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An Open-Label, Multi-Center Study to Investigate the Objective Response Rate of Dabrafenib in Combination with Trametinib in Subjects with BRAF V600 Mutation-Positive Melanoma

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Amendment 08 (27-Nov-2019)

Amendment rationale

The primary purpose of this amendment is to align the dose modification section of the protocol related to severe cutaneous adverse reaction(s) (SCAR(s)), as updated in the dabrafenib and trametinib Investigator's Brochure (IB) Edition 11.

Change to the protocol

Please refer to section 12.8: Appendix 8: Protocol Amendment Changes.

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.

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N167722_00	2013-JUL-08	Original
2013N167722_01	2015-MAR-27	Amendment No. 1
Eligibility criterion was changed to permit both cutaneous melanoma and acral melanoma that is BRAF v600E/K mutation positive. Additional updates to sections to align with current dose modification guidelines.		
2013N167722_02	2015-SEP-17	Amendment No. 2
This is a country specific protocol amendment to specify the exclusion criteria xiii to reflect the comments from Korea regulatory authority to change "history of RVO" to "history and current RVO" in exclusion criteria xiii.		
2013N167722_03	2016-MAR-04	Amendment No. 3
1. The study sample size is increased. 2. Remove the two-stage Green-Dahlberg design and related interim analysis. 3. Addition of medical knowledge in melanoma. 4. Revision of some inclusion and exclusion criteria. 5. Change in tumor biopsy schedule for [redacted] purpose.		
2013N167722_04	2016-OCT-25	Amendment No. 4
1. Addition of PK samples in Chinese patients only 2. Revision of secondary objectives and endpoints in relation with the updated PK schedule		

3. Clarify the requirements for enrolment of patients with a history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (exclusion criterion # 6 and Table 22). 4. Addition of the optional non-melanoma skin biopsy in Table 20. 5. Addition of contraception requirements in male participants.		
2013N167722_05	2016-DEC-16	Amendment No. 5
1. Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. 2. Make administrative changes to align with Novartis processes and procedures. **This amendment is not applicable for China as sponsorship will not change in China until the end of the study.**		
2013N167722_06	2018-MAR-22	Amendment No.6
1. Revise contact details 2. Remove duplicate sentence regarding population PK parameters in study endpoint section. 3. Correct a typo and a discrepancy in the Dose Modification Guidelines for Pyrexia. 4. Clarify that the liver PK samples will stop being collected 8 weeks after last patient first treatment**.** 5. Change the required duration of contraception for male subjects. 6. A new reference added in sample size assumption. 7. Correct the typo in creatinine clearance calculation formula.		
2013N167722_07	2019-FEB-15	Amendment No.7
1. Update the contraception method for female subjects. 2. Update the contraception duration after dabrafenib discontinuation		
2013N167722_08	2019-NOV-27	Amendment No.8
1. Replace “vials” wording by “bottles” as study treatments are supplied in bottles, and not in vials. 2. Align the dose modification section of the protocol related to severe cutaneous adverse reaction(s) (SCAR(s)), as updated in the dabrafenib and trametinib Investigator’s Brochure (IB) Edition 11.		

SPONSOR SIGNATORY

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Novartis Pharmaceuticals Corporation

SPONSOR INFORMATION PAGE

Clinical Study Identifier: Protocol 200104

Sponsor Contact Information:

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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.

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Regulatory Agency Identifying Number(s):

Investigational New Drug (IND) Number	[redacted]

Investigator PROTOCOL Agreement Page

For protocol number 200104

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

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

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

Investigator Name: _____

Investigator Signature Date

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LIST OF ABBREVIATIONS

150/2	Dabrafenib 150 mg BID + trametinib 2 mg QD
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event(s)
ALT	Alanine transaminase (SGPT)
ALM	Acral lentiginous melanoma
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
ATS	All treated subjects
AUC	Area under the concentration-time curve
AUC (0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BAL	Bronchoalveolar lavage
BCC	Basal Cell Carcinoma
BID	Twice daily
BP	Blood pressure
BRAT	Banana, rice, apples, toast
BUN	Blood urea nitrogen
CDK	Cyclin dependent kinase
[redacted]	[redacted]
CHF	Congestive heart failure
CI	Confidence interval
CL/F	Clearance following oral dosing
Cmax	Maximum peak concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modeling & Simulation
CR	Complete response
CrCl	Creatinine clearance
CRO	Clinical Research Organisation
CRP	C-reactive protein
CSR	Central serous retinopathy
CT	Computed tomography
Ctrough	Trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte antigen
cuSCC	Cutaneous Squamous Cell Carcinoma
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DTIC	Dacarbazine
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
EGFR	Epidermal growth factor receptor
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GI	Gastro-intestinal
GSK	GlaxoSmithKline
G6PD	Glucose-6-phosphate dehydrogenase
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HFSR	Hand-foot skin reaction
Hg	Mercury
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPMC	Hydroxypropyl methylcellulose
HR	Hazard ratio
HRT	Hormone-replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonization
IDSL	International data standards library
IEC	Independent Ethics Committee
IL2	Interleukin-2
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent review committee
IUO	Investigational use only
LDH	Lactate dehydrogenase
LLN	Lower limit of normal

