-Jul-2016) from Amendment 04 (dated 14 Dec 2015)

This amendment is applicable to all investigational study sites in all countries.

Amendment Summary of Main Changes: Global Changes

Section(s)	Change	Rationale
Header/Footer	Changed as per Novartis Requirements	Change in study sponsorship from GSK to Novartis
Title Page	Title Page replaced as per Novartis Requirements	Change in study sponsorship from GSK to Novartis
Sponsor Information Page	GSK contact information has been replaced with Novartis contact details	Change in study sponsorship from GSK to Novartis
Sponsor signatory	Change of sponsor signatory	Change in study sponsorship from GSK to Novartis
Multiple	The term 'GSK medical monitor' has been replaced by Novartis Global Clinical Lead	Change in study sponsorship from GSK to Novartis
Multiple	References to GSK concomitant medications deleted	Change in study sponsorship from GSK to Novartis
Multiple	References to GlaxoSmithKline or its staff replaced with with that of Novartis and its authorized agents	To align with the change of sponsorship from GSK to Novartis.
Multiple	Make administrative changes	To align with the change of sponsorship from GSK to Novartis.

Amendment Details:

Section: **List of abbreviations:**

Text added:

Clinical Research Organization (CRO)

Global Clinical Program Head (GCPH)

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 5.4: Treatment Assignment:

Text changed:

Upon obtaining consent from the subject for the study the subject will be registered into ~~the Registration and Medication Ordering System (RAMOS), the GSK~~ interactive voice response system (IVRS), by the investigator or authorized site staff to register and record subject activity. Study-specific instructional worksheets will be provided for the use of ~~RAMOS~~IVRS.

Once the target number of each cohort has been enrolled, that cohort will be closed to further enrolment and ~~RAMOS~~IVRS will no longer allow a subject to be entered.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 7: Study Assessments and procedures:

Table 19 Time and Events table:

Text changed:

Sentence added to Footnote 19 - Adverse events and Serious Adverse Events will be recorded form the time of first dose of study treatment is administered until 30 days after discontinuation of study treatment. All SAEs assessed as related to study participation (e.g. related to study procedures) should be collected from time of informed consent. Please refer to section 7.4.2.6 for reporting timelines. ~~Serious adverse events will be collected over the same time period as AE's except SAEs assessed related to study participation (e.g. protocol mandated procedures, invasive tests, or change in existing therapy), study treatment, or a GSK concomitant medication which must be recorded from the subjects consents to participate in the study up to and including any follow up contact.~~

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 7.4.2.5: Time Period and Frequency for detecting AEs and SAEs:

Text changed:

All SAEs and ~~A~~adverse events (AEs) will be collected from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment regardless of initiation of a new anti-cancer therapy or transfer to hospice.

~~Serious adverse events (SAEs) will be collected over the same time period as stated above for AEs. In addition,~~ From the time a subject consents to participate in and completes the study (See Section 4.2), ~~any~~ all SAEs assessed as **related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), ~~study treatment, or a 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 promptly to ~~GSK~~ Novartis ~~within 24 hours,~~ as indicated in Section 7.4.2.6.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 7.4.2.6: Prompt Reporting of Serious Adverse Events and Other Events to ~~GSK~~Novartis

Table 23 Time Frames for Reporting SAEs and Other Events

Text changed:

Pregnancy	~~2 weeks~~ 24 hours	Pregnancy notification form	2 weeks	Pregnancy follow-up form

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 7.4.3.2: Pregnancy Reporting:

Text changed:

To ensure subject safety, each pregnancy must be reported to ~~GSK~~Novartis within ~~2 weeks~~24 hours of learning of its occurrence.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 8. Data Management:

Text added:

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets that support the protocol objectives.

Text changed:

~~Management of e~~Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures with the objective of resolving errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. ~~to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.~~ All AE~~dverse event~~s and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and ~~an internal validated~~ a custom medication dictionary~~, GSKDrug~~.

