NOVARTIS

Clinical Development

DRB436 (GSK2118436) +TMT212 (GSK1120212)

Protocol BRF115532 / NCT01682083

COMBI-AD: A phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection

Document type	Amended Protocol Version (Clean)
EUDRACT number	2012-001266-15
Version number	10
Clinical Trial phase	III
Document status	FINAL
Release date	08-Feb-2023
Novartis internal reference number	CDRB436F2301

Table of contents

List of tables

List of figures

SPONSOR INFORMATION PAGE

Clinical Study Identifier BRF115532

Sponsor Contact Address

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, 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.

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

Regulatory Agency Identifying Number(s):

Investigational New Drug (IND) Number	113,557
European Drug Regulatory Authorities Clinical Trials (EudraCT) Number	2012-001266-15
Universal Trial Number (UTN)	U1111-1148-3778

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BCC	Basal cell carcinoma
BID	Twice daily
bMX	bioMerieux
BRAF	Protein with an important role in cell signalling
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence Interval
CL/F	Apparent clearance following oral dosing
CPK	Serum creatine phosphokinase
CR	Complete Response
CRO	Clinical Research Organization
CRAF	protein functioning in the MAPK/ERK signal transduction pathway as part of a protein kinase cascade
CRP	C-reactive protein
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
cuSCC	Cutaneous squamous cell carcinoma
DBP	Diastolic blood pressure
DMFS	Distant metastasis-free survival
DMSO	Dimethyl sulfoxide
DTIC	Dacarbazine
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERK	Extracellular signalling-regulated kinase
[redacted]	[redacted]
FDA	United States Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFR	Freedom From Relapse
GCP	Good Clinical Practice
GCPH	Global Clinical Program Head
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HA	Health Authority
Hg	Mercury
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropylmethylcellulose

HR	Hazard ratio
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to Treat
IUO	Investigational Use Only
IVRS	Interactive Voice Response System
KA	Keratoacanthoma
KRAS	KRAS gene makes KRAS protein which is involved in cell signaling pathways, cell growth and apoptosis. When mutated the KRAS gene may cause cancer.
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LN	Lymph node
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK1 and MEK2	Mitogen-activated extracellular signal-related kinases 1 and 2
mm	Millimeter
MRI	Magnetic resonance imaging
msec	milliseconds
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NR	Not Reached
NRAS	NRAS gene makes NRAS protein which is involved in regulating cell division
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive Disease
PFS	Progression-free survival
[redacted]	[redacted]
PK	Pharmacokinetic
PPES	Palmar-Plantar Erythrodysesthaesia Syndrome
PR	Partial Response
PT	Prothrombin time
PTT	Partial thromboplastin time
QT	Electrocardiogram interval from onset of the QRS complex to the end of the T wave representing duration of repolarisation
QTcB	QT duration corrected for heart rate by Bazett's formula
RAF	Serine threonine-protein kinase activating downstream effectors involved in tumorigenesis
RAP	Reporting and Analysis Plan

RAS	Protein activating signaling cascades (promoting cell proliferation, neoplastic transformation and oncogenesis)
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Relapse Free Survival
RR	Response Rate
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
SGPT	Serum glutamic pyruvic transaminase
SPM	Study Procedures Manual
ULN	Upper limit of normal
US/USA	United States
V/F	Volume of distribution
WBC	White blood cell

Amendment rationale

Amendment 10 (08-Feb-2023)

First Patient First Visit in this study occurred on 31-Jan-2013, Last Patient Last Treatment occurred on 01-Dec-2015 which at the time, all patients were off study treatment. As of 03-Jan-2023, 446 patients are still in follow-up. The patients and investigators are still blinded to the treatment assignments. The original protocol planned an interim OS analysis at 153 events (26%) and a final OS analysis at 597 events. Due to an unexpectedly slow event accrual rate, this was revised with Amendment 8 to perform a final OS analysis at 299 events. As the event rate has slowed even more (to less than 2 events per month), the analysis plan has been amended to perform a final OS analysis when 260 events occur (or by the end of Jul-2023, whichever comes first). This change is applied in the interest of bringing the study conclusions to the medical community in a timely manner. The anticipated impact of this change in event number from 299 to approximately 260 on the power of the final analysis is expected to be minimal (see Section 9).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section	Brief description of the change and/or new text
Amendment Rationale	Moved to after glossary.
Medical Lead Information page	Removed as no longer applicable.
Section 1.2 Study Rationale	Changed from “side” to “adverse” effect.
Section 3 Study Design Section 4.2 Permanent Discontinuation from Study Treatment and Subject Completion Criteria Section 9.3.2 Analysis Data Sets Section 9.3.4 Interim Analysis & IDMC	Updated the Final OS analysis to occur when 260 events occur (or by the end of Jul-2023, whichever comes first).
Section 9.2 Study Design Considerations	Updated the Final OS analysis to occur when 260 events occur (or by the end of Jul-2023, whichever comes first). Added the following: All remaining alpha will be spent for this final OS analysis by taking into account alpha spent at the first interim analysis corresponding to the information fraction of 25.6%.
Section 9.2.2 Sample Size Sensitivity	Table 15: Updated number of OS events and updated the percentage (%) of statistical power for 255, 260 and 299 events. Additional text regarding statistical power added.
Section 10.5 Study and Site Closure	Updated percentage (%) and number of OS events for study completion
Appendix 11	Appendix 11removed as it is not applicable, available in prior amendments

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do not affect the Informed Consent.

Amendment 9 (05-Nov-2021)

Amendment rationale

As of 01-Dec-2015, all subjects have discontinued from study treatment and are in follow up. As of 20-Oct-2021, 287 subjects remain in follow-up for recurrence and 184 subjects remain in the follow-up for survival.

The main purpose of this protocol amendment is to:

1. Cease central imaging collection.
2. Include disruption proof language in the event of a public health emergency.
3. Make clarifications, editorial and typographic changes.

Rationale for stopping central imaging collection:

The primary and secondary endpoints are based on investigator's assessment of CT/MRI scans. The primary endpoint was reached for Relapse Free Survival (RFS), and now the patients are only being followed for long term RFS/Overall Survival (OS) milestones.

There were no central assessments done in the study and no plans to perform in the future, therefore central imaging collection will cease, as the vendor function was only to collect and hold the CT/MRI scans. Tumor response will continue to be assessed locally as per investigator's assessment and imaging data will continue to be collected in EDC and archived locally.

Additional summary of changes:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section	Brief description of the change and/or new text
Sponsor Signatory page	Removed as per Novartis SOPs
Sponsor Information page	Medical lead and Study lead contact details have been updated
Investigator Agreement page	Removed as per Novartis SOPs
3 Study Design	Annual visit calculation has been clarified.
3.2 Rational for Public Health Emergency mitigation procedures. 7 Study assessments and procedures. 7.2.1.4 Assessment Guidelines. 7.3.2.7 Regulatory reporting requirements for SAEs. 7.3.3.2 Pregnancy reporting. 7.3.4 Laboratory Assessments. 7.4.2 Health Outcomes Assessments	Disruption proof language has been added in the event of a public health emergency how the site should proceed if the subject cannot attend study visits at site
5.8.3.2 Visual Changes	Clarification provided, PK samples for ocular events are no longer required for subjects that have discontinued study treatment.
Table 11 Time and Events Table – Follow-Up Assessments	Footnote has been updated to clarify: [redacted] • Annual visit calculation

Section	Brief description of the change and/or new text
	• Chemistry and hematology sample collection after month 60 and upon disease recurrence • Typo regarding non-contrast CT has been corrected • QoL collection after month 60 only required for subjects before recurrence
7.2.1.3 Efficacy Assessment 7.2.1.4 Assessment Guidelines	Typo regarding non-contrast CT has been corrected. Reference to SPM has been removed as central imaging scan collection will cease and sites to continue to follow standard of care for performing imaging scan collection.
7.3.2.6 Prompt reporting of SAEs and other events for Novartis	This has been updated based on feedback from the Federal Institute for Drugs and Medical Devices (BfArM) in Germany to require prompt SAE follow up reporting.
7.3.8 Dermatologic Exam	Clarified Table 11. Dermatologic examination is not required for subjects that have had disease recurrence and are in follow up after Month 60 visit
9.3.4 Interim analysis & IDMC	As per Protocol Amendment 8 the final OS analysis will be conducted at 299 events. Corrected the typo of 597 events.
10.5 Study and Site Closure	As per Protocol Amendment 8 summary of changes the study will be considered complete when approximately 50 percent of the initially planned target number of randomized subjects have died or are otherwise lost to follow-up (approximately 299), at which time final OS analysis will be performed. The previous protocol V8.0 did not update section 10.5 to reflect this change, and this has now been corrected.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

Amendment 8 (21-Dec-2018)

Amendment rationale

Primary analysis was conducted on the data cut-off of 30-June-2017. At the time there were 410 recurrence events and 153 deaths were reported. These results were presented to health authorities in support of the marketing authorization application for dabrafenib and trametinib in the adjuvant treatment of melanoma.

Based on a Health Authority request, the RFS analysis was updated on the basis of extended study follow-up with an additional 10 months of data (cut-off date 30-April-2018) and a cure-rate model analysis was presented to estimate the fraction of patients expected to remain relapse free long term. As of 30-Apr-2018, 355 patients remained in the follow-up for recurrence and 577 patients remained in the follow-up for survival. This additional assessment evidenced a continuation of the slower than anticipated trend for recurrence and death events. As a result, the final analysis of OS is being changed from 597 events to approximately 299 death events with this amendment. This represents approximately 50% information fraction of the original target which was communicated to FDA and EMA to be an adequate milestone for final assessment given the event predictions and maturity of data at that time point.

Furthermore, the follow-up assessment schedule has been updated to extend the time between clinic visits to annually after patients have been on study beyond Month 60 (~5 years from randomization).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Updated the Final OS analysis to occur after 50% of OS events rather than at 70% and addressed statistical considerations in the relevant sections
- Section 9: Statistical assumptions and Table 15 updated for Statistical Power Scenarios for Overall Survival:
  - Additional analyses added for 5-year and study completion RFS rates
  - Additional descriptive analysis added for post-recurrence antineoplastic treatment.
- Section 7 and Table 11: Updates made to the Time and events Schedule to reduce the number of assessments for both pre-and post-recurrence after patients have been on study for more than 60 months.
- Formatting changes and updated Sponsor Contact information

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 07 (31-May-2017)

Amendment rationale

[redacted]

[redacted]

The purpose of this protocol Amendment 07 is:

- Perform the primary analysis of RFS using a data cut-off at approximately 2.5 years after Last patient First Dose which also corresponds to a projected median follow up of 3.3 years for all subjects.
- Add an additional interim OS analysis when approximately 299 death events have occurred, i.e. at 50% information fraction of originally targeted 597 OS events.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Updated Sponsor Contact information
- Section 9.1.: Added language to state the primary analysis of RFS can be performed using a data cut-off at approximately 2.5 years after Last patient First Dose. Updated data-cut-off date for final RFS analysis and provided related updated statistical assumptions.
- Section 9.2.1: Clarified that the primary analysis for RFS will be a first interim analysis for Overall Survival and added a second interim analysis for survival after approximately 299 events. Statistical rationale and updated assumptions were also added.
- Section 11 References: Section updated to include additional reference noted in the rationale for this amendment.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol do not change any study procedures or the safety management of the on-going patients, and therefore, do not require IRB/IEC approval prior to implementation.

Summary of previous amendments

Revision Chronology:		
2012N135295_00	2012-JUL-05	Original
2012N135295_01	2012-OCT-10	Amendment No. 1
Amendment No. 1: 1. Updated RFS and OS analysis and study completion definitions. 2. Deleted the formal interim efficacy analysis. 3. Added details of randomization capping and interim analysis for OS at the time of the RFS analysis. 4. Updated male contraception requirements to align with current standard for dabrafenib and trametinib. 5. Updated dosage and administration guidelines for grapefruit and grapefruit juice, Seville oranges, or pommelos consumption before randomization from 7 days to 24 hours. 6. Updated Table 3 Dose Modification Guidelines for General Toxicity and corresponding text. 7. Revised Dose Modification Guidelines for: • Pyrexia • Visual Changes • LVEF 8. Changes to the Time and Events Tables including modification to [redacted], addition of PK sample at Month 1, update to instruction for MRI substitution of CT, correction of typographical errors, modification of visit window during the treatment period, clarification of central lab schedule during follow-up and removal of Month 21 CT scan. 9. Added table showing statistical power scenario for OS analysis. 10. Minor changes for clarification and consistency throughout the protocol including: • Patients that present with initial resectable lymph node recurrence after a diagnosis of Stage I or II melanoma are eligible. • Patients with history of another malignancy including melanoma or concurrent malignancy are not eligible. • Clinical examination and biopsy of recurrence are considered efficacy assessments. • Ophthalmic examination must be performed by an ophthalmologist. • Added text referring to information and requirements for head and neck examinations and dermatologic examinations provided in the SPM. 11. Minor administrative changes, and correction to typographical errors throughout the document		
2012N135295_02	2012-NOV-12	Amendment No. 2
Amendment No. 2: [redacted]		
2012N135295_03	2012-DEC-13	Amendment No. 3:
Amendment No. 3: 1. Added CT/MRI assessment at Month 21. 2. Included 80% power calculation for OS. 3. Provide the rationale for use of the Pike estimator of the treatment hazard ratio. 4. Updated male and female contraception requirements. 5. Clarified exclusion #12. 6. Added reference.		
2012N135295_04	2013-JAN-17	Amendment No. 04: [redacted]
Amendment No. 04: [redacted]		
2012N135295_05	2013-OCT-24	Amendment No. 05

Revision Chronology:		
Amendment No. 05: 1. Clarifications and updates to eligibility criteria. 2. Deleted exclusion for glucose-6-phosphate dehydrogenase (G6PD) deficiency. 3. Clarified follow-up assessments required for subjects that discontinue treatment prior to Month 12 without evidence of disease recurrence. 4. Updated dosing instructions. 5. Updated dose modification guidelines for visual changes. 6. Updated guidance for symptomatic decreased left ventricular ejection fraction (LVEF). 7. Updated guidelines for QTc prolongation. 8. Updated prohibited and cautionary medications. 9. Clarifications and updates to the Time and Events tables including: • Addition of dermatologic skin assessments at Months 8 and 10. • Deletion of dermatologic skin assessment at Month 9. • Addition of column and footnotes to describe follow up assessments for subjects that discontinue treatment prior to Month 12 without evidence of disease recurrence. • Clarification of PK, [redacted]. 10. Clarified imaging requirements for efficacy assessments. 11. Added collection of new malignancy information. 12. [redacted] 13. Minor administrative changes, clarifications and corrections to typographical errors throughout the document.		
2012N135295_06	2016-Oct-05	Amendment No. 6:
Amendment No. 6: • Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. • Make administrative changes to align with Novartis processes and procedures.		

PROTOCOL SUMMARY

Rationale

Cutaneous melanoma is the most aggressive form of all skin cancers. Although it represents only 4% of all cancers, its incidence is continuing to rise in the world at a rate exceeding all other cancers (Jemal, 2007). Worldwide it is expected that approximately 132,000 people will be diagnosed with melanoma each year and approximately 37,000 people are expected to die of the disease annually (WHO, 2012).

Surgical resection is the treatment of choice for localized melanoma and frequently results in cures for early stage (I and II) disease, with a 90% long term (10-year) survival rate for stage I disease (Balch, 2009). However, patients with lymph node involvement ≥1mm, including those detected only by sentinel lymph node biopsy, are at high risk of both local and distant relapse after definitive surgery due to the frequent presence of distant micrometastatic disease at presentation (Kirkwood, 2001; Van Akkooi, 2009). Approximately half of these patients will ultimately die of metastatic disease (Markovic, 2007), and the morbidity from uncontrolled relapses is also considerable. Thus there is a need for effective adjuvant therapy for high-risk patients to prevent disease relapse after surgical resection of the primary tumor.

Although significant progress has been made recently with new treatments for metastatic melanoma, therapeutic options in the adjuvant setting remain limited. Many agents have been evaluated as potential therapies for the adjuvant treatment of melanoma however almost all have demonstrated little or no benefit (Schuchter, 2004). The National Comprehensive Cancer Network (NCCN) treatment guidelines for melanoma recommend clinical trials, observation and interferon as the three therapy options for the adjuvant treatment of melanoma with clinical trials as the preference (NCCN, 2012). Although high-dose interferon is currently the only approved therapy for the adjuvant treatment of melanoma it is not widely accepted as the standard of care. Increasing evidence surrounding a questionable survival benefit, a high incidence of serious toxicities, and negligible benefit for patients with bulkier disease makes it an unattractive therapy for most patients and clinicians (Schuchter, 2004). Thus there is a need for more effective therapies with an acceptable safety profile in the adjuvant setting.

The RAS/RAF/MEK/ERK pathway (i.e., the MAP kinase pathway) is a critical proliferation pathway in many human cancers, including melanoma. Oncogenic mutations in BRAF signal through MEK1 and MEK2, and occurrence of this is an early event. This study will evaluate the combination of two small-molecule, oral agents, dabrafenib and trametinib. Dabrafenib is a potent and selective RAF kinase inhibitor of human wild type BRAF and CRAF enzymes as well as the mutant forms BRAFV600E, BRAFV600K and BRAFV600D. The mode of action of dabrafenib is consistent with competitive inhibition of adenosine triphosphate (ATP) binding. By contrast, trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. Trametinib is non-competitive towards ATP and inhibits both MEK activation and kinase activity. Because BRAF and MEK are in the same pathway, and because MEK is a substrate of activated BRAF, inhibiting both proteins simultaneously rather than individually could provide more effective pathway inhibition and also decrease the likelihood of developing resistance. Preliminary clinical experience, along with data generated in cell line, mouse xenograft, and rat safety models with BRAF and MEK inhibitor combinations suggest enhanced effects on efficacy and less

potential for proliferative skin lesions or stimulation of dormant tumors containing RAS mutations compared to treatment with a BRAF inhibitor alone.

Objective(s)

Primary Objective

The primary objective for this study is to evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival (RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K high-risk, stage III cutaneous melanoma.

Secondary Objectives

1. To evaluate the overall survival (OS) of dabrafenib and trametinib combination therapy compared to placebo
2. To assess distant metastasis-free survival (DMFS)
3. To assess freedom from relapse (FFR)
4. To evaluate the safety of dabrafenib and trametinib in combination

[redacted]

Study Design

This is a two-arm, randomized, double-blind Phase III study of dabrafenib (BRAF inhibitor) in combination with trametinib (MEK inhibitor) versus two placebos in the adjuvant treatment of melanoma after surgical resection. Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [Stage IIIa (maximum diameter of the largest lymph node (LN) metastasis >1 mm), IIIb or IIIc] cutaneous melanoma will be screened for eligibility. Approximately 852 subjects will be randomized in a 1:1 ratio to receive either dabrafenib [150 mg, twice daily (BID)] and trametinib [2 mg, once daily] combination therapy or two placebos for each for 12 months. Subjects will be stratified by BRAF mutation status (V600E, V600K) and stage of disease (IIIa, IIIb, IIIc).
Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment (Section 5.8).