~~In all cases, subject initials will not be collected or transmitted to GSK in accordance with GSK policy.~~

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 10.2 Regulatory and Ethical Considerations, Including the Informed Consent Process:

Text changed:

Prior to initiation of a study site, Novartis ~~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 including those required under a US IND.

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

- ~~Institutional Review Board (~~IRB~~)/Independent Ethics Committee (~~IEC~~)~~ review and favourable opinion/approval of study protocol and any subsequent amendments.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 10.3. Quality Control (Study Monitoring)

Text changed

In accordance with applicable regulations, GCP, and Novartis ~~GSK~~ procedures, Novartis personnel (or designated Clinical Research Organisation [CRO]) will contact 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 Novartis ~~GSK~~ requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF 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.~~

Novartis (or designated CRO) personnel will monitor the study to ensure that the:
~~Monitoring visits will be conducted in a manner to ensure that the:~~

- Study is conducted in accordance with the currently approved protocol and any other study agreements, ~~ICH~~ GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 10.5. Study and Site Closure:

Text changed:

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

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Section 10.6. Records Retention:

Text changed:

~~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.~~

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Novartis provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

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

Text changed:

Novartis ~~GSK~~aims to post a results summary to the Novartis ~~GSK~~Clinical ~~Study Register~~Trial Results website www.novartisclinicaltrials.com and other publicly available registers no later than 12~~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. Novartis~~GSK~~ also aims to publish the full study protocol on the Novartis~~GSK~~ Clinical ~~Study Register~~Trial Results website (www.novartisclinicaltrials.com) at the time the results of the study are published as a manuscript in the scientific literature.

Reason for change:

Change in study sponsorship and to bring into line with Novartis processes

Appendix 15: Protocol Changes for Amendment 07 (and 6 on GSK template only)

Page 22 last Paragraph

From:

Study closure is defined by where all subjects still in follow up have had at least 3 years follow-up from the date of first dose of study treatment, whichever is earlier.

To:

Study closure is defined by where all cohort A subjects still in follow up have had the opportunity for at least 3 years follow-up from the date of first dose of study treatment or 70% of cohort A patients have died or are lost to follow up, whichever is earlier.

Reason for change

The extension is required due to immaturity of cohort A data, the primary efficacy population, which is a result of slow recruitment in this cohort.

Page 34 last paragraph

From:

Study closure is defined by where all subjects still in follow up have had at least 3 years follow-up from the date of first dose of study treatment, whichever is earlier.

To

Study closure is defined by where all cohort A subjects still in follow up have had the opportunity for at least 3 years follow-up from the date of first dose of study treatment or 70% of cohort A patients have died or are lost to follow up, whichever is earlier

Reason for change

The extension is required due to immaturity of cohort A data, the primary efficacy population, which is a result of slow recruitment in this cohort.

Page 108 section 10.5

From:

The study will be considered closed when 70% of the total enrolled study population has died or been lost to follow-up, which is estimated to be approximately 3 years after the start of the study.

To:

The study will be considered closed when all cohort A subjects still in follow up have had the opportunity for at least 3 years follow-up from the date of first dose of study treatment or 70% of cohort A patients have died or are lost to follow up, whichever is earlier

Reason for change

The extension is required due to immaturity of cohort A data, the primary efficacy population, which is a result of slow recruitment in this cohort.

Page 35 paragraph 5

From:
The study is designed to have **84%** statistical power to detect an IR of 50% in V600E mutation-positive subjects who receive dabrafenib in combination with trametinib in Cohort A.
To:

The study is designed to have **82%** statistical power to detect an IR of 50% in V600E mutation-positive subjects who receive dabrafenib in combination with trametinib in Cohort A.

Reason for change – typographical error between protocol and SAP.

Page 108 paragraph 4

From

The study is designed to have **84%** statistical power to detect an IR of 50% in V600E mutation-positive subjects who receive dabrafenib in combination with trametinib in Cohort A.