Study Assessments

The RFS, DMFS and FFR endpoints will be determined by investigator assessment of disease recurrence. Subjects will be assessed with computed tomography (CT) or magnetic resonance imaging (MRI) at Screening and during treatment and the post-treatment follow-up period (refer to the Time and Events Schedule in Section 7 for scanning frequency). Subjects will also be followed for survival. Safety will be evaluated by clinical assessments including vital signs and complete physical examinations, eye exams, 12-lead electrocardiograms (ECG), and echocardiograms (ECHO), chemistry and hematology laboratory values and adverse events (AEs).

1 INTRODUCTION

1.1 Background

Cutaneous melanoma is the most aggressive form of all skin cancers. Although it represents only 4% of all cancers, its incidence is continuing to rise in the world at a rate exceeding all other cancers (Jemal, 2007). Worldwide it is expected that approximately 132,000 people will be diagnosed with melanoma each year and approximately 37,000 people are expected to die of the disease annually (WHO, 2012).

Surgical resection is the treatment of choice for localized melanoma and frequently results in cures for early stage (I and II) disease, with a 90% long term (10-year) survival rate for stage I disease (Balch, 2009). However, patients with lymph node involvement ≥1mm, including those detected only by sentinel lymph node biopsy, are at high risk of both local and distant relapse after definitive surgery due to the frequent presence of distant micrometastatic disease at presentation (Kirkwood, 2001; Van Akkooi, 2009). Approximately half of these patients will ultimately die of metastatic disease (Markovic, 2007), and the morbidity from uncontrolled relapses is also considerable. Thus there is a need for effective adjuvant therapy for high-risk patients to prevent disease relapse after surgical resection of the primary tumor.

Although significant progress has been made recently with new treatments for metastatic melanoma, therapeutic options in the adjuvant setting remain limited. Many agents have been evaluated as potential therapies for the adjuvant treatment of melanoma however almost all have demonstrated little or no benefit (Schuchter, 2004). The National Comprehensive Cancer Network (NCCN) treatment guidelines for melanoma recommend clinical trials, observation and interferon as the three therapy options for the adjuvant treatment of melanoma with clinical trials as the preference (NCCN, 2012). Although high-dose interferon is currently the only approved therapy for the adjuvant treatment of melanoma it is not widely accepted as the standard of care. Increasing evidence surrounding a questionable survival benefit, a high incidence of serious toxicities, and negligible benefit for patients with bulkier disease makes it an unattractive therapy for most patients and clinicians (Schuchter, 2004). Thus, there is a need for more effective therapies with an acceptable safety profile in the adjuvant setting.

The RAS/RAF/MEK/ERK pathway (i.e., the MAP kinase pathway) is a critical proliferation pathway in many human cancers, including melanoma. Over 80% of cutaneous melanomas harbor activating mutations of either BRAF or NRAS (Nikolaev, 2011). Oncogenic mutations in BRAF signal through MEK1 and MEK2 and this is an early event. This study will evaluate the combination of two, small-molecule, oral agents, dabrafenib and trametinib. Dabrafenib is a potent and selective RAF kinase inhibitor of human wild type BRAF and CRAF enzymes as well as the mutant forms BRAFV600E, BRAFV600K and BRAFV600D. The mode of action of dabrafenib is consistent with competitive inhibition of ATP binding. By contrast, trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. Trametinib is non-competitive towards ATP and inhibits both MEK activation and kinase activity. Because BRAF and MEK are in the same pathway, and because MEK is a substrate of activated BRAF, inhibiting both proteins simultaneously rather than individually could provide more effective pathway inhibition and also decrease the likelihood of developing resistance. Data

generated in cell line, mouse xenograft, and rat safety models with BRAF and MEK inhibitor combinations suggest enhanced effects on efficacy and less potential for proliferative skin lesions or stimulation of dormant tumors containing RAS mutations compared to treatment with a BRAF inhibitor alone.

Based on the demonstrated efficacy of both dabrafenib and trametinib as monotherapies along with preliminary clinical data suggesting that the combination may prevent resistance and improve efficacy, phase III clinical studies of the dabrafenib/trametinib combination are being initiated in advanced melanoma and as adjuvant therapy for high-risk Stage III disease.

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 (37%), headache (32%), pyrexia (28%), arthralgia (27%), skin papillomas (24%), alopecia (22%), palmar-plantar erythrodysaesthesia syndrome (2%). Serious adverse events (SAEs) (>1%) on the dabrafenib arm included pyrexia (4%), squamous cell carcinomas (6%), and new primary melanomas (2%).

Further evidence for the safety and efficacy of dabrafenib has been established in a large (N=172) study of patients (BREAK-MB) with both controlled and uncontrolled brain metastases (Kirkwood, 2012). Activity in subjects with the V600K mutation was also seen.

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 (2 mg 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 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.

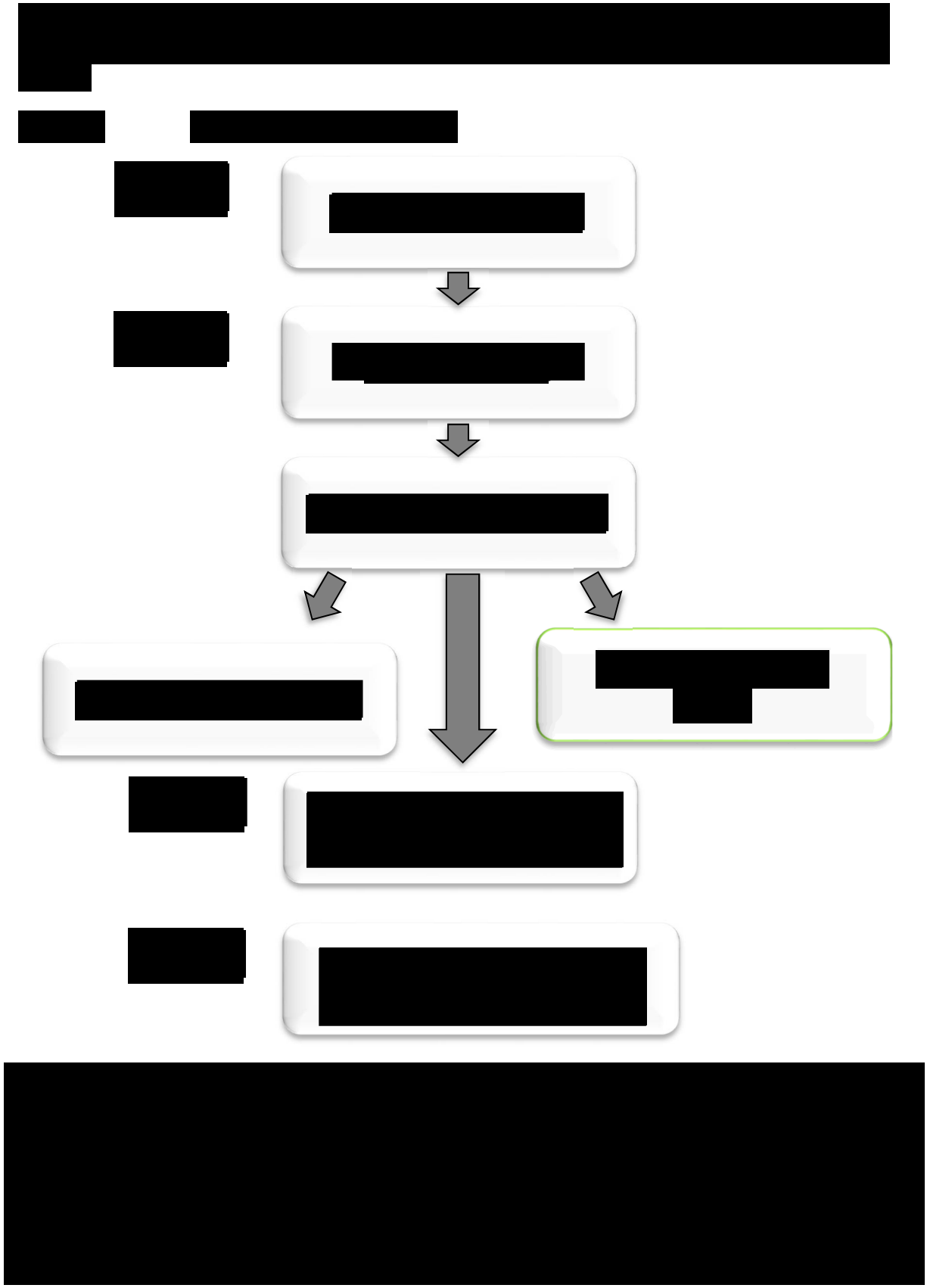
The most frequent AEs (≥20%) with trametinib were skin rash (57%), diarrhea (43%), fatigue (26%), and edema (26%). Known MEK inhibitor class effects were observed in this study including chorioretinopathy (<1%) and decreased ejection fraction (7%).

1.1.3 BRAF and MEK Inhibitors as Combination Therapy

1.1.3.1 Nonclinical Biology

In vitro and in vivo preclinical data provide evidence to support the potential benefit of combining BRAF and MEK inhibitors. In cell culture, the combination of dabrafenib and trametinib is significantly more effective than the single agents in inhibiting the growth of BRAF-mutant, dabrafenib-resistant cell lines. This combination has also demonstrated enhanced activity against parental (non-drug-resistant) BRAF-mutant cells, suggesting that potential benefits of the combination may result from overall improved activity relative to single agents. This cell-line data generated by GlaxoSmithKline (GSK) using GSK BRAF and MEK inhibitors is similar to *in vitro* results of other BRAF and MEK inhibitor combinations (Corcoran, 2010; Emery, 2009). The combination of dabrafenib and trametinib also has greater activity in mouse xenografts than either single agent alone, supporting the *in vitro* observations. Furthermore, in skin toxicity studies performed in rats, the addition of a MEK inhibitor to a BRAF inhibitor prevented the development of proliferative skin lesions observed following treatment with a BRAF inhibitor alone. This result suggests that the addition of a MEK inhibitor to a BRAF inhibitor may suppress pro-proliferative effects, including cutaneous squamous cell carcinoma (cuSCC), which have been observed in the clinic following BRAF monotherapy (Flaherty, 2010; Chapman, 2011). Similar results have been published with another combination of BRAF and MEK inhibitors (Carnahan, 2010).

1.1.3.2 Clinical



1.2 Study Rationale

Although the role of the MAP kinase pathway has not yet been studied in early melanoma, there is adequate scientific rationale and data to expect that the combination of dabrafenib and trametinib will provide similar responses on V600 mutant cells in the adjuvant setting as for more advanced disease. BRAF mutations are present in primary lesions, and are preserved in corresponding metastatic lesions indicating a common clonal origin (Nissan, 2011). Based on early and continued involvement of V600 mutation throughout melanoma disease progression, MAP kinase inhibition would be expected to provide similar responses regardless of disease stage.

The combination of dabrafenib with trametinib in the adjuvant setting is further supported by *in vitro* and *in vivo* preclinical data which has demonstrated that the combination can enhance the levels of apoptosis, abrogate the onset of resistance, and prevent the development of proliferative skin lesions compared to BRAF monotherapy. This combination has demonstrated enhanced activity against parental (non-drug-resistant) as well as dabrafenib-resistant cell lines, suggesting that potential benefits of combination may result from overall improved activity relative to single agents as well as an attenuation of tumor growth resulting from acquired resistance. Although the mechanisms of resistance to BRAF treatment are not completely understood, emerging data have demonstrated MEK activation at the time of relapse, thus the addition of a MEK inhibitor to dabrafenib

represents an attractive therapeutic strategy (Goetz, 2012). Cell line data generated by GSK are similar to *in vitro* data with other BRAF/MEK inhibitor combinations (Corcoran, 2010; Emery, 2009). Similar to cell line data, in mouse xenograft studies with A375 cells which harbor a BRAFV600E mutation, the combination of dabrafenib and trametinib was significantly better than either agent alone.

The combination in the adjuvant setting also prevents MEK activation in normal tissues, a mechanistic adverse effect of BRAF monotherapy, which can lead to development of low-grade squamous-cell carcinomas. The combination of BRAF/MEK inhibitors prevented the development of proliferative skin lesions (epithelial hyperplasia and hyperkeratosis of the skin, nonglandular stomach and/or footpads) observed in rats following treatment with a BRAF inhibitor alone, suggesting that the addition of MEK to BRAF may potentially mitigate the risk of developing epithelial proliferative effects (i.e., cutaneous squamous cell carcinoma) as observed in the clinic. Observations on proliferative skin effects are similar to those published with another BRAF/MEK inhibitor combination (Carnahan, 2010).

More importantly, emergence of clinically-significant RAS-driven tumors is far less likely to occur when there is combined BRAF/MEK inhibition than with BRAF alone (Lacouture, 2012). Together the preclinical studies and clinical data support further clinical evaluation of dabrafenib and trametinib combination therapy in subjects with BRAF-V600E/K mutation-positive melanoma in the adjuvant setting.

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival (RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K high-risk, stage III cutaneous melanoma	Relapse Free Survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. Recurrence of or death from the same cancer and all deaths from other causes are events. Treatment emergent malignancy(ies) other than second melanomas will not be considered as events, and loss to follow-up is censored. Patients without RFS events will be censored at the last adequate assessment.
Secondary	
To compare overall survival (OS) of dabrafenib and trametinib as a combination therapy versus two placebos.	OS defined as the interval from randomization to the date of death, irrespective of the cause of death; patients still alive will be censored at the date of the last contact.
To compare distant metastasis-free survival (DMFS) of dabrafenib and trametinib as a combination therapy versus two placebos.	DMFS defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurs first. Patients alive and without distant metastasis are censored at the date of last assessment.
To compare freedom from relapse (FFR) of dabrafenib and trametinib as a combination therapy versus two placebos.	FFR defined as interval from randomization to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death. Patients alive without recurrence or with second primary cancer will be censored at the date of last assessment.

Objectives	Endpoints
To evaluate the safety of dabrafenib and trametinib as a combination therapy in the overall study population including incidences of squamous cell carcinoma (SCC), new cancers in other sites, and other proliferative cutaneous lesions	Safety as measured by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), eye exams, chemistry and hematology laboratory values, and adverse events (AEs).
[redacted]	

Refer to Section 7 for further details on endpoint definitions.

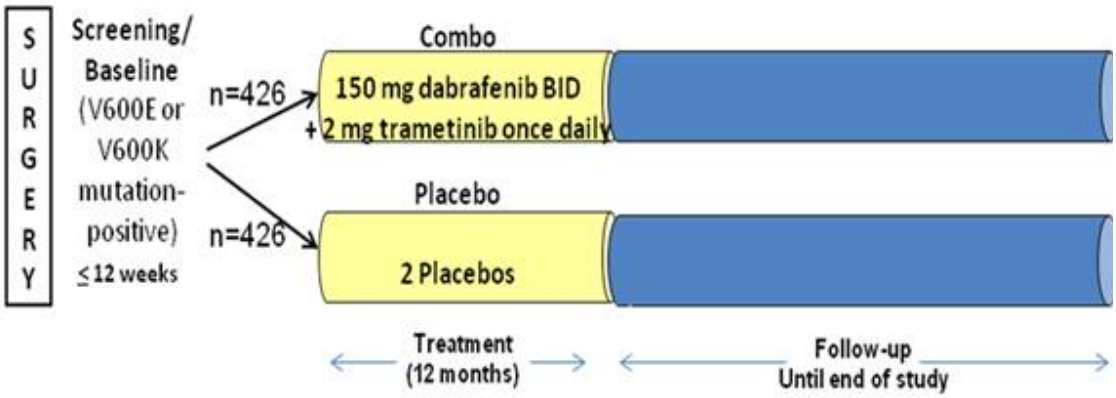
3 STUDY DESIGN

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 Tables (Section 7), are essential and required for study conduct

This is a two-arm, randomized, double-blind Phase III study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of melanoma after surgical resection (Figure 2). Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [Stage IIIa (lymph node metastasis >1 mm), IIIb or IIIc] cutaneous melanoma will be screened for eligibility. Approximately 852 subjects will be randomized in a 1:1 ratio to receive either dabrafenib (150 mg BID) and trametinib (2 mg once daily) combination therapy or two placebos for each for 12 months. Subjects will be stratified by BRAF mutation status (V600E, V600K) and stage of disease (Stage IIIa, IIIb, IIIc).

Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment (Section 5.8). Refer to Section 5.8.3 for guidelines for events of special interest and Section 5.9.1 for liver stopping criteria.

Figure 2 BRF115532 Study Design Schema (N=852)



The benefit of the dabrafenib/trametinib combination compared to placebos will be evaluated through the primary endpoint of investigator-assessed RFS. Crossover is not permitted. The treatment effect of dabrafenib and trametinib combination therapy is anticipated to improve RFS by 40% over placebos (median RFS of 21 months and 15 months, respectively). See Section 9 for statistical considerations.

Subjects in both arms will receive treatment for 12 months or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent. Subjects will be followed for disease recurrence and survival during and after the treatment period. Refer to the Time and Events Tables (Section 7) for required assessments for the following study periods:

Screening: Assessments must be completed within 28 days of randomization, unless stated otherwise in the Time and Events table (Table 10).

Treatment: The treatment period is 12 months. Discontinuation of study treatment may occur earlier than 12 months for disease recurrence, death, unacceptable toxicity or withdrawal of consent.

Post Treatment Follow-Up (Before Recurrence): Subjects will be followed for disease recurrence every 3 months after the end of treatment until Month 24, every 6 months after Month 24 and annually after Month 60 (365 days ±14 days from last visit, assessments to be completed as per Table 11).

Post Treatment Follow-Up (After Recurrence): After disease recurrence subjects will remain on study for follow-up assessments every three months until Month 24, every 6 months after Month 24, and annually after Month 60 (365 days ±14 days from last visit, assessments to be completed as per Table 11). Follow-up assessments will include updates on anti-cancer treatments and responses to those treatments as well as survival and quality of life information. Subjects who have not died, but are no longer being followed for disease recurrence or survival are considered to have discontinued from the study. The study will be considered complete, and the final OS analysis will be conducted when approximately 260 OS events occur or at the data cut-off by the end of Jul-2023, whichever occurs first.

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 ultimate goal of adjuvant therapy is to improve the cure rate after surgery through eradication of occult micrometastatic disease. Notable successes have been achieved in oncology when highly effective therapies were available for advanced stage disease (e.g., breast cancer, Hodgkin's and non-Hodgkin's lymphoma, embryonal tumors, osteosarcoma). High-risk, resected BRAF V600E/K mutation positive melanoma represents another attractive setting for testing this paradigm since: 1) the population is at high risk for relapse and death without further therapy; 2) the BRAF/MEK combination is both highly effective and can be targeted to the population most likely to benefit, and 3) the combination of dabrafenib and trametinib should be at least as well tolerated as cytotoxic chemotherapy or high-dose interferon and thus have acceptable risk:benefit if the study objectives are met.

This study is designed to compare dabrafenib and trametinib in combination versus two placebos with regard to RFS, which is a direct measurement of anti-tumor effect. RFS was selected as the primary endpoint based upon historical precedent (peginterferon alfa- 2b, Sylatron) and because it will not be subject to confounding from subsequent therapy, as would OS. Since relapses are accompanied by considerable disease- and treatment-related morbidity, RFS is a true measure of patient benefit.

Data from preclinical studies and clinical experience with the dabrafenib/trametinib combination in patients with BRAF V600E or V600K mutations suggest that efficacy may be observed in the adjuvant setting for either population, thus both mutation types have been included.

Placebo has been selected as the control arm due to the absence of an acceptable standard of care for the adjuvant treatment of patients with high-risk resectable melanoma. Although high-dose interferon is currently the only approved therapy for the adjuvant treatment of melanoma it is not widely accepted as the standard of care. Increasing evidence surrounding a questionable survival benefit, a high incidence of serious toxicities, and negligible benefit for patients with bulkier disease makes it an unattractive therapy for most patients and clinicians (Schuchter, 2004). Dabrafenib and trametinib will be administered at the dose recommended for further development of the combination (150 mg BID and 2.0 mg once daily, respectively), based on the extensive monotherapy experience for both inhibitors along with the preliminary results of BRF113220 with combination therapy. An Independent Data Monitoring Committee (IDMC) will be chartered to regularly review safety data.

3.1.1 Dose Rationale

Preliminary clinical data for the proposed dabrafenib/trametinib combination are described in Section 1.1.3.2. Approximately 168 subjects have received combination therapy with dabrafenib and trametinib at the proposed study doses (150 mg BID dabrafenib and 2 mg once daily trametinib) with a median follow-up time of 12.8 months. n the dose-escalation phase (Part B), PFS was longest for the group receiving the highest doses of dabrafenib and trametinib with an acceptable safety profile. Based on these data the combination of

150 mg BID of dabrafenib and 2.0 mg once daily of trametinib has been selected for further development.

Considerable experimental and clinical evidence has been amassed demonstrating the importance of maintaining dose intensity in the adjuvant setting. Studies of high-risk breast cancer patients have repeatedly demonstrated inferior outcomes, including diminished survival, when attenuated dose regimens were compared to standard chemotherapy (Muss, 2009; Budman, 1998; Citron, 2003; EBCTCG, 2011). Since the dabrafenib/trametinib combination induces apoptosis in BRAF V600 mutation-positive melanoma cells, the same theoretical considerations should apply as with cytotoxic chemotherapy. Specifically, maximum clinical benefit should occur when the disease burden is lowest, i.e. in the adjuvant setting when micrometastases can be eliminated with effective therapy. Therefore, the adjuvant study will use the combination regimen that has already been selected as providing optimal efficacy for use in metastatic disease.

The duration of therapy (12 months) is based upon expert consensus and does not exceed that administered in other pivotal studies of adjuvant treatment in similar populations where treatment ranged from 12 to 60 months [EORTC18991, EORTC18071, DERMA, EORTC18592, ECOG1690, AVAST-M, GO27826]. In the absence of a reliable biomarker for minimal residual disease, empiric dosing for durations much shorter than the predicted median relapse free interval (median of 15 months) may increase the risk of treatment failure. [redacted] Safety of continuous dosing of dabrafenib and trametinib for over a year as monotherapies has been established along with preliminary safety of combination dosing for a similar interval. Safety precautions will include clear guidelines for management of toxicity, including enhanced surveillance for adverse events of special interest along with instructions for dose modification (Section 5.8). An IDMC will regularly review safety data, starting at an early timepoint (e.g. N~100). The inclusion/exclusion criteria will also serve to minimize participation of those at greatest risk for known or suspected toxicities of the combination.

3.2 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure subject safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

4 SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1 Subject Selection Criteria

4.1.1 Number of Subjects

Approximately 852 subjects will be randomized, 1:1 to combination therapy (n=426) and to placebos (n=426). Refer to Section 9.2.1 for sample size assumptions.

4.1.2 Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on dabrafenib and trametinib that may impact subject eligibility is provided in the Investigator's Brochures

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. Completely resected histologically confirmed high-risk [Stage IIIa (LN metastasis >1 mm), IIIb or IIIc; refer to Appendix 1 for Staging Guidelines] cutaneous melanoma determined to be V600E/K mutation positive using the bioMerieux (bMX) THxID BRAF Assay. The testing will be conducted by a central reference laboratory. Patients presenting with initial resectable lymph node recurrence after a diagnosis of Stage I or II melanoma are eligible. Patients with an unknown primary melanoma are not eligible.
4. Must be surgically rendered free of disease (defined as the date of the most recent surgery) no more than 12 weeks before randomization.
5. Recovered from definitive surgery (e.g. no uncontrolled wound infections or indwelling drains). For minimum surgical requirements see Appendix 2.
6. 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.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 (Oken, 1982) (See Appendix 3).
8. Must have adequate organ function as defined in Table 1:

Table 1 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	≤ 1.5 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 (Appendix 4). Creatinine clearance must be 50 mL/min to be eligible.
c. ECHO scans must be used throughout the study

9. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 7.3.3 from 14 days prior to randomization, throughout the treatment period and for 4 months after the last dose of study treatment.
10. French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

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. Known mucosal or ocular melanoma or the presence of unresectable in-transit metastases.
2. Evidence of distant metastatic disease on screening evaluation.
3. Prior anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment) including radiotherapy for melanoma. Prior surgery for melanoma is allowed.
4. Taken an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to randomization.
5. Current or expected use of a prohibited medication (See Protocol Section 6.2 for a list of prohibited medications).
6. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).
7. Known Human Immunodeficiency Virus (HIV).
8. History of another malignancy including melanoma or a concurrent malignancy except as noted below. Patients who have previously had Stage III melanoma or any malignancy with confirmed activating RAS mutation **at any time** are not eligible. *Note:*

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

Exceptions:

- Patients with a history of **any** malignancy that have been disease-free for at least 5 years are eligible except those with confirmed activating RAS mutations.
- Patients with a history of completely resected **non-melanoma** skin cancer (e.g. basal cell carcinoma, squamous cell carcinoma) are eligible irrespective of the time since the resection.
- Patients with successfully treated *in situ* carcinoma are eligible.
- Patients presenting with multiple primary melanomas are eligible only if the lesions are **concurrent.** Patients who have concurrent multiple primary melanomas that are "distant" are eligible provided each lesion is considered local disease or resectable regional disease. These cases should be discussed with the Medical Lead.

1. A history or evidence of cardiovascular risk including any of the following:
    a. A QT interval corrected for heart rate using the Bazett's formula (QTcB; Appendix 5) ≥480 msec;
    b. A history or evidence of current clinically significant uncontrolled arrhythmias;
    c. A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization
    d. A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines (See Appendix 6)
    e. Patients with intra-cardiac defibrillators.
    f. 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.
    g. Treatment refractory hypertension defined as a blood pressure of systolic> 140 mm Hg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy.
2. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including:
    a. Presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or
    b. Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as:
        i. Evidence of new optic disc cupping;
        ii. Evidence of new visual field defects on automated perimetry;
        iii. Intraocular pressure >21 mm Hg as measured by tonography.
3. History of clinically significant or active interstitial lung disease or pneumonitis.

4. 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.
5. Pregnant or nursing females.

4.2 Permanent Discontinuation from Study Treatment and Subject Completion Criteria

Subjects will receive study treatments for twelve months or until disease recurrence. During the protocol defined treatment period study treatment(s) may be permanently discontinued for the following reasons:

- death
- unacceptable adverse event, including meeting stopping criteria for liver chemistry defined in Section 5.9.1 and/or for hematologic and other non-hematologic toxicity.
- deviation(s) from the protocol
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

The primary reason each study treatment was permanently discontinued must be documented in the subject's medical records and in the electronic case report form (eCRF). Refer to Section 5.2 for additional information on discontinuation of dabrafenib and/or trametinib.

If disease recurs prior to the completion of the 12 month treatment period, study treatment should be discontinued and follow-up assessments should be conducted according to the schedule for "Follow-up after recurrence" (Table 11). Such follow-up assessments should start at the next regularly scheduled disease assessment visit (i.e. Month 3, 6, 9 or 12) and continue thereafter according to Table 11. For example, if disease recurrence is observed at Month 6, the subject would complete the discontinuation visit and follow-up assessments after recurrence would start at Month 9, and continue according to the visit schedule in the Time and Events Table (Table 11).

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

All subjects who permanently discontinue from study treatment will have assessments at the time of discontinuation and during post study treatment follow-up as specified in Time and Events Tables (See Section 7). In addition, all subjects who permanently discontinue study treatment without evidence of disease recurrence will also be followed for disease recurrence according to the protocol schedule until:

- Withdrawal of consent
- Death, or
- Study completion (as defined in Section 3)

Subjects that permanently discontinue from study treatment before the end of the 12 month treatment period without evidence of disease recurrence will return for disease assessment visits starting at the next regularly scheduled disease assessment visit (i.e. Month 3, 6, 9 or 12) and continue thereafter according to Table 11. If a subject experiences disease recurrence at any time subsequent follow up visits should be conducted according to the "After Recurrence" follow-up schedule in Table 11.

Follow-up for survival, new anti-cancer therapy (including radiotherapy) and response to new anti-cancer therapy will continue for all subjects including those with disease recurrence, according to the Time and Events Tables (Table 10 and Table 11) until the study is considered to be complete after which all protocol-required assessments and procedures will be discontinued. The study will be considered complete, and the final OS analysis will be conducted when approximately 260 OS events occur or at the data cut-off by the end of Jul-2023, whichever occurs first. Follow-up contact to assess survival and new anti-cancer therapy may be made via clinic visit or another form of communication (e.g. phone, email, mail etc.). Additional information on declaring subjects lost to follow-up can be found in the SPM.

4.2.1 Subject Completion

A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period. Document the cause of death 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, at the investigator's discretion is no longer being followed or if the study is closed/terminated. Subjects who are ongoing at the time the study is closed/terminated will be considered to have completed the study.

5 STUDY TREATMENT

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

5.1 Investigational Products

No special preparation of study treatment 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 will be provided as 50 mg and 75 mg capsules to sites by Novartis. The contents of the label will be in accordance with all applicable regulatory requirements. Each capsule will contain 50 mg or 75 mg of free base (present as the mesylate salt).

5.1.2 Trametinib

Trametinib study treatment will be provided as 0.5 mg and 2.0 mg tablets to sites by Novartis. The contents of the labels will be in accordance with all applicable regulatory

requirements. Each tablet will contain 0.5 mg or 2.0 mg of trametinib parent (present as the DMSO solvate).

5.1.3 Placebos

Matching placebo capsules for dabrafenib (50 mg and 75 mg) and placebo tablets for trametinib (0.5 mg and 2.0 mg) will be provided to sites by Novartis. The placebo capsules/tablets will contain the same inactive ingredients and film coatings as the dabrafenib and trametinib study treatment.

The contents of the labels will be in accordance with all applicable regulatory requirements.

5.2 Dosage and Administration

- Dabrafenib, 150 mg twice daily (BID) or placebo.
- Trametinib, 2.0 mg, once daily or placebo.

Both study treatments should be administered **in the morning** at approximately the same time every day. The second dose of dabrafenib (150 mg) or dabrafenib placebo 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 or trametinib placebo is interrupted or permanently discontinued, administration of dabrafenib or dabrafenib placebo may be continued. If administration of dabrafenib or dabrafenib placebo is interrupted or permanently discontinued, administration of trametinib or trametinib placebo may continue.

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

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

Subjects should start treatment as soon as possible after randomization and no later than 72 hours post-randomization.

5.3 Handling and Storage of Study Treatment

Dabrafenib, dabrafenib placebo, trametinib and trametinib placebo must be stored in a secure area under the appropriate physical conditions for the products. Study treatments are 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 the study treatment will be limited to the investigator and authorized site staff. Dabrafenib, dabrafenib placebo, trametinib and trametinib placebo must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

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

5.4 Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the interactive voice response system (IVRS), by the investigator or authorized site staff.

The following information for stratification must be entered into the system in order to obtain the blinded treatment assignment:

- Mutation type (V600E or V600K);
- Disease stage (IIIa, IIIb, IIIc)

Randomization will be done centrally using a randomization schedule generated by the GSK Biostatistical Department, the sponsor at the time will assign subjects in a 1:1 ratio to:

- dabrafenib and trametinib combination therapy.
- dabrafenib and trametinib placebos

Once a randomization number has been assigned it must not be re-assigned even in cases of errors.

Detailed RAMOS user instructions, worksheets and telephone contact numbers will be provided to the study site at study start.

5.5 Blinding

Study treatment will be double-blinded. Novartis, the site personnel (including the investigator) and the subject will not know the treatment assignment. Every effort must be made to maintain the blind until all analyses have been performed.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the Novartis Medical Lead or appropriate Novartis study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify Novartis as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the eCRF. A subject should remain in the study for survival follow-up even if the treatment code is unblinded.

Novartis' Chief Medical Office & Patient Safety (CMO&PS) Department staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or Novartis policy.

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. Reer 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 through querying the subject during the site visits and documented in the source documents and eCRF.

A record of the number of study treatment capsules/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 or dose reductions will also be recorded in the eCRF. The investigator will make every effort to bring non-compliant subjects in to compliance.

5.8 Dose Modification Guidelines

The severity of adverse events will be graded utilizing the National Cancer Institute (NCI) CTCAE, version 4.0. This section includes:

- Supportive guidelines for managing common toxicities
- General dose modification guidelines for toxicities related to study treatments
- Specific management guidelines for pyrexia, cardiovascular adverse events, and cutaneous squamous cell carcinoma/keratoacanthoma
- Guidelines for management of hepatobiliary events are given separately in Section 5.9. Investigators should also refer to the dabrafenib and trametinib combination Investigator's Brochure for the most current product safety information.

5.8.1 General supportive guidelines

5.8.1.1 Skin Toxicity (Rash, Palmar-Plantar Erythrodysesthaesia syndrome)

Rash and Palmar-Plantar Erythrodysesthaesia Syndrome (PPES) are frequently observed in subjects receiving trametinib, dabrafenib, or the combination of both therapies. Guidelines for management are based on experience with other MEK inhibitors and EGFR inhibitors (Balagula, 2010; Lacouture, 2012) and include:

- Prevention/prophylaxis: promote sunscreen use and avoidance of unnecessary sun exposure, use alcohol-free emollient creams, topical steroids and antibiotics as needed.
- Pruritic lesions: cool compresses and oral antihistamines
- Fissuring lesions: Monsel's solution, silver nitrate or zinc oxide cream
- Desquamation: thick emollients and mild soap
- Paronychia: antiseptic bath, local potent corticosteroids, antibiotics, surgery as needed

- Infected lesions: topical or systemic antibiotics

Additional 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 (refer to Table 3 - General Dose Modification Guidelines).

5.8.1.2 Diarrhea

Episodes of diarrhea have been reported in subjects receiving dabrafenib and trametinib combination therapy. Other 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 ruled out. Supportive measures should include the following as clinically indicated:

- Dietary modifications (e.g. small, frequent meals, low fiber, and lactose-avoidance)
- Maintain hydration with clear liquids or IV fluids as needed
- Loperamide and/or oral antibiotics

Dose modification may also be required (refer to Table 3 – General Dose Modification Guidelines).

5.8.2 Dose Modification for General Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and for which specific guidelines do not apply are provided in Table 3. These guidelines are intended primarily for non-hematological 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 use 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:

- **Renal insufficiency** – close monitoring of serum creatinine, treatment of associated pyrexia (see Table 4 - Management and dose modification guidelines for pyrexia), and treatment interruption for increased serum creatinine >2 mg/dl (or >0.5 mg/dl above baseline). Nephrology consultation should also be obtained if no obvious cause for persistent creatinine elevation (e.g. volume depletion).
- **Pneumonitis** – initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary function testing, bronchoscopy and/or brochoalveolar lavage, and empiric steroids may be indicated for more severe cases. Pulmonary consultation is recommended. For Grade 2 to 3 (if no recovery to grade ≤1 within 4 weeks) and grade 4 pneumonitis, permanently discontinue trametinib. Treatment with dabrafenib may continue.
- **Rash** – For mild rash, follow Grade 1 general dose modification guidelines (Table 3). For moderate (Grade 2), reduction of dose is allowed by at least one dose level, however, dose interruption may be required until resolution to Grade 1. If toxicity resolves, can consider re-escalation to initial dose level. For Grade 3, if event resolves to Grade 1 or less, suggest to also consider restarting at a reduced dose. If Grade 2 or 3 rash does not resolve or worsens after 2 weeks of dose modification/interruption and clinical treatment, discontinue trametinib. Treatment with dabrafenib may continue.
- **Pancreatitis** – In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis.

Investigators should always err on the side of caution in these settings if treatment-related toxicity is a possibility. Note that guidelines for management of hepatobiliary adverse events are provided separately in Section 5.9.

General dose modification guidelines are provided in Table 3 below. Dose levels referred to in Table 2 are as follows:

Table 2 Dose Levels

	Dabrafenib/placebo	**Trametinib/placebo**
Starting dose	150 mg BID	2 mg once daily
L-1 (1st level dose reduction)	100 mg BID	1.5 mg once daily
L-2 (2nd level dose reduction)	75 mg BID	1 mg once daily

Table 3 Dose Modification Guidelines - General

CTCAE Grade	**Action and Dose Modification[a,b,c]**
Grade 1 or Grade 2 (tolerable)	Continue study treatments at same dose level (no dose modification)
Grade 2 (Intolerable)	
1st or 2nd occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at same dose level
3rd or occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at next lower dose level
4th or greater occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at two dose levels lower than the starting dose or discontinue treatments per investigator discretion

CTCAE Grade	Action and Dose Modification[a,b,c]
Grade 3	
1st occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level
2nd occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 or baseline then restart at two dose levels lower than the starting dose
3rd occurrence	Discontinue treatments.
Grade 4	
1st occurrence	Discontinue treatments

a. Treatments should be discontinued if more than 2 dose reductions are required
b. Approval from the Novartis Medical Lead is required to restart study treatments after ≥21 days interruption
c. These guidelines are intended for non-hematological toxicities not easily managed with routine supportive care (see above).

5.8.3 Dose Modification Guidelines - Adverse Events of Special Interest

5.8.3.1 Pyrexia

Pyrexia has been observed in subjects receiving dabrafenib, either as monotherapy or in combination with trametinib. In a minority of cases pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness and required hospitalization.

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 (e.g. ibuprofen) as appropriate to control fever. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, or hypotension, renal function should be monitored carefully and oral corticosteroids should be started after the event resolves (see Table 4).

Pyrexia accompanied by hypotension, dehydration requiring IV fluids, renal insufficiency, or severe rigors/chills in the absence of an obvious infectious cause should be reported as an SAE (Section 7.3.2.2).

Guidelines regarding management and dose reduction for pyrexia considered to be related to dabrafenib are provided in Table 4.Pyrexia is defined as a body temperature equal to or above 38.0 ° Celsius or 100.4° Fahrenheit.

Trametinib dose modification is not required for pyrexia.