To

The study is designed to have **82%** statistical power to detect an IR of 50% in V600E mutation-positive subjects who receive dabrafenib in combination with trametinib in Cohort A.

Reason for change – typographical error between protocol and SAP.

Page 71 Table 19 From

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	then Monthly	Unscheduled	Discontinued	Follow up[9]	Conclusion
Informed consent	X															
Tumour tissue sample for BRAF V600 mutation[3]	X															
Intracranial target and non –target lesion assessment and response[21]	X		X	X		X		X		X		X		X		
Extracranial target and non-target lesion assessment and response[22]	X		X	X		X		X		X		X		X		
Inclusion / exclusion criteria[4]	X															
Register subject	X															
Chemistry and Haematology[5]	X	X	X	X	X	X	X	X	X	X	X	X		X		
Serum pregnancy test[6]	X															
Coagulation	X															
Physical examination	X													X		
Height[7]	X															
Weight, Temp, BP, Resp and HR[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographic data	X															
Disease characteristics[9]	X															
Prior anti-cancer therapy, radiotherapy and surgical procedures	X															
Past and current medical conditions, family history	X															

Alcohol consumption	X															

Reason for change – correction of transcription error carried from protocol amendment 4

Section 7.4.3.1 From:

Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment and agree to use effective contraception, Subjects with a positive pregnancy test result must be excluded from the study.

To

Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and agree to use effective contraception, Subjects with a positive pregnancy test result must be excluded from the study.

Reason for change: - correction of error carried from protocol amendment 4

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	then Monthly	Unscheduled	Discontinued	Follow up[9]	Conclusion
Past and current tobacco consumption	X															
[redacted]																
Cytokine[12]	X		X													
Neurological assessment[13]	X		X	X		X		X		X		X		X		
Ophthalmic Examination[14]	X		X													
Dermatologic skin assessment[15]	X		X	X	X	X	X	X	X	X	X	X		X	X	
Dispense oral study treatment and assess compliance[16]		X	X	X	X	X	X	X	X	X	X	X				
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[17]	X		X	X	X			X			X			X		
ECHO[18]	X		X		X			X			X			X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood products and blood supportive care products	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up contact, anti-cancer therapy[20]															X	
Subject completion																X
Death record																X

To:

Study Assessments[1]	Screen[2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	monthly Until Treatment	Treatment Disc[26]	Follow up[9] [27]	Conclusion
Informed consent	X														
Tumour tissue sample for BRAF V600 mutation[3]	X														
Intracranial target and non –target lesion assessment and response[21] [27]	X		X	X		X		X		X		X	X		
Extracranial target and non-target lesion assessment and response[22] [27]	X		X	X		X		X		X		X	X		
Inclusion / exclusion criteria[4]	X														
Register subject	X														
Chemistry and Haematology[5]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test[6]	X														
Coagulation	X														
Physical examination	X												X		
Height[7]	X														
Weight, Temp, BP, Resp and HR[8]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographic data	X														
Disease characteristics[9]	X														
Prior anti-cancer therapy, radiotherapy and surgical procedures	X														
Past and current medical conditions, family history	X														
Alcohol consumption	X														
Past and current tobacco consumption	X														
Cytokine[12]	X		X												
Neurological assessment[13]	X		X	X		X		X		X		X	X		
Ophthalmic Examination[14]	X		X					X							
Dermatologic skin assessment[15]	X		X	X	X	X	X	X	X	X	X	X	X		
Dispense oral study treatment and assess treatment compliance[16]		X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG[17]	X		X	X	X			X			X		X		
ECHO[18]	X		X		X			X			X		X		
Concomitant medications[25]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood products and blood supportive care products	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up monthly dermatologic skin														X	

Study Assessments[1]	Screen[-2]	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	monthly Until Treatment	Treatment Disc[26]	Follow up[9, 27]	Conclusion
assessment contact, anti-cancer therapy[20]															
Survival Follow-up, anti-cancer therapy[24]														X	
Subject completion or withdrawal															X
Death record (if applicable)															X