Table 4 Management and Dose Modification Guidelines for Pyrexia[a,b]

Occurrence	Action and Dose Modification
Any	• Clinical evaluation for infection and hypersensitivityc • Laboratory work-upc • Hydration as requiredd [redacted]
1st Event[b]:	• Administer anti-pyretic treatment if clinically indicatedf • Interrupt dabrafenib/placebo • Continue trametinib or placebo • Once pyrexia resolves to baseline, restart dabrafenib/placebo at the same dose level

Occurrence	Action and Dose Modification
	• If fever was associated with dehydration, hypotension, or renal insufficiency, reduce dabrafenib/placebo by one dose level and begin oral corticosteroids (prednisone 10 mg or equivalent) for at least 5 days or as clinically indicated[g]
2nd Event[g]	• Same as for 1st event, and • Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[g]

Subsequent Events:	• Interrupt **dabrafenib/placebo**
	• Continue trametinib or placebo
	  • Once pyrexia resolves to baseline, **restart dabrafenib/placebo (consider dose reduction by one level)[h]** 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 or escalating doses are required, consult Medical Lead

BUN = blood urea nitrogen; CRP = C-reactive protein

a. Pyrexia is defined as a body temperature equal to or above 38.0° Celsius or 100.4° Fahrenheit.
b. For subjects experiencing pyrexia complicated by severe rigors/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 oral corticosteroids are recommended when restarting dabrafenib.
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
[redacted]
f. Anti-pyretic treatment may include acetaminophen (paracetamol), ibuprofen, or suitable anti-pyretic medication according to institutional standards. Ibuprofen is preferred and the maximum recommended daily dose of acetaminophen should not be exceeded to reduce risk of liver toxicity. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
g. In subjects experiencing pyrexia complicated by severe rigors/chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started after the 1st event and doses should be gradually increased for subsequent events.
h. Dabrafenib/placebo should be reduced by one dose level at discretion of the investigator if pyrexia is accompanied by severe recurring rigors which cannot be managed by best supportive care, including increasing doses of oral steroids. Re-escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

5.8.3.2 Visual changes

Episodes of visual changes have been observed in subjects receiving trametinib. 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 for subjects still on study treatment.

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided in Table 5.

Table 5 Management and Dose Modification Guidelines for Visual Changes

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

a. Abbreviations: CSR = central serous retinopaty; CTCAE = Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; SAE = serious adverse event
b. Refers to CTCAE Version 4.0 'Eye disorders – Other, specify
c. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

5.8.3.3 Cardiovascular toxicity

Cardiovascular adverse events have been seen in subjects receiving trametinib and dabrafenib, either as monotherapy or in combination. Dose modification of either agent may be required for decreased LVEF, hypertension or QTc prolongation.

5.8.3.3.1 Decreased Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and with trametinib in combination with dabrafenib.

Therefore, ECHOs must be performed to assess cardiac ejection fraction at regular intervals as outlined in the Time and Events Table (Table 10). All ECHOs will be collected; instructions are provided in the Study Procedures Manual (SPM). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6.

Table 6 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

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

Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's low LLN	• Interrupt study treatments 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 Novartis Medical Lead and request approval for restart
		  • Restart with trametinib/placebo reduced by one dose level
		  • Restart dabrafenib/placebo at previous dose level
		  • Repeat ECHO 2 , 4 , 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter
		• If repeat LVEF does not recover within 4 weeks
		  • Consult with cardiologist
		  • **Permanently discontinue trametinib/placebo**
		  • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
		  • Consult with Novartis Medical Leadc

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

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. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
c. Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with Novartis Medical Lead.

5.8.3.3.2 Hypertension

Any level of hypertension should be actively managed. Trametinib does not need to be interrupted while mild hypertension is brought under control; however treatment interruption and dose-reduction are recommended for more severe or symptomatic hypertension (e.g. persistent systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure (DBP) ≥100 mmHg despite antihypertensive treatment).

5.8.3.3.3 QTc prolongation

Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided in Table 7 below:

Table 7 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
QTcB ≥501 msec	Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Recommend Testing serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. Restart at current dose level[b] If event recurs, permanently discontinue study treatments
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and Novartis Medical Lead agree that the subject will benefit from further treatment.	

5.8.3.3.4 Valvular Toxicity

- Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per NCI CTCAE v4.0) should temporarily discontinue dabrafenib/placebo 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 Medical Lead, the subject may be restarted on dabrafenib/placebo 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/placebo. 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/placebo. 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/placebo at a reduced dose after consultation and approval of the Novartis Medical 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 possible review.

5.8.3.4 Cutaneous squamous cell carcinoma (cuSCC) and keratoacanthoma (KA)

Both cuSCC and KA have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib [redacted]. These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however they should be reported as an SAE (refer to Section 7.3.2.2). In addition, a biopsy of the lesion should be taken, where possible, and submitted for further analyses as described in the SPM.

5.9 Monitoring, Interruption, and Stopping Criteria for Hepatobiliary Events

NOTE: if serum bilirubin fractionation is not immediately available, if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN, discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

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, fda.gov).

Liver chemistry stopping criteria 1-5 are defined as follows:

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

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

3 ALT ≥ 8xULN

4 ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

5 ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

6 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 eCRF 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 (excluding studies of hepatic impairment or cirrhosis)**.
  - NOTE: if serum bilirubin fractionation is not immediately available, and if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required or Novartis Medical Governance approval of drug restart is granted, as described in Section 5.9.1.3).
  - Follow-up for overall survival or disease recurrence is required following discontinuation from study treatment
- Do not restart investigational product unless written approval is granted by Novartis Medical Governance (details for restarting investigational product are described in Section 5.9.1.3), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 5.9.1.2).
- Subjects meeting criterion 5 should be monitored as frequently as possible.

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 eCRF. 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 creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia as relevant on the AE 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 Medical Lead as needed.
- Record use of concomitant medications such as acetaminophen (paracetamol), 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, 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 high performance liquid chromatography (HPLC) assay more than 1 week following acetaminophen use).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.

NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) – as outlined in: //.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 Medical 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 7 for algorithm of liver chemistry monitoring, stopping and follow up criteria.

5.9.1.3 Restarting Investigational Product

5.9.1.3.1 Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Treatment

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 drug 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 investigational product (IP) 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 IP 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.

5.9.1.3.2 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 drug restart/rechallenge must be obtained, as required.
- If restart of drug 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 IP 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 drug 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. Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior surgical procedures will be recorded in the eCRF.

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

6.2 Prohibited Medications and Non-Drug Therapies

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

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known HIV are ineligible for study participation);
- Herbal remedies (e.g., St. John’s wort);

- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibitor, 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 (for examples see Table 8) 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 MedicalLead is required in these situations. A partial list of these medications is provided in Table 8. The list may be modified based on emerging data. Refer to the SPM for the most current list.

Table 8 Prohibited Medications

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

6.3 Medications to be Used with Caution

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

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19 , UDP-glucuronyl transferases 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 consider substitutions of these medications. A partial list of these medications is provided in Table 9. 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 Medical Lead and close monitoring of PT/INR by the site. Exposure decreased by 37% due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure

may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.

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

Table 9 Medications to be used with Caution

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

Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib.	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine
Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.	

Questions regarding concomitant medications should be directed to the Novartis Medical Lead for clarification.

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

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

Treatment after relapse or study discontinuation will not be provided as part of the protocol. Upon relapse or study discontinuation, subjects may receive additional (non protocol) anti-cancer therapy at the discretion of the treating physician which may include inhibitors of the MAP-kinase pathway. If treatment occurs after relapse the new anti-cancer therapy and the subject's best response to treatment should be documented in the eCRF. Every effort should be made to complete the required follow up evaluations (refer to Table 11 for follow-up assessments and procedures). At a minimum subjects should be followed for survival even if other assessments are not performed.
Refer to Section 4.2 for follow-up assessment of subjects who are to be followed up for disease recurrence and/or survival after permanently discontinuing from study treatment.

6.5 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 Medical 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.

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

A plasma sample for PK analysis may be requested by the Novartis Medical 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.

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

7 STUDY ASSESSMENTS AND PROCEDURES

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

Refer to the Time and Events Tables for the timing of all assessments (Table 10 and Table 11). Details on efficacy and safety assessments are presented in Section 7.2 and Section 7.3, respectively. [redacted] Further details of study procedures and assessments can be found in the study procedures manual (SPM).

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

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

As per Section 3.2, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls or virtual contacts (e.g. tele consult) can replace on-site study visits for the duration of the disruption until it is safe for the subject to visit the site again. Refer to protocol specific sections for further details.

Table 10 Time and Events Table – Screening and Treatment

	SCREENING	TREATMENT														
Study Assessments[1]	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Treatment Discon[25]**	**Unsch**
Visit Window (Days)	**≤28 days except where noted[2, 4]**	**N/A**	**± 3 days**												**± 30 days from last dose**	**N/A**
Informed consent[3]	X															
Tumor tissue sample for BRAF V600E/K mutation [redacted]	X															
Inclusion / exclusion criteria[5]	X															
Demographic data[6]	X															
Pregnancy test[7]	X Serum (__7 days)				X urine			X urine			X urine			X urine	X urine	
Coagulation[8]	X															
Central Labs[9] (Hematology & Chemistry)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease characteristics[10]	X															
Medical history[11]	X															
Tobacco and alcohol consumption	X															
Randomization		X														
Dispense Oral study treatment and Assess compliance[12]		X	X	X	X	X	X	X	X	X	X	X	X			

	SCREENING	TREATMENT														
Study Assessments[1]	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Treatment Discon[25]**	**Unsch**
Visit Window (Days)	**≤28 days except where noted[2,4]**	**N/A**	**± 3 days**												**± 30 days from last dose**	**N/A**
Performance status (ECOG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[13]	X		X±7 days		X±7 days			X±7 days			X±7 days			X±7 days	X	
ECHO[14]	X		X±7 days		X±7 days			X±7 days			X±7 days			X±7 days	X	
Ophthalmic examination[15]	X		X±7 days		X±7 days			X±7 days						X±7 days	X	
Dermatologic skin assessment[16]	X			X± 7 days		X±7 days		X±7 days		X± 7 days		X±7 days		X±7 days	X	
Physical examination[17]	X Complete	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Brief	X Complete	X Complete	X Brief
Chest, abdomen and pelvic CT scans[18]	X				X±7 days			X±7 days			X±7 days			X±7 days	X	
Brain CT/MRI[26]	X															
[redacted]																
Concomitant medications[20]	X	X	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	X	X
Adverse events[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																

	SCREENING	TREATMENT													
Study Assessments[1]	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Treatment Discon[25]**	**Unsch**
Visit Window (Days)	**≤28 days except where noted[2,4]**	**N/A**	**± 3 days**												**± 30 days from last dose**	**N/A**
[redacted]																
Tumor tissue sample for biomarker research[28]		At the time of disease recurrence only														

Abbreviations: [redacted]; [redacted]; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted]; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; [redacted]; SPM = Study Procedures Manual.

1. All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. For monthly visits (i.e. Month 1, 2, 3, etc.) subjects should return to the clinic approximately every 4 weeks. A post baseline study visit window of ±3 days is allowed for visits during treatment. A window of 7 days is permitted for some post baseline assessments, where noted in Table 10.

	SCREENING	TREATMENT													
Study Assessments[1]	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Treatment Discon[25]**	**Unsch**
Visit Window (Days)	**≤28 days except where noted[2,4]**	**N/A**	**± 3 days**												**± 30 days from last dose**	**N/A**

2. Screening procedures may be performed up to 28 days prior to randomization, unless otherwise noted in the table. Screening visits with a different window are noted in parentheses.
3. Informed consent may be given at any time prior to the performance of any study-related procedures. [redacted]
4. Tumor tissue must be collected to assess the BRAF V600E/K mutation status via central lab testing [redacted] A positive BRAF result from the central lab need not be repeated if randomization falls outside the 28-day screening window.
5. Only subjects who meet all inclusion and exclusion criteria will be eligible to enter into the study.
6. Record date of birth, race, ethnicity, and gender.
7. For all women of childbearing potential a serum pregnancy test will be required within 7 days prior to randomization; preferably, as close to the first dose as possible. Subsequent tests may be urine tests, and should be performed at Months 3, 6, 9, and 12 or discontinuation if discontinuation occurs prior to Month 12. Additionally if study treatment is interrupted for more than 7 days, regardless of the reason for the disruption, a urine test must be performed to confirm the subject is not pregnant prior to re-starting study treatment.
8. Coagulation sample to be obtained at screening only and analyzed by a central laboratory.
9. Analysis of clinical chemistry and hematology samples including those at screening will be performed by a central laboratory. Screening labs must be performed within 28 days prior to randomization.
10. Record date of diagnosis, primary tumor type, histology, stage, and other disease characteristics as indicated in the eCRF.
11. Record past and current medical conditions, surgical procedures and cardiovascular family history.
12. Dosing instructions must be provided to the subject. Subjects should start treatment as soon as possible after randomization but no later than 72 hours post-randomization. Study treatment will be dispensed at randomization and monthly. Site must call IVRS to register each study visit. Compliance will be assessed at all visits after Day 1 (Randomization). To assess compliance subjects should be instructed to return study drug at each visit; compliance will be assessed by querying the subject and counting tablets/capsules. Dose reductions, dose interruptions/delays, and/or dose escalations must be recorded in the eCRF.
13. ECG must be performed at Screening, Months 1, 3, 6, 9, and 12 or discontinuation if discontinuation occurs prior to Month 12, unless clinically indicated sooner. For subjects that discontinue study treatment before Month 12 an ECG must be performed at the discontinuation visit within 30 days of the last dose. 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

	SCREENING	TREATMENT														
Study Assessments[1]	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Treatment Discon[25]**	**Unsch**
Visit Window (Days)	**≤28 days except where noted[2,4]**	**N/A**	**± 3 days**												**± 30 days from last dose**	**N/A**

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. ECGs should be done in triplicate when the initial test is abnormal.

14. ECHO must be performed at the Screening, Months 1, 3, 6, 9, and 12 or discontinuation if discontinuation occurs prior to Month 12, unless clinically indicated sooner. For subjects that discontinue study treatment before Month 12 an ECHO must be performed at the discontinuation visit within 30 days of the last dose. While on treatment, subjects who have asymptomatic, absolute decrease in LVEF of >10% compared to screening AND whose ejection fraction is below the institution's LLN, must be followed according to LVEF guidelines for study drug management and requirements for subsequent ECHO.
15. An ophthalmic examination must be performed by an ophthalmologist at Screening, Months 1, 3, 6, and 12, or at discontinuation if discontinuation occurs prior to Month 12. Additional ophthalmic exams will be performed only as symptomatically warranted.
16. A thorough dermatologic exam should be performed by the Investigator at Screening, and Months 2, 4, 6, 8, 10, and 12 or at discontinuation if discontinuation occurs prior to Month 12. Refer to Table 11 for the schedule of assessments during follow-up. This may be referred to a dermatologist at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations. These visits should include periodic patient counseling on primary and secondary melanoma prevention measures including self-examination.
17. All physical exams will include the measurement of height (screening only) and weight using the metric scale, collection of vital signs including blood pressure, body temperature, pulse rate, and respirations. In addition a complete physical exam including a thorough genitourinary (pelvic) examination, inspection of the head and neck region, and digital rectal examination for both male and female subjects must be performed at Screening, and Month 12 or discontinuation if discontinuation occurs prior to Month 12. For female subjects the genitourinary exam must include a PAP smear. If the subject has had a genitourinary and rectal exam within 6 months of randomization these do not need to be repeated at screening. Brief physical examinations will be performed at all other timepoints as indicated. Refer to protocol Section 7.3.7 for additional detail on these examinations.
18. Diagnostic quality, contrast enhanced CT scan of the chest, abdomen and pelvis must be performed at all visits indicated in the table. Intravenous contrast should be used, for the CT scans, and preferably with oral contrast as well. A non-contrast CT of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT scanning frequency is not permitted per country or ethics requirements or if CT contrast is contraindicated. If MRI scanning is not possible, and CT intravenous contrast is contraindicated, CT without contrast is allowed, but it is the least preferable option. Method of imaging should be consistent throughout the study (i.e. if CT is done at screening, CT must be done at all future timepoints). For scanning during follow-up prior to disease recurrence refer to Table 11.

	SCREENING	TREATMENT													
Study Assessments[1]	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Treatment Discon[25]**	**Unsch**
Visit Window (Days)	**≤28 days except where noted[2,4]**	**N/A**	**± 3 days**												**± 30 days from last dose**	**N/A**

[redacted]

20. All medications taken by the subject during the study from the time of screening until 30 days after the last dose of study treatment will be recorded; any new anti-cancer therapy, if taken after study treatment discontinuation will be recorded as detailed in Table 11, Footnotes 7 & 10.
21. Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events (SAEs) will be collected over the same time period as AEs except SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, concomitant medication which must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

[redacted]

25. If treatment discontinuation occurs prior to Month 12 the treatment discontinuation visit should be performed within 30 days of the subject's last dose. Laboratory assessments and other required assessments do not need to be repeated at the discontinuation visit if they were performed within 30 days of the discontinuation visit. Follow-up should occur until death or study completion according to the follow-up assessment schedule in the table unless the subject withdraws from the study.
26. Baseline MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain must be performed on all subjects. Post-baseline scans should be performed as clinically indicated.

[redacted]

Table 11 Time and Events Table – Follow-Up Assessments

	FOLLOW-UP[10]										**STUDY COMPLETION[12]**
	BEFORE RECURRENCE						***AFTER RECURRENCE[13]***				**CONCLUSION**
Study Assessments[1]	**Unsch**	**Every 3 Months (M3-M12)[14]**	**Month 15**	**Every 3 Months (M18-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months After Month 60**	**Every 3 Months (M3-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months after Month 60**	**Unsch**	**Conclusion**
Visit Window (Days)	**N/A**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**N/A**	**N/A**
Central Labs[2] (Hematology & Chemistry)			X	Labs to be drawn at M18 then annually during follow-up up to M60 and at the time of disease recurrence		At the time of disease recurrence only.					
Performance status (ECOG)	X	X	X	X	X	X					
Dermatologic skin assessment[3]		X	X	X	X	X	X[16]				
Physical examination[4]	X (Brief)	X (Brief)	X (Brief)	X (M18 complete; all others brief)	X (Brief)	X (Brief)					
Chest, abdomen and pelvic CT scans[5]		X[15]	X	X	X	X					
[redacted]											
Concomitant medications[7]	X	X									

	FOLLOW-UP[10]										STUDY COMPLETION[12]
	BEFORE RECURRENCE						***AFTER RECURRENCE[13]***				CONCLUSION
Study Assessments[1]	**Unsch**	**Every 3 Months (M3-M12)[14]**	**Month 15**	**Every 3 Months (M18-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months After Month 60**	**Every 3 Months (M3-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months after Month 60**	**Unsch**	**Conclusion**
Visit Window (Days)	**N/A**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**N/A**	**N/A**
Adverse events[8]	X	X									
[redacted]											
Follow-up contact, anti-cancer therapies and best response[10]							X	X	X	X	X
[redacted]											
Subject completion											X
Death record											X

Abbreviations: CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; [redacted]; MRI = magnetic resonance imaging

1. All assessments mandated throughout the study must be performed on a calendar schedule. After month 60, the next annual visit will be 365 days from the last study visit. A study visit window of 14 days is allowed for all follow-up visits.
2. Analysis of clinical chemistry and hematology samples will be performed by a central laboratory. Labs should be drawn at Month 18 then annually until month 60, thereafter during follow-up prior to disease recurrence and at the time of disease recurrence. After month 60, at the time of disease recurrence only, clinical chemistry and hematology samples will be performed by a central laboratory (Refer to protocol Section 7.3.4 for further details).

	FOLLOW-UP[10]										STUDY COMPLETION[12]
	BEFORE RECURRENCE						***AFTER RECURRENCE[13]***				CONCLUSION
Study Assessments[1]	**Unsch**	**Every 3 Months (M3-M12)[14]**	**Month 15**	**Every 3 Months (M18-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months After Month 60**	**Every 3 Months (M3-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months after Month 60**	**Unsch**	**Conclusion**
Visit Window (Days)	**N/A**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**N/A**	**N/A**

3. A thorough dermatologic exam should be performed every three months Month 3-24, every six months after month 24 up to month 60 and then annually thereafter during the follow up period prior to disease recurrence. This may be referred to a dermatologist at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations. These visits should include periodic patient counseling on primary and secondary melanoma prevention measures including self-examination.
4. All physical exams will include the measurement of height (screening only) and weight using the metric scale, collection of vital signs including blood pressure, body temperature, pulse rate, and respirations. In addition, a complete physical exam including a thorough genitourinary (pelvic) examination, inspection of the head and neck region, and digital rectal examination for both male and female subjects must be performed at Month 18. For female subjects the genitourinary exam must include a PAP smear. Brief physical examinations will be performed at all other timepoints as indicated. Refer to protocol Section 7.3.7 for additional detail on these examinations.
5. Diagnostic quality, contrast enhanced CT scan of the chest, abdomen and pelvis must be performed at all visits indicated in the table. Intravenous contrast should be used, for the CT scans, and preferably with oral contrast as well. A non-contrast CT of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT scanning frequency is not permitted per country or ethics requirements or if CT contrast is contraindicated. If MRI scanning is not possible, and CT intravenous contrast is contraindicated, CT without contrast is allowed, but it is the least preferable option. Method of imaging should be consistent throughout the study (i.e. if CT is done at screening, CT must be done at all future timepoints). MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain should be performed as clinically indicated.
[redacted]
7. All medications taken by the subject during the study from the time of screening until 30 days after the last dose of study treatment will be recorded; any new anti-cancer therapy, if taken after study treatment discontinuation will be recorded as detailed in Footnote 10.

	FOLLOW-UP[10]										STUDY COMPLETION[12]
	BEFORE RECURRENCE						***AFTER RECURRENCE[13]***				CONCLUSION
Study Assessments[1]	**Unsch**	**Every 3 Months (M3-M12)[14]**	**Month 15**	**Every 3 Months (M18-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months After Month 60**	**Every 3 Months (M3-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months after Month 60**	**Unsch**	**Conclusion**
Visit Window (Days)	**N/A**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**N/A**	**N/A**

8. Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events (SAEs) will be collected over the same time period as AEs except SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, concomitant medication which must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

[redacted]

10. Follow-up will start once treatment is complete and continue through the end of the study even if disease recurs. Follow-up contact prior to disease recurrence will include clinic visits. Follow-up after disease recurrence should follow the schedule as noted in Table 11; however the information collected will be limited to: quality of life information, any radiotherapy, surgical procedure or new anti-cancer therapy initiated until study completion, withdrawal or death, best response to any follow-up treatment, method of assessment of best response, subsequent progression dates, and survival data. Subjects beyond month 60, in follow-up period after recurrence, are expected for their follow up visit every 365 days +/- 14 days (365 days to be calculated from the last study visit).

	FOLLOW-UP[10]										STUDY COMPLETION[12]
	BEFORE RECURRENCE						***AFTER RECURRENCE[13]***				CONCLUSION
Study Assessments[1]	**Unsch**	**Every 3 Months (M3-M12)[14]**	**Month 15**	**Every 3 Months (M18-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months After Month 60**	**Every 3 Months (M3-M24)**	**Every 6 months (M 24 – M60)**	**Every 12 Months after Month 60**	**Unsch**	**Conclusion**
Visit Window (Days)	**N/A**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**(± 14 days)**	**N/A**	**N/A**

[redacted]

12. To be completed if the subject permanently withdraws from the study (i.e. death, withdrawal of consent, lost to follow-up).
13. For subjects that experience disease recurrence prior to Month 12 the discontinuation visit should be performed and follow-up assessments should start at the next 3 month interval following the recurrence and continue according to the schedule defined in Table 11 until study completion, withdrawal or death. For example, if a subject experiences disease recurrence at Month 2, the discontinuation visit should be performed according to Table 10 and the follow-up assessments would start at Month 3 and continue thereafter according to the schedule defined in Table 11 until study completion, withdrawal or death.
14. For subjects that discontinue study treatment prior to Month 12 with no evidence of disease recurrence follow-up visits should start at the next 3 month interval following treatment discontinuation. For example, if a subject discontinues treatment at Month 1, the discontinuation visit should be performed according to Table 10 and the follow-up visits would start at Month 3 and continue thereafter according to the schedule defined in Table 11. At the time of disease recurrence follow-up assessments should start at the next 3 month interval after the recurrence and continue thereafter according to the schedule defined in Table 11 until study completion, withdrawal or death.
15. Chest, abdomen and pelvic CT scans do not need to be repeated at the first follow-up visit if they have been performed within 6 weeks of the first follow-up visit.
16. Subjects that discontinue study treatments due to disease recurrence should be monitored every 3 months for six months following discontinuation of the study treatments or until the initiation of another anti-cancer therapy.

7.1 Critical Baseline Assessments

Efficacy assessments conducted at baseline are described in Section 7.2, tumor tissue [redacted] Safety assessments conducted at baseline and during treatment are described in Section 7.3. Cardiovascular medical history/risk factors will be assessed at baseline.

7.1.1 Baseline Confirmation of BRAF Mutation-positive Melanoma

Subjects with completely resected histologically confirmed high-risk (Stage IIIa [LN metastasis >1 mm], IIIb or IIIc) cutaneous melanoma will be screened for eligibility after signing the informed consent form. Subjects will be screened prior to treatment to determine whether their tumor sample has a BRAF V600E or V600K mutation, indicating their eligibility for the study. Tumor BRAF mutation testing will be conducted using the bioMerieux BRAF THxID IUO assay (IDE: G120011), and testing will be performed in a central reference laboratory. Details related to BRAF mutation testing are provided in Section 7.7.1 and in the SPM.

7.2 Efficacy

7.2.1 Efficacy Endpoints

7.2.1.1 Primary Endpoint

The primary efficacy endpoint of this study is relapse free survival (RFS) which is defined as the time from randomization to disease recurrence or death from any cause. Recurrence of or death from the same cancer and all deaths from other causes are events. Treatment emergent malignancies (excluding second melanomas) will not be considered as events, and loss to follow-up is censored.

- Types of recurrence to be considered as an event include loco-regional, distant metastases and second primary melanoma.
- **Any** death occurring without prior documentation of tumor recurrence will be considered as an event (and will not be censored in the statistical analysis).
- If no event has occurred by the time of the analysis, then the time to event will be censored as the date of the last adequate assessment of the patient in question.
- Any new primary cancer at another site, squamous cell carcinoma, or keratoacanthoma, will not be considered as a recurrence and should be reported as a SAE (See Section 7.3.2.2). A second primary melanoma will be considered as a recurrence. [redacted]

7.2.1.2 Secondary Endpoints

The secondary efficacy endpoints of this study are:

- Overall Survival (OS) defined as the interval from randomization to the date of death, irrespective of the cause of death; patients still alive will be censored at the date of the last contact.
- Distant metastasis-free survival (DMFS), defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurs first. Patients alive and without distant metastasis are censored at the date of last assessment.
- Freedom from relapse (FFR), defined as interval from randomization to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death. Incidence of non-melanoma malignancy will not be considered as an event. Patients alive without recurrence or with second primary cancers will be censored at the date of last assessment.

7.2.1.3 Efficacy Assessment

See the Time and Events Tables (Table 10, Table 11) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline efficacy assessments Month 1 through Month 12, a window of ±3 days (physical exam) or ±7 days (CT scans, dermatologic skin assessment) is permitted to allow for flexible scheduling. After Month 12 a post-baseline assessment window of ±14 days is permitted.

The following are required for efficacy assessment:

- Clinical examination
- Diagnostic quality, contrast-enhanced CT scan of the chest, abdomen and pelvis should be performed at baseline and subsequent timepoints as indicated in the Time and Events Tables (Table 10 and Table 11). Intravenous contrast should be used for the CT scans preferably with oral contrast as well. A non-contrast CT of the chest (MRI of the chest will be accepted but is not recommended), with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT frequency prescribed in the Time and Events Table is not permitted per country or ethics requirements or if CT contrast is contraindicated. The method of imaging should be consistent throughout the study (i.e. if CT is done at screening, CT will be done at all future timepoints).
- A baseline MRI of the brain is required for all subjects. CT may be performed only if MRI contraindicated or unavailable. Subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS recurrence).

[redacted]

7.2.1.4 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast, when applicable, must be used throughout the study. Ultrasound is not a suitable modality of disease assessment for distant metastases. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.

- Fluorodeoxyglucose positron emission tomography (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. The sites should follow their standard of care for subject and radiopharmaceutical preparation. The scanning protocol should be conducted in accordance with the local imaging facility guidance.
- If PET/CT is performed then the CT component can only be used for standard disease 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.

Clinical examination: New lesions detected by clinical examination must be biopsied, where possible, to confirm disease recurrence. If a biopsy cannot be obtained then CT/MRI must be done to confirm disease recurrence.

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended. MRI is acceptable (refer to Section 7.2.1.3), but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type of disease. Whenever possible the same scanner and scanning parameters should be used for all exams acquired.

Brain Scan: For the baseline brain scan and any post-baseline brain scans, contrast enhanced MRI with 2.5 mm contiguous slices is preferable to contrast enhanced CT.

As per Section 3.2, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, the collection of images may be modified by Novartis and will be communicated to the investigator.

7.2.1.5 Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment prior to protocol treatment period (12 months)

Refer to Section 4.2 Permanent Discontinuation from Study Treatment and the Time and Events Schedule (Table 11) for follow-up assessment of subjects for disease recurrence and survival after permanently discontinuing from study treatment.

7.2.1.6 Assessment of Subject Completion

If a subject withdraws from the study during Months 1 through Month 24, the last radiographic assessment was more than 3 months prior to withdrawal from study and disease recurrence has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

If a subject withdraws from the study after Month 24, the last radiographic assessment was more than 6 months prior to withdrawal from study and disease recurrence has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

7.3 Safety

7.3.1 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, eye exams, chemistry and hematology laboratory values, and AEs will be monitored and evaluated.

7.3.2 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 7.3.2.1and Section 7.3.2.2, respectively.

7.3.2.1 Definition of an AE

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

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

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

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

7.3.2.2 Definition of an SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject 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.

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect.

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

g. Protocol-Specific SAEs:

   - All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to 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, keratoacanthoma and second 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.
- Laboratory abnormalities as referenced in Section 7.3.2.3
- LVEF that meets stopping criteria Section 5.8.3.3.1.
- Central serous retinopathy (CSR) or retinal vein occlusion (RVO)
- Pyrexia accompanied by hypotension, dehydration requiring IV fluids, renal insufficiency, and/or severe rigors/chills in the absence of an obvious infectious cause.

7.3.2.3 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 events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

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

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

7.3.2.4 Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease recurrence or hospitalization due to disease recurrence) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death CRF form. However, if the underlying disease (i.e., recurrence) 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 GSK1120212 and GSK2118436 or protocol design/procedures and the disease recurrence, then this must be reported as an SAE.

Local or distant relapse is the primary efficacy endpoint of the study and should not be reported as an SAE.

7.3.2.5 Time Period and Frequency of Detecting AEs and SAEs

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

From the time a subject consents to participate in and completes the study (See Section 4.2.1), 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 12.SAEs will be collected over the same time period as stated above for AEs. In addition, any **new malignancy** (defined in Section 7.3.2.2) or any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or Novartis concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to Novartis within 24 hours, as indicated in Section 7.3.2.6. For any new malignancy, every effort should be made to identify the RAS mutation status; the mutation test should be performed locally and reported within 12 weeks of diagnosis. Additional genetic analysis may be performed depending on the tumor types, and the results reported at the discretion of the investigator.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days from the last dose of study treatment the investigator may report any adverse event that they believe is possibly related to study treatment. Treatment emergent malignancies should be reported regardless of the time from treatment discontinuation to occurrence of the event.

7.3.2.6 Prompt Reporting of SAEs and Other Events to Novartis

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

Note: If more stringent, local regulations regarding reporting timelines prevail.

Table 12 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[4]	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT≥3xULN **PLUS** Bilirubin≥2xULN (>35% direct) (or ALT 3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event CRF and liver imaging and/or biopsy CRFs if applicable[2]	24 hours[4]	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists ≥4 weeks	24 hours[1]	Liver event CRF[2]	24 hours[4]	Updated Liver Event CRF[2]

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT≥5xULN plus bilirubin <2xULN	24 hours[1]	Liver event CRF does not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[2]	24 hours[4]	
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[1]	Liver event CRF[2]	24 hours[4]	Updated liver event CRF[2]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[1]	Liver event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

1. Novartis to be notified at onset of liver chemistry elevations to discuss subject safety.
2. 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
3. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.
4. All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Liver chemistry stopping, follow-up, and monitoring criteria are provided in Section 5.9.

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. Procedures for post-study AEs and SAEs are provided in the SPM.

7.3.2.7 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 the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are 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.

As per Section 3.2, during a public health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

7.3.3 Pregnancy Testing, Prevention and Reporting

7.3.3.1 Pregnancy Test and Prevention

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.
A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

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

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.
If a female subject is of childbearing potential, she must have a serum β-HCG pregnancy test performed within 7 days prior to randomization. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 4 months following 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 follow:

- **An** intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 4 months after the last dose of study treatment.

  Note: Abstinence is acceptable only when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) 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 recommended due to potential drug-drug interactions with dabrafenib.
Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

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

7.3.3.2 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 the 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.

As per Section 3.2, during a public health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, the mitigation procedure to ensure subject safety and trial integrity is listed in Section 7.3.2.7 if the investigator considers that the pregnancy is possibly related to study treatment.

7.3.4 Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 10 and Table 11 should be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule in Table 10 and Table 11). Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

If any additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinical significant by the investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's eCRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplication and/or additional blood draws.

Clinical chemistry and hematology parameters to be tested are listed in Table 13. Female subjects will have a serum pregnancy test at Screening; urine pregnancy testing will be done during study treatment at the visits indicated in the Time and Events Tables (Table 10 and Table 11). Post-baseline urine pregnancy testing may be done by local laboratory.

As per Section 3.2, if subjects cannot visit the site for safety lab collection conducted through central labs, local lab collection and assessments may be used during a public health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

Table 13 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)
Bicarbonate
Blood Urea Nitrogen (BUN) or urea
Calcium
Chloride
Creatinine[c]
Glucose (random)
Lactate Dehydrogenase (LDH)
Phosphate
Potassium
Sodium
Total Bilirubin[b]
Total Protein
Hematology Parameters
White Blood Cell (WBC) Count
Hemoglobin
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
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 4).

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.

7.3.5 Ophthalmic Examination

Subjects are required to have a standard ophthalmic examination performed by an ophthalmologist at Screening, Months 1, 3, 6, and 12 or at discontinuation if discontinuation occurs prior to Month 12. Additional ophthalmic exams will be performed only as symptomatically warranted. The exam will include a fundoscopic examination (direct or indirect), visual acuity (with correction), visual field examination, and tonometry with special attention to retinal abnormalities that are predisposing factors for RVO or CSR.

In subjects with clinical suspicion of RVO or CSR, flourescein angiography and/or optical coherence tomography are highly recommended.

7.3.6 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.

All blood pressure assessments should be performed under optimal conditions i.e. after (i) subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor, (ii) subject is relaxed comfortably for at least 5 minutes, (ii) preparatory steps including removal of any restrictive clothing over the cuff area and selection of the right cuff size have been ensured, (iii) the arm is supported so that the middle of the cuff is at the heart level, and (iv) 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. Only the averaged value should be entered in the eCRF.

7.3.7 Physical Examinations

All physical exams (brief and complete) will include the measurement of height (screening only) and weight using the metric scale, collection of vital signs including blood pressure, body temperature, pulse rate, and respirations as well as assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. A complete physical exam will also include a thorough genitourinary (pelvic) examination, inspection of the head and neck region, and digital rectal examination for both male and female subjects. For female subjects the genitourinary exam must include a PAP smear. Complete physical exams must be performed at Screening, Month 12 or discontinuation if discontinuation occurs prior to Month 12 and Month 18. If the subject has had a genitourinary and rectal exam within 6 months of randomization these do not need to be repeated at screening. Brief physical examinations will be performed at all other timepoints as indicated in the Time and Events Tables (Table 10 and Table 11). Refer to the SPM for additional detail regarding the exam requirements for the inspection of the head and neck region.

7.3.8 Dermatologic Examination

Dermatologic exams are required at Screening, Month 2, Month 4, Month 6, Month 8, Month 10 and Month 12 (or discontinuation if subject discontinues prior to Month 12), every three months from Month 12 until Month 24 every 6 months after Month 24 until Month 60 and then annually thereafter. Dermatologic examination is not required for subjects that have had disease recurrence and are in follow up after Month 60 visit. Exams may be performed by the investigator or may be referred to a dermatologist, at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations. Refer to the SPM for additional detail regarding the dermatologic examination including exam requirements and required training for investigators that will be performing the exam.

7.3.9 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.

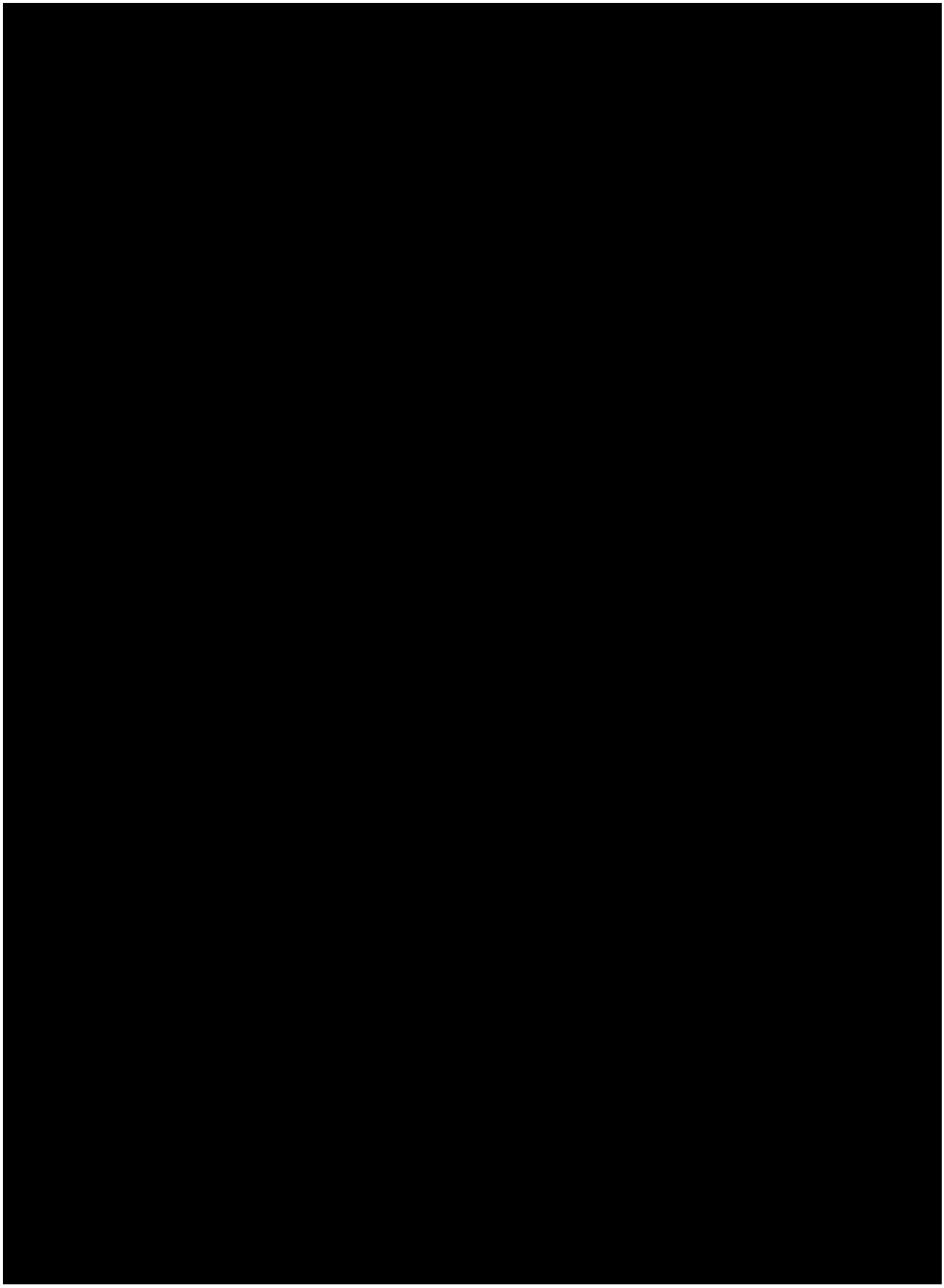
Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the Sponsor if necessary. See Section 5.8.3.3.3 for instructions if QTc withholding criteria are met.

7.3.10 Echocardiograms (ECHO)

Echocardiograms (ECHO) will be performed to assess cardiac ejection fraction and cardiac valve morphology. The echocardiographer's evaluation should include an evaluation for left ventricular ejection fraction and both right and left-sided valvular lesions. Copies of all ECHO scans may be collected by the sponsor for possible future central/independent review. Collection details and Image Acquisition Guidelines (IAG) will be provided in the SPM.

[redacted]

[redacted]



7.7 Translational Research

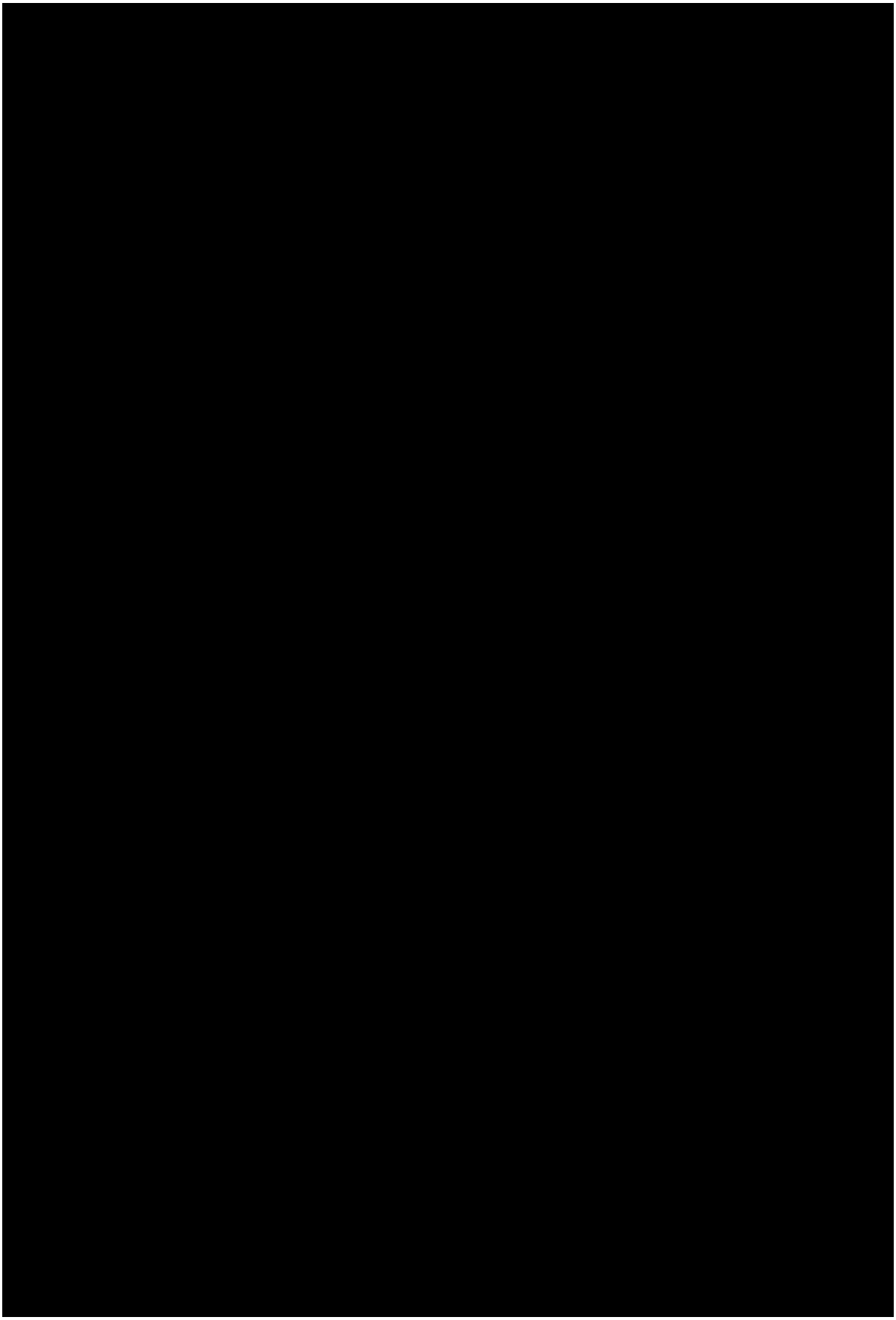
[redacted]

7.7.1 BRAF mutation assay

To determine BRAF V600E/K status, tumor tissue will be assessed from all subjects at Screening. The tissue will be tested for the BRAFV600E or V600K mutations using the bioMerieux THxID BRAFassay performed in a CLIA certified central reference laboratory. Tissue from either the primary tumor or metastatic lymph nodes is acceptable, however the most recently obtained tumor tissue (either archived material or fresh biopsy) is preferred. The tissue requirements for the BRAF mutation assay evaluating patient eligibility for the study are provided in the SPM.

[redacted]

[redacted]



[redacted]

8 DATA MANAGEMENT

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

Management of clinical data will be performed in accordance with applicable Novartis standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) andcustom drug 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 objective of this two-arm study is to evaluate the efficacy of dabrafenib/trametinib combination therapy compared to placebos with respect to Relapse-Free Survival (RFS) for subjects with Stage III, resected BRAF V600E/K mutation-positive melanoma.

The study is designed to provide evidence with respect to RFS to either support the null hypothesis, H_0: $\lambda = 1$ or reject it in favor of the alternative hypothesis, H_A: $\lambda \neq 1$, where λ is the hazard ratio (HR) of combination therapy relative to two placebos.

As per the initial protocol design (i.e. before Amendment 7), with 467 RFS events the study would have 95.3% power to detect HR=0.7143 (corresponding to median RFS of 15 and 21 months in the placebo arm and the combination therapy arm, respectively)

Final RFS analysis (as per Protocol Amendment 7):

The cutoff date for the final RFS analysis will be 30-June-2017 and the actual number of RFS events observed by that date will be used. At the time of Amendment 7, it is predicted to observe approximately 410 RFS events by the analysis cutoff date and this will provide more than 90% power to detect the originally targeted HR.

5-year RFS rate (as per Protocol Amendment 8):

To estimate long term relapse free survival, a RFS analysis analysis will be performed after all patients have completed a minimum of 5-years follow up and at the time of study completion.

9.2 Study Design Considerations

9.2.1 Sample Size Assumptions

As per the initial protocol design (i.e. before Amendment 7), the following assumptions were made in the estimation of the required sample size:

- Exponential survival distributions;
- A HR of 0.7143 (median RFS times of 15 and 21 months in the placebo arm and the combination therapy arm, respectively);
- A 1:1 randomization scheme;
- An overall 5%, two-sided risk of erroneously claiming superiority of the combination therapy in the presence of no true underlying difference (i.e., overall Type I error);
    - A 95% chance of successfully claiming superiority of the combination therapy in the presence of a true underlying difference (i.e., power or 1-Type II error);
- An accrual rate of 42 subjects per month over 20.3 months; and
- A dropout rate of 5% for the placebo group and 15% for the combination group.

To enable the observation of 467 total events, an estimated total of 852 subjects (i.e., 426 subjects in each of the arms) would need to be enrolled, leading to implementation of final analyses at approximately 32 months after the start of the study.

As per Protocol Amendment 7, the final primary RFS analysis will be performed at the pre-defined cut-off date, by which time it is expected that approximately 410 RFS events will have been accrued. The study power would be approximately 92% assuming 410 RFS events are observed by the data-cut and assuming originally targeted treatment effect represented by a hazard ratio equal to 0.7143. The choice of final RFS analysis timing is independent of the underlying treatment effect which is unknown. With the amended design, the type I error in this study is therefore preserved.

Secondary Endpoint: Overall Survival

At the time of the primary analysis of RFS, all secondary endpoints will also be summarized. If the primary efficacy analysis of RFS is statistically significant, statistical analyses of secondary endpoints will be performed to supplement the primary analysis and facilitate a comprehensive description of the efficacy results. All statistical tests, unless otherwise specified, will be stratified for treatment and stratification factors. Detailed information on the statistical methods will be provided in the Reporting and Analysis Plan (RAP).

OS is identified as the key secondary endpoint. A hierarchical approach will be taken to control for the overall type-I error rate for testing of multiple endpoints. Therefore OS will be formally statistically tested only if the primary efficacy endpoint RFS is statistically significant. As per the initial protocol design (before Amendment 7), the first potential time point for OS analysis will be at the time of the RFS final analysis when 467 RFS events will be observed:

1. If RFS is significant, an interim analysis for OS will be performed:

a. If OS is not significant at this stage, based on O'Brien-Fleming adjustments detailed below, the final OS analysis will be performed when 50% of the total number of randomized subjects have died (approximately 299 deaths).
b. If OS is significant, no further formal analysis will be performed.

2. If RFS is not significant, OS will not be formally statistically tested.

As per the initial protocol design (before Amendment 7), the type I error rate will be controlled by using a group-sequential design for testing OS at multiple time points. Specifically, Lan-DeMets method (Lan, 1983) with O'Brien-Fleming type stopping boundary (as in EAST 5.3) will be used to maintain the cumulative type-I error rate at 2.5% (one-sided). The exact nominal p-values that will be needed to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses.

Changes made in Protocol Amendment 7

Following the Protocol Amendment 7, the first OS interim analysis will be performed at the same time as the revised final RFS analysis; an additional 2nd OS interim analysis will be performed when approximately 299 OS events have occurred; the final OS analysis remains to be conducted at approximately 597 events. Approximately 150 OS events are projected to be observed by the new proposed data cut-off date of primary RFS analysis (~25% of the originally targeted number of OS events). The proposed additional OS interim analysis will be performed at approximately 299 events which represents ~50% of the originally targeted number.

O'Brien-Fleming type stopping boundary will be used for all OS tests planned in the Amendment 7 to maintain the cumulative type-I error rate at 2.5% (one-sided). With O'Brien-Fleming boundaries (as in EAST 6), the interim thresholds for claiming statistical significance are HR=0.493 (at 1st interim analysis assuming that exactly 150 OS events) and HR=0.710 (at 2nd interim assuming exactly 299 OS events) and the final threshold for claiming statistical significance is HR=0.851 (at final OS analysis assuming exactly 597 OS events). If any of the OS interim analyses is significant, no further formal analysis will be performed.

Changes made in Protocol Amendment 8

In protocol amendment 8, the group sequential scheme for OS will be modified and the final analysis will be conducted when approximately 299 OS events are observed. (planned as 2nd interim analysis for OS in amendment 7). All remaining alpha will be spent for this final analysis of OS by taking into account alpha spent at the first interim analysis corresponding to the information fraction of 25.6%

The study will be double blinded with randomization stratified for:

- Mutation type (V600E or V600K);
- Disease stage (IIIa, IIIb, IIIc)

Randomization to the Stage IIIa strata will be capped at 40% of the total number of subjects. Randomization to the Stage IIIb and IIIc strata will not be capped. All randomized subjects will be included in the analyses to test the hypotheses of interest regardless of length of

follow-up or whether or not study treatment was administered (i.e., subjects will not be replaced).

Changes made in Protocol Amendment 10

In protocol amendment 10, the group sequential scheme for OS will be modified and the

final analysis will be conducted when approximately 260 OS events are observed or at the number of events have occurred by the end of Jul-2023, whichever comes first.

All remaining alpha will be spent for this final OS analysis by taking into account alpha spent at the first interim analysis corresponding to the information fraction of 25.6%.

9.2.2 Sample Size Sensitivity

As per the initial protocol design (before Amendment 7), Table 14 shows the various power scenarios at the time of the RFS analysis under the assumed risk reduction (29%) and for scenarios where percent improvement and underlying medians vary assuming 467 events (relapses and all-cause deaths) have accrued.

Table 14 Statistical Power Scenario for RFS Analysis

Median RFS		% Improvement	Hazard Ratio	Power
Placebos	Combination Therapy			
14 months	20 months	42.8%	0.7	96.9%
15 months	21 months	40%	0.714	95%
16 months	21 months	31.3%	0.762	83.1%
16 months	22 months	37.5%	0.727	92.7%

The final OS analysis will be performed when approximately 260 deaths are observed. Table 15 shows the power to detect various treatment effects. For example with 260 deaths, the study would have approximately 80% power to detect a hazard ratio of 00.70. Conducting final analysis at 260 OS events affects the statistical power by 2%-13% (depending on different HR assumptions) compared to 299 OS events.

Table 15 Statistical Power Scenario for OS Analysis

Placebo	Combination Therapy	% Improvement	Hazard Ratio	% Power at 255 OS events	% Power at 260 OS events	% Power at 299 OS events
47 months	72 months	53%	0.65	93%	93%	96%
48 months	74 months	54%	0.65	93%	94%	96%
49 months	75 months	53%	0.65	92%	93%	96%
47 months	67 months	43%	0.70	81%	81%	86%
48 months	68 months	42%	0.70	79%	80%	84%
49 months	70 months	43%	0.70	81%	82%	86%
47 months	63 months	34%	0.75	65%	65%	70%
48 months	64 months	33%	0.75	63%	64%	69%
49 months	65 months	33%	0.75	62%	62%	75%
47 months	59 months	26%	0.79	44%	45%	49%
48 months	61 months	27%	0.79	48%	49%	53%
49 months	62 months	27%	0.79	47%	47%	52%

9.2.3 Sample Size Re-estimation

There will be no sample size re-estimation.

9.3 Data Analysis Considerations

9.3.1 Analysis Populations

The **Intent-to-Treat Population** (ITT) will consist of all randomized subjects whether or not randomized treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy data. Any subject who receives a treatment randomization number will be considered to have been randomized.

The **Safety Population** will consist of all subjects who received at least one dose of randomized treatment and will be based on the actual treatment received. This population will be used for the analysis of clinical safety data.

[redacted]

9.3.2 Analysis Data Sets

The primary dataset for efficacy (RFS, OS, DMFS, FFR) will be comprised of the ITT population as defined in Section 9.3.1

The primary dataset for assessing safety will be the Safety Population as defined in Section 9.3.1.

The primary objective will be supported by the test for superiority of combination therapy over placebo in relation to RFS (refer to Section 9.1) using the ITT population. The cutoff date for the final RFS analysis [redacted] the actual number of RFS events observed by that date will be used. Subjects will continue to be followed for OS until approximately 260 deaths have occurred (or by the end of Jul-2023, whichever occurs first).

Details on the handling of missing data are provided in the RAP.

9.3.3 Treatment Comparisons

9.3.3.1 Primary Comparisons of Interest

The primary treatment comparison will be between the combination therapy arm and the placebo arm, with respect to RFS within the ITT population.

9.3.3.2 Other Comparisons of Interest

Treatment comparisons for secondary efficacy (including subgroup analyses) and safety endpoints will be between the combination therapy arm and the placebo arm.

Overall survival (OS) is a key secondary comparison of interest. At the time of the primary RFS analysis, OS will be estimated for each group and compared. At the end of study, OS will be tested provided the initial RFS analysis was statistically significant, hence the

testing will be treated hierarchically and no adjustments for multiplicity are planned. At the time of the primary RFS analysis, DMFS and FFR will be estimated for each group and compared.

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery as post study treatment anti-cancer therapy will be summarized along with duration of treatment and best reported response achieved.

As these are supportive analyses, no adjustments for multiplicity are planned. P-values will be used to provide guidance on the weight or the evidence of any observed effect.

9.3.4 Interim Analysis & IDMC

No interim analyses will be performed for efficacy or futility for the primary endpoint RFS unless otherwise requested by the independent data monitoring committee (IDMC).

Following the Protocol Amendment 7, the first OS interim analysis will be performed at the same time as the revised final RFS analysis (i.e. at the [redacted] cutoff date); an additional OS interim analysis was planned to be performed when approximately 299 OS events have occurred however with Amendment 10 the final OS analysis will be conducted at approximately 260 events or by the end of Jul-2023, whichever comes first. Interim data cut was performed to conduct a 5-year RFS update upon request for additional descriptive data for health authority information.

An IDMC will be chartered to review accumulating safety data to provide an opportunity to terminate the study early if there are concerns regarding safety. The IDMC will be convened after approximately 100 subjects have been randomized, and will review safety data at intervals specified in the IDMC Charter. The recommendations of the IDMC will be communicated to Novartis, and in the event of a recommendation to halt the trial early due to safety concerns to the appropriate regulatory agencies.

The IDMC responsibilities, review schedules and mechanism for communicating recommendations will be outlined in an 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 centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

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

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently, there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

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.

As noted in Section 9.3.3.2 there will be no adjustments for multiplicity.

All significance tests, unless otherwise noted, will be stratified by mutation type (V600E or V600K), and disease stage (IIIa, IIIb, IIIc) for a total of 6 strata.

Additional details on efficacy analyses are provided in Section 9.3.5.1. Similarly, additional details on safety analyses are provided in Section 9.3.5.2.

9.3.5.1 Efficacy Analyses

9.3.5.1.1 Primary Analysis

If a subject has neither relapsed or died or started new anti-cancer therapy, then RFS will be censored at the date of last adequate assessment. If no post-baseline disease assessments exist, the subject will be censored at the date of randomization. In the primary analysis if a non-protocol anti-cancer therapy is started before the occurrence of a RFS event, then RFS will be censored at the last adequate assessment prior to the start of such therapy. Definition of "adequate assessment" and censoring rules will be detailed in the RAP.

RFS will be summarized using Kaplan-Meier estimates and compared between treatment arms using a stratified log-rank test. The Pike estimator (Bernstein, 1981, Berry, 1991) of the treatment hazard ratios (HR) will be provided, together with a 95% confidence interval (CI). The Pike estimator, which is a nonparametric estimator of the HR, has been specifically developed for survival data and is used as a measure of the relative survival experience of two groups. Within the range of values of the ratio of the hazard rates of interest in clinical trials, Pike estimator is more efficient in terms of mean square error than the Cox proportional hazard method (Bernstein, 1981).

Median times to RFS, first and third quartiles will be presented, along with 95% CI if there are a sufficient number of relapses or deaths. A graph of RFS curves and a listing of RFS times will also be provided.

Following the final analysis of RFS, the study will remain open for further follow-up to collect additional survival and safety data. Updated safety and efficacy analyses may be performed at the close of the study.

Sensitivity Analyses for RFS:

Sensitivity analyses using the ITT population will be conducted in order to confirm the results of the primary analysis. Some key sensitivity analyses are provided below.

Additional sensitivity analyses will be defined in the RAP.

The following sensitivity analyses will be performed for RFS and will be detailed in the RAP:

- **RFS** regardless of start of new anticancer therapy prior to documented relapse. Namely, all RFS events will be included regardless of whether or not subsequent anti-cancer therapy was initiated prior to the event.

- **Cox** Regression analysis including baseline prognostic factors as covariates will be performed. Factors included in the model will be pre-specified in the RAP.
- RFS Analysis ignoring new melanoma as an event.

9.3.5.1.2 Secondary Analyses

OS will be estimated using the Kaplan Meier method and treatment comparisons, when performed, will be made using a stratified log-rank test (based on the two stratification factors defined in Section 9.2). All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive at the time of analysis. The hazard ratio along with 95% confidence intervals will be provided.

DMFS will be estimated using the Kaplan Meier method and treatment comparisons will be made using a log-rank test. The first appearance of distant metastasis or all cause mortality will be used as events. Censoring will be performed using the date of last assessment for those who are alive without distant metastasis at the time of analysis. The hazard ratio along with 95% confidence intervals will be provided.

FFR will be estimated using the Kaplan Meier method and treatment comparisons will be made using a log-rank test. The first appearance of local/distant metastasis or mortality due to disease recurrence or toxicity will be used as events. Censoring will be performed using the date of last assessment for those who are alive without local/distant metastasis or new primary melanoma at the time of analysis. FFR will be censored if patients died from causes other than melanoma or treatment-related toxicity at the date of death. The hazard ratio along with 95% confidence intervals will be provided.

Other efficacy analyses will be detailed in the RAP.

9.3.5.2 Safety Analyses

Safety endpoints are described in Section 2 and Section 7.3.

The Safety population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

9.3.5.2.1 Extent of Exposure

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

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).

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

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

Characteristics (e.g. number of occurrences, action taken, grade, etc) of AEs of special interest (including SCC and other proliferative lesions) will be summarized separately as detailed in the RAP.

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

9.3.5.2.3 Clinical Laboratory Evaluations

Hematology 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 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 (i.e. no visit windows will be applied). Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

9.3.5.2.4 Other Safety Measures

The results of scheduled assessments of vital signs, ECOG performance status, 12-lead ECG, and ECHO will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in 'worse case' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. All data will be listed. Further details will be provided in the RAP.

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 enrollment of subjects begins.

10.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

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

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

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

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

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 Organization [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.

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

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

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

10.4 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, 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 complete when approximately 43.5 percent of the initially planned target number of randomized subjects have died or are otherwise lost to follow-up (approximately 260) or at the end of Jul-2023, whichever comes first. At which time final analyses will be performed.

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

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 the Sponsor 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.

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.

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 will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

Novartis aims to post a results summary to the Novartis Clinical Trial Results website (.novartisclinicaltrials.com) and other publicly available registers no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication.

When publication is not feasible, please refer to the Novartis Clinical Trial Results website (novartisclinicaltrials.com) for a summary of the trial results.

10.8 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (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 and the analysis plan for IDMC review are described in the charter.

11 REFERENCES

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

Balch C, Gershenwald J, Soong SJ, Thompson J, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol. 2009; 27:6199-6206.

Bernstein L., Anderson J., Pike M.C. Estimation of the Proportional Hazard in Two-Treatment-Group Clinical Trials. *Biometrics.* 1981; 37:513-519.

Berry G., Kitchin, R.M., Mock. P. A comparison of Two Simple Hazard Ratio Estimators Based on the Logrank Test. *Statistics in Medicine.* 1991:749-55.

Budman DR,et al. Dose and Dose Intensity as Determinants of Outcome in the Adjuvant Treatment of Breast Cancer. J Natl Cancer Inst 1998;90: 1205–11.

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

Chapman PB, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med 2011;364:2507-16.

Citron ML, et al. Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node- Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-1439.

Clinicaltrials.gov. EORTC18991, EORTC18071, DERMA, EORTC18592, ECOG1690, AVAST-M, GO27826. 25 May 2012.

Corcoran RB, Dias-Santagata D, Bergethon K, Iafrate AJ, Settleman J, Engelman JA. BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation. Sci Signal. 2010 Nov 23;3(149):ra84.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome in 100,000 women in 123 randomised trials. Lancet, Published Online December 6, 2011.

Eggermont A, Chiarion-Sileni V, Grob JJ, Dummer R, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomized, double-blind, phase 3 trial. Lancet, Published Online April 1, 2015.

Eggermont A, Suciu S, Santinami M, Testori A, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. The Lancet. 2008; 372:117-26.

Emery C.M., Vijayendran K.G., Zipser M.C., Sawyer A.M., Niu L., Kim J.M., Hatton C, Chopra R., Oberholzer P.A., Karpova M.B., MacConaill L.E., Zhang J., Gray N.S., Sellers W.R., Dummer R., Garraway L.A. MEK1 mutations confer resistance to MEK and BRAF inhibition. Proceedings of the National Academy of Science. 2009; 106 (48):20411–20416.

Flaherty KT, Hersey RC, Garbe NP et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012; [Epub ahead of print].

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.

GlaxoSmithKline Document Number 2011N126811_00. GSK1120212 + GSK2118436 Investigator's Brochure. Report Date 15 Feb 2012.

GlaxoSmithKline Document Number 2012N136095_00, Dabrafenib Investigator's Brochure. Report Date 15 May 2012.

GlaxoSmithKline Document Number HM2009/00151/02, GSK1120212 Investigator's Brochure. Report Date 23 June 2011.

Goetz E and Garraway L. Mechanisms of resistance to mitogen-activated protein kinase pathway inhibition in BRAF-mutant melanoma. American Society of Clinical Oncology 2012.

Hauschild A, Jacques-Grob J, Demidov L et al. (2012). Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. The Lancet, Available online 24 June 2012, ISSN 0140-6737. doi: 10.1016/S0140-6736(12)60868-X (httpwww.sciencedirect.com/science/article/pii/S014067361260868X).

Jemal A, Siegel R, Ward E et al. Cancer statistics, 2007. CA Cancer J Clin 2007; 57: 43-66.

[redacted]

Kirkwood JM, Ibrahim JG, Sosman JA et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage II-III melanoma: Results of Intergroup Trial E1694/S9512/C509801. *J Clin Oncol* 2001;19: 2370-80.

Kirkwood JM, Long GV, Trefzer U et al. BREAK-MB: A phase II study assessing overall intracranial response rate (OIRR) to dabrafenib (GSK2118436) in patients (pts) with BRAF V600E/K mutation-positive melanoma with brain metastases (mets). *J Clin Oncol* 2012; 30:15s (suppl abstr 8501).

Lacouture M., O'Reilly K., Rosen N., Solit D. Induction of Cutaneous Squamous Cell Carcinomas by RAF Inhibitors: Cause for Concern? *J Clin Oncol*. 2012;30(3):329-330.

Lan K.K., DeMets, D. L. Discrete Sequential Boundaries for Clinical Trials 659-663. *Biometrika.* 1983:659-63.

Markovic SN, Erickson LA, Rao RD et al. Malignant melanoma in the 21st century, part 2: staging, prognosis and treatment. Mayo Clin. Proc. 2007; 82: 490 – 513.

Muss HB, et al. Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer. N Engl J Med 2009;360:2055-65.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology:Melanoma. NCCN, Ft. Washington, PA; 2012.

Nikolaev SI, et al. Exome sequencing identifies recurrent somatic MAP2K1 and MAP2K2 mutations in melanoma. Nature Genetics (*published online 25 December 2011*).

Nissan MH, Solit DB. The "SWOT" of BRAF inhibition in melanoma: RAF inhibitors, MEK inhibitors, or both? Curr Oncol Rep 2011;13:479-87

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.

[redacted]

Schuchter L. Adjuvant Interferon Therapy for Melanoma: High-Dose, Low-Dose, No Dose, Which Dose? J Clin Oncol 2004; 22:7-10.

Van Akkooi AC, Rutkowski P, va der Ploeg M, Voit C, et al. Long-term follow-up of patients with minimal sentinel node tumor burden (<0.1mm) according to Rotterdam criteria: A study of the EORTC Melanoma Group. J Clin Oncol, 2009; 27:15s (suppl abstr 9005).

Weber J, Flaherty K, Infante J, et al. Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with oral MEK ½ inhibitor trametinib (GSK1120212) in patients with BRAFi-naive metastatic melanoma. J Clin Oncol 2012;30 (suppl; abstr 8510).

World Health Organization (WHO). Skin cancers. In *Ultraviolet radiation and the INTERSUN Programme*. Retrieved 07 February 2012, from.who.int/uv/faq/skincancer/en/index1.html.

12 APPENDICES

12.1 Appendix 1: Melanoma of the Skin Staging

American Joint Committee on Cancer

Melanoma of the Skin Staging

7th EDITI

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:

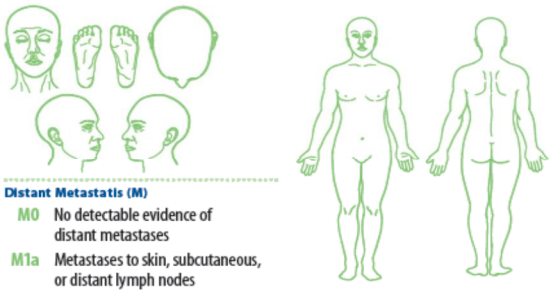
T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS/MITOSES
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

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 Metastatis (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 wwwcancerstaging.org/staging/posters/melanoma8.5x11.pdf.

12.2 Appendix 2: Surgical Guidelines

Management of the primary

Wide excision with a minimal 1 cm margin surrounding the primary lesion or biopsy scar will be required. For lesions with Breslow's thickness >2 mm, a 2 cm margin is preferred only when anatomically feasible (i.e., for lesions of the trunk and proximal extremities). On other sites narrower margins are recommended to avoid mutilation. For subungual melanoma, a distal interphalangeal amputation with histologically negative margins constitutes an adequately wide excision. The specimen should be excised to include skin and all subcutaneous tissue down to the muscular fascia. Inclusion of the fascia is not recommended, but fascia may be included at the discretion of the operating surgeon. Closure of the defect may be via primary closure, split thickness skin graft, or rotation flap at the discretion of the surgeon.

Completion Lymph node dissection (CLND)

Patients should have a complete lymphadenectomy with no clinical or radiographic evidence of regional node disease remaining.

Specific considerations apply to the following drainage areas (Garbe, 2008):

Head and Neck

- Radical or modified radical neck dissection is required
- Parietal/frontal regions (excluding chin and neck) – include superficial parotoidectomy
- Dorsal regions – include retroauricular and occipital lymph nodes

Axilla

- Level I and II lymph nodes
- Level III lymph nodes medial to lesser pectoralis (note: muscle may need to be removed if lymph nodes are extensively involved)

Inguinal

- Dissection should extend from femoral triangle and lower abdominal rectus from the pubic tubercle to the anterior iliac crest (including saphenous foramen and inguinal ligament and removal of saphenous vein if no contraindications)
- Include iliac lymph nodes if clinically positive (including Cloquet's node) to level of iliac bifurcation, along with obdurator lymph nodes

Reference:

Garbe C, et al. Evidence and interdisciplinary consensus-based German guidelines: surgical treatment and radiotherapy of melanoma. Melanoma Res 18:61–67 (2008).

12.3 Appendix 3: 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.

12.4 Appendix 4: 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:

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

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

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.

12.5 Appendix 5: 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.

12.6 Appendix 6: New York Heart Association (NYHA) Guidelines

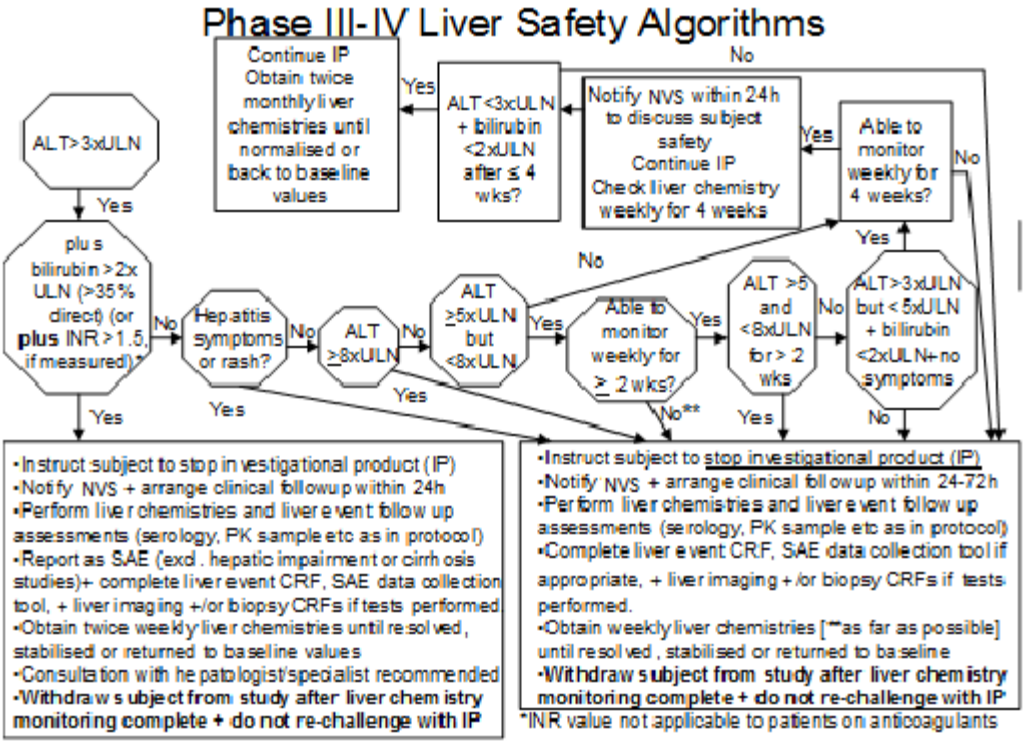
The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure (The Criteria Committee of the New York Heart Association, 1994). It places subjects in 1 of 4 categories based on the level of limitation experienced during physical activity:

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 of severe cardiovascular disease.

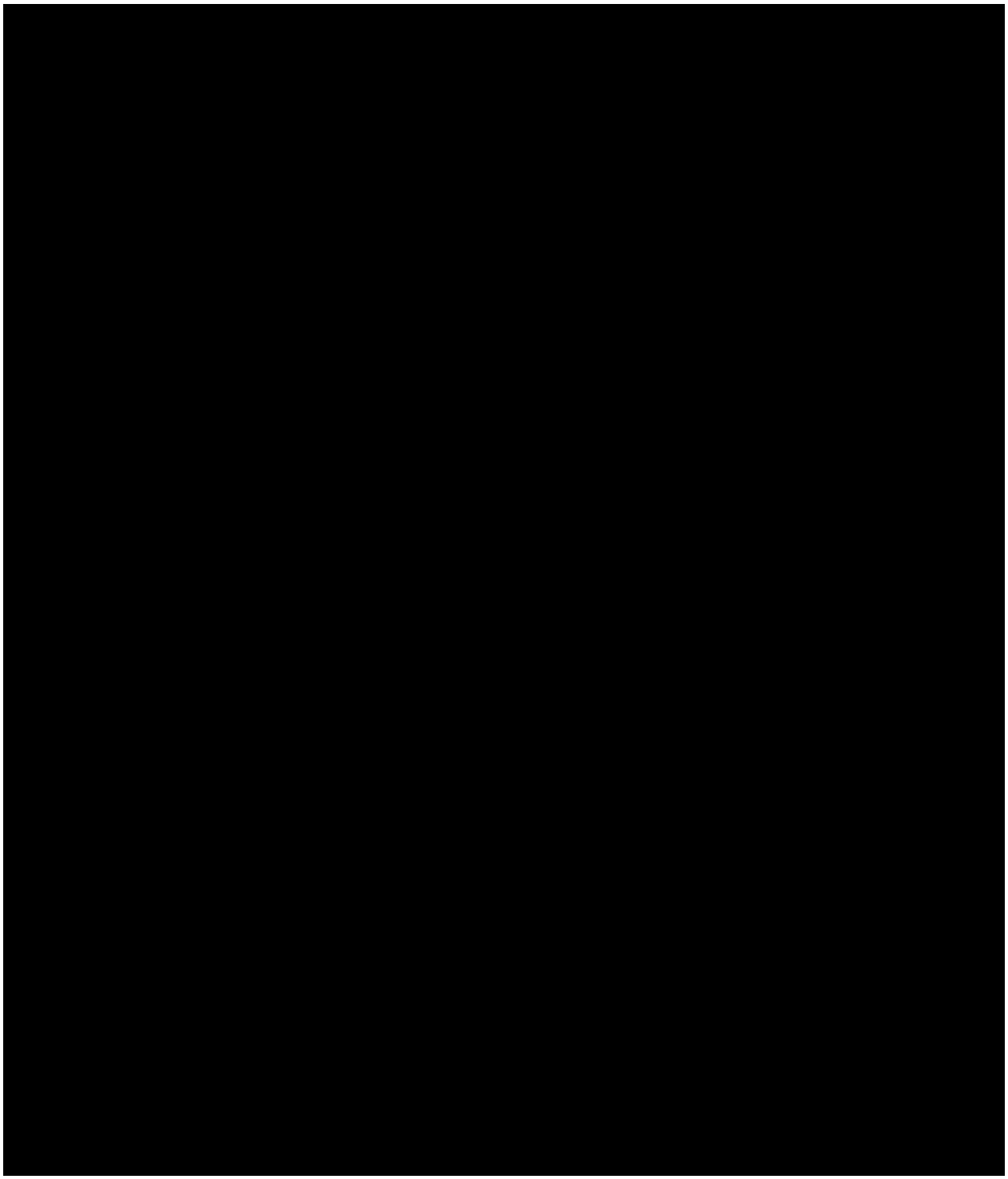
Reference:

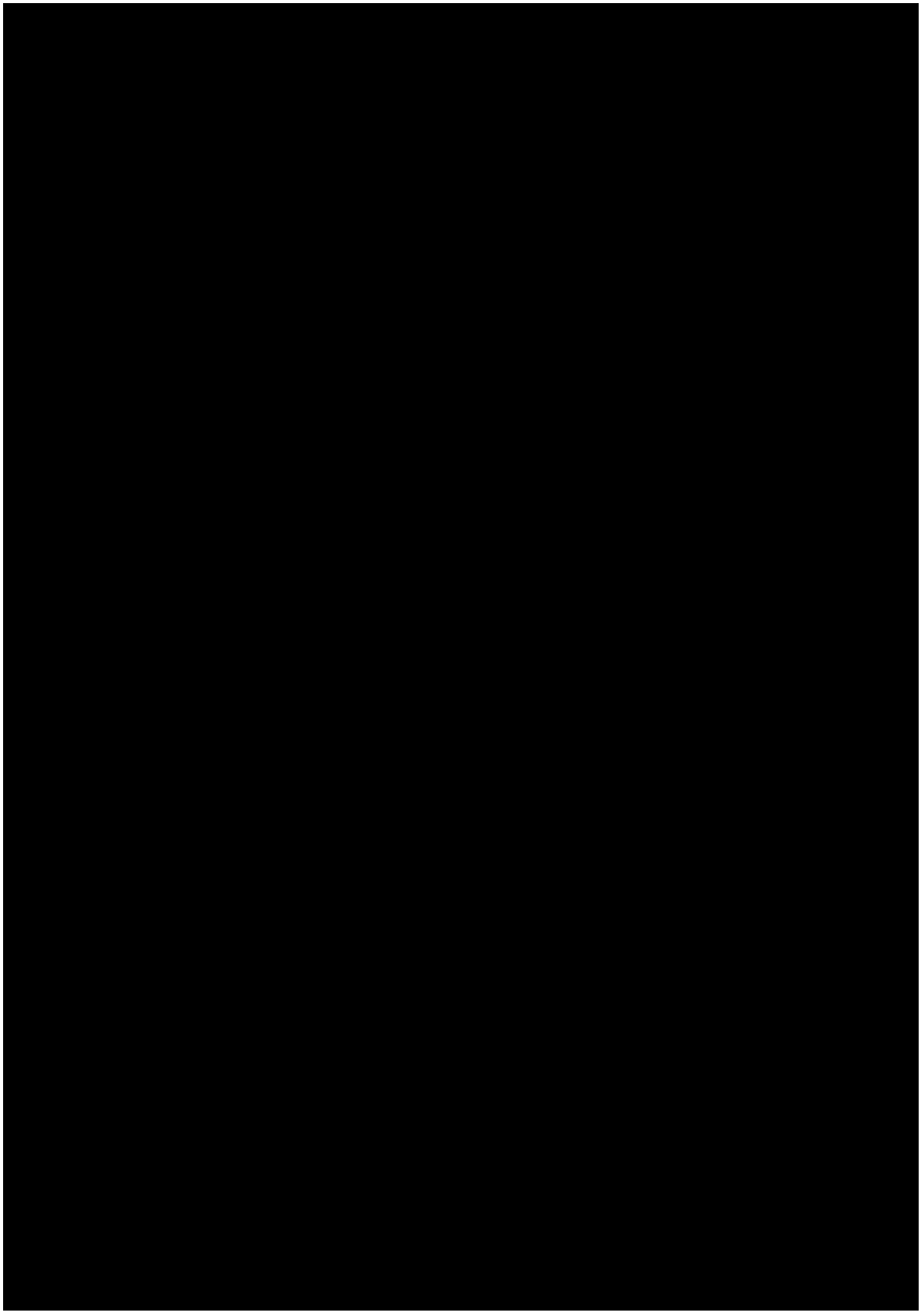
The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown, & Co; 1994:253-256.

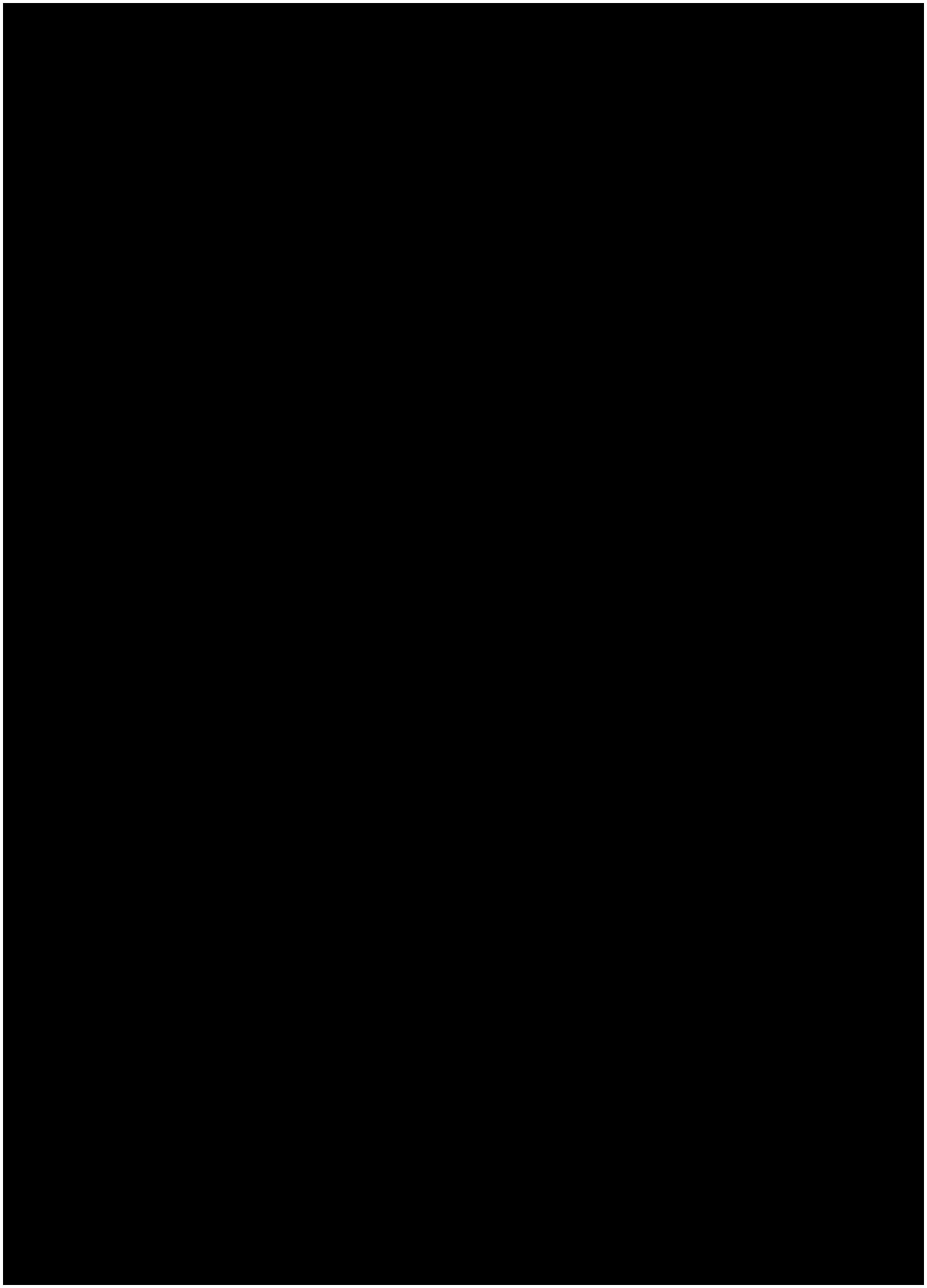
12.7 Appendix 7: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

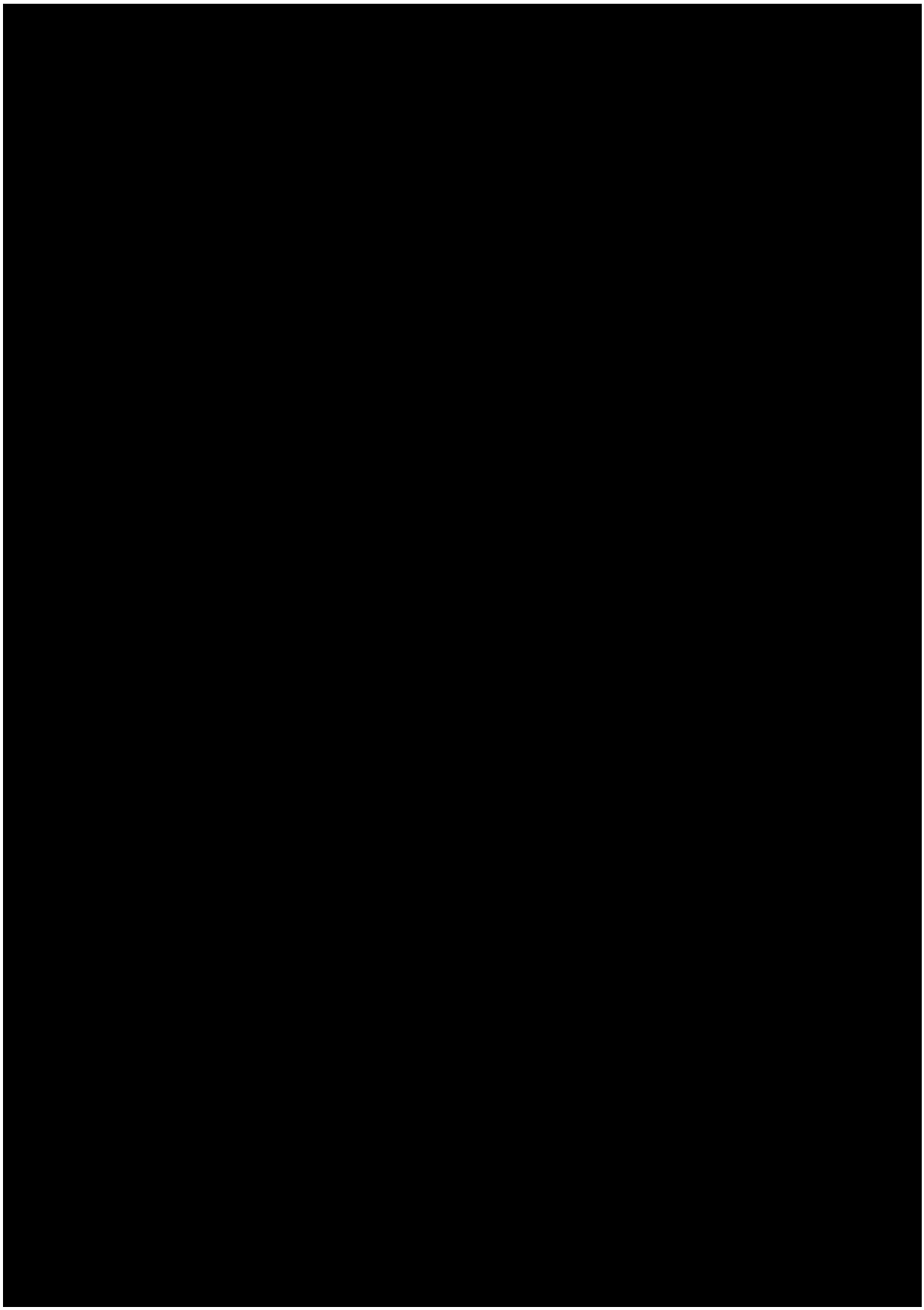


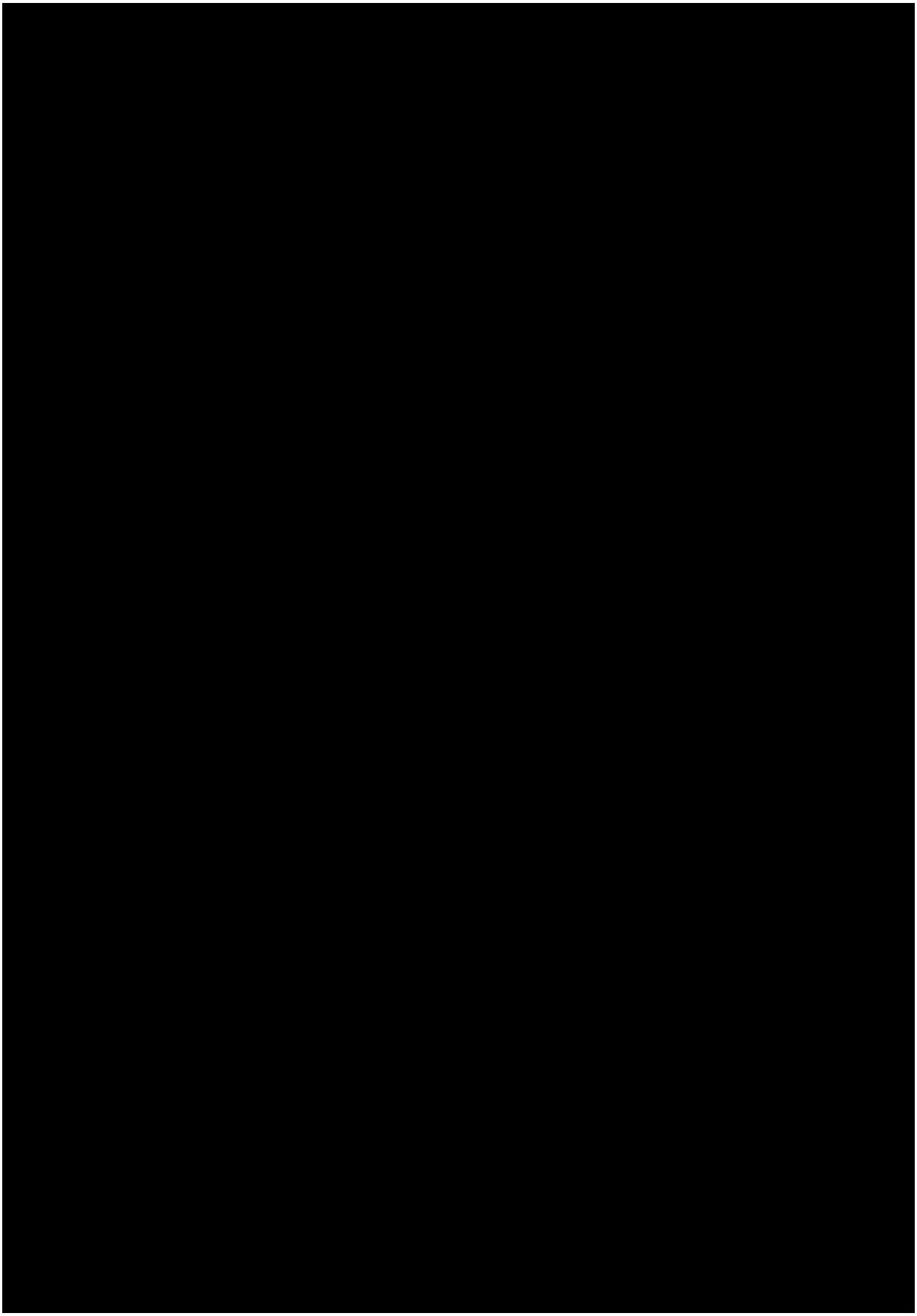
IP may be re-challenged if protocol provides this option.

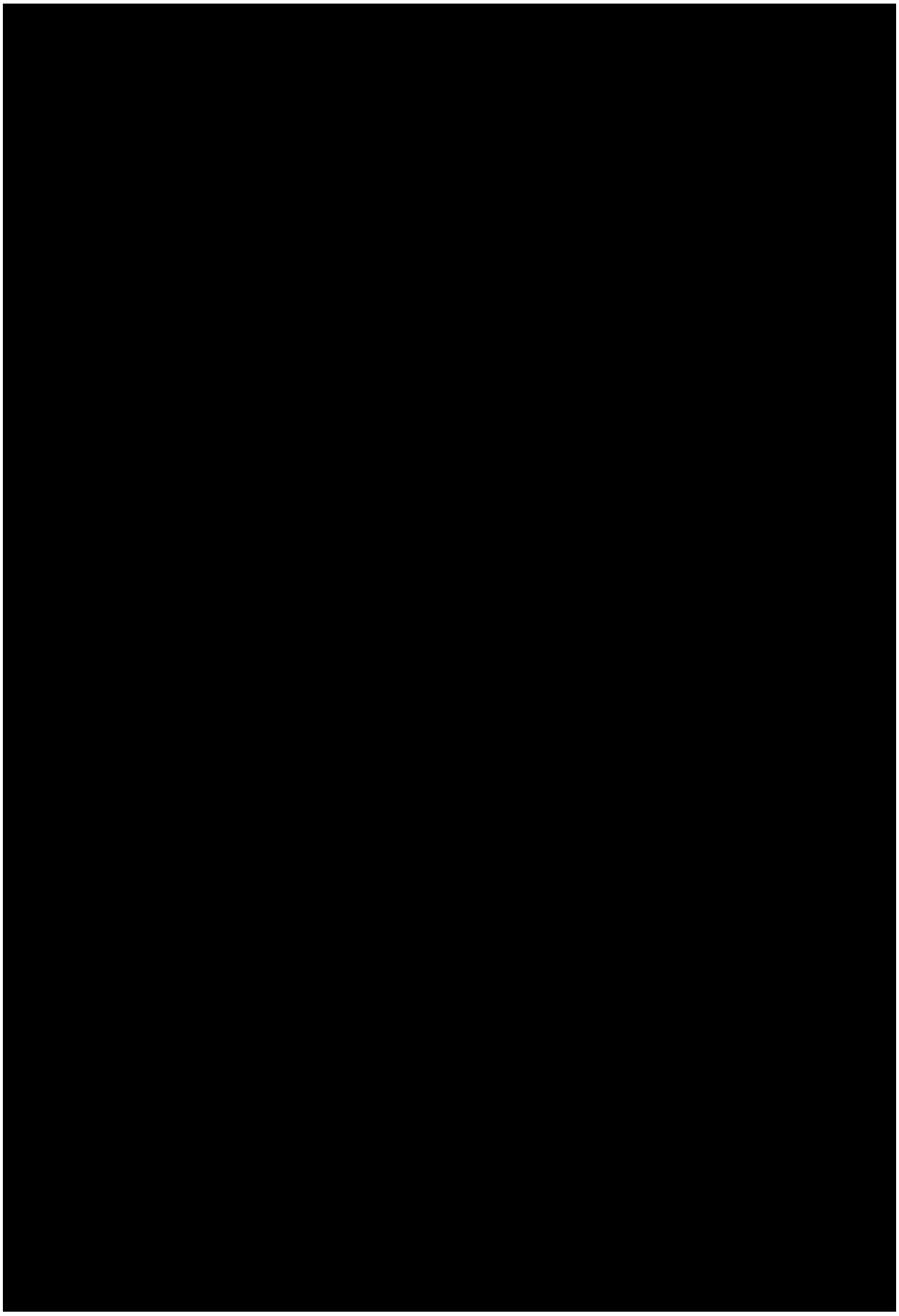












12.10 Appendix 10: Country Specific Requirements

Not Applicable.

12.11 Appendix 11: Protocol Changes

Refer to prior protocol versions for full details of amendments.