LSLV	Last subject's last visit
LVEF	Left ventricular ejection fraction
MAP	My Access Program
MAPK	Mitogen-activated protein kinases
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter(s)
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NSAIDS	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
[redacted]	[redacted]
PK	Pharmacokinetics
PPES	Palmar-plantar erythrodysesthesia
PR	Partial response
PT	Prothrombin time
PTS	Platform technology and science
PTT	Partial thromboplastin time
QTc	Corrected QT interval on electrocardiogram
QTcB	QT interval on electrocardiogram corrected using Bazett's formula
QTcF	QT interval on electrocardiogram corrected using Fridericia's formula
SCARs	Severe Cutaneous Adverse Reactions
SAP	Statistical Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RPED	Retinal pigment epithelial detachment
RVO	Retinal vein occlusion
SAE	Serious adverse event(s)
SBP	Systolic blood pressure
SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)

SLD	Sum of longest diameters
SNPs	Single nucleotide polymorphisms
SPD	Sum of the products of the two largest perpendicular diameters
SPF	Skin protection factor
SPM	Study Procedures Manual
tmax	Time to Cmax
ULN	Upper limit of normal
UP	Upper Providence
US/USA	United States
V/F	Volume of distribution
WBC	White blood cell
XRT	Radiation therapy

PROTOCOL SUMMARY

Rationale

Cutaneous melanoma is the most aggressive form of all skin cancers. Historically, the median survival time for subjects with Stage IV melanoma has been approximately 6 months and a median time to progression-free survival (PFS) at 1.7 months [Korn EL, 2008].

Dependence on MAPK signaling is a key feature of BRAF V600 mutant melanoma, as demonstrated by the clinical efficacy of vemurafenib, dabrafenib, and trametinib Phase III results [Chapman PB, 2011; Hauschild A 2012; Flaherty KT, 2012b]. While monotherapy with MAPK inhibitors represents a significant advance in the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma, approximately half of patients treated with a BRAF or MEK inhibitor as monotherapy will develop resistance and progress within 5 to 7 months of starting treatment [Sosman JA, 2012; Hauschild A, 2012; Flaherty KT, 2012a]. Concomitant inhibition of BRAF and MEK may lead to greater response rates, provide more durable responses, and increase progression free survival and overall survival. Furthermore, hyperproliferative skin lesions, including cuSCC and keratoacanthoma, have been associated with paradoxical activation of the MAPK pathway by BRAF inhibition.

Much has changed in the treatment landscape of melanoma since the past 5 years. The immunotherapy as anti-cancer treatment in melanoma has significantly advanced. Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen or CTLA-4, was approved by the US-Food and Drug Administration (FDA) for unresectable or metastatic melanoma in 2011. 2 immune check-point therapy, Programmed Death (PD) receptor-1 antibody (pembrolizumab and nivolumab) were also approved in 2014 for the treatment of metastatic melanoma following the standard treatment. The combination of ipilumumab and nivolumab also received FDA approval as first line treatment for metastatic melanoma in September, 2015 for BRAF wild-type patients, and extended to BRAF mutation patients in January2016. However these medicines are not readily accessible in some countries, such as China.

The selective small molecule BRAF kinase inhibitor demonstrated significant clinical benefit as monotherapy in metastatic melanoma patients with V600 mutation. However the efficacy of BRAF inhibitor was not durable. In addition, BRAF-inhibitor-induced paradoxical activation of the MAPK pathway which is associated to proliferative reaction of cells with wild type BRAF. Clinically this was reflected as increase hyperproliferative skin lesions including cutaneous squamous cancer.

Single agent MEK inhibitor trametinib has proved to improve survival in metastatic melanoma with BRAF mutation and not associated with paradoxical activation of MAPK pathway [Flaherty KT, 2012b July].

Combination of MEK and BRAF inhibitor was tolerable and delayed the emergence of resistance and decreased the incidence of cutaneous hyperproliferation. This was initially observed in a phase I/II study (BRF113220, Flaherty KT 2012a) and later confirmed by 3 randomized phase III studies. Long and colleagues reported the result of COMBI-D study. In this study, combination treatment of MEK and BRAF inhibitor (dabrafenib and trametinib) compared with BRAF inhibitor (dabrafenib) alone, significantly improved progression free survival in previously untreated patients who had metastatic melanoma with BRAF V600E or

V600 K mutations [Long GV 2014]. Another phase III study in the similar population reported same result using a different combination of MEK and BRAF inhibitor (cobimetinib and vermurafenib) [Larkin J,2014]. Additionally, a third phase III study was published, which demonstrated the combination of trametinib and dabrafenib significantly improved overall survival compared with vemurafenib in metastatic melanoma with BRAF V600 mutation [Robert C 2015].

In United States, Australia, Canada and most other countries, dabrafenib in combination with trametinib has been approved to treat metastatic melanoma with BRAF V600 mutation and had become a standard treatment for these patients. The above mentioned randomize phase III studies were mainly conducted in Caucasian population. The efficacy and safety of trametinib plus dabrafenib need to be evaluated in Asian melanoma patients. Patients in countries where this combination is not yet approved, such as China, are still in urgent unmet medical need for the new treatment.

Acral lentiginous melanoma (ALM) is one of 4 major histological subtypes of cutaneous melanoma. It is characterized by lesions presenting on non-hair bearing skin including the palm, soles, and nail beds. Although ALM accounts for only 2% to 3% of all melanomas, ALM makes up a much higher proportion (40-50%) of cutaneous malignant melanomas in darker-skinned individuals (i.e., blacks, Asians, and Hispanics) [Bradford PT 2009]. BRAF V600 mutations are less frequent (25 – 30%) in acral melanoma not associated with chronic sun-damage. In contrast, c-Kit mutations are more common in mucosal (39%) and acral melanomas (36%), which can also be accompanied by an increase in c-Kit copy numbers [Curtin JA 2006]. Very few patients with ALM have been treated with dabrafenib and trametinib combination since the vast majority subjects enrolled were Caucasians.

The original objective of the study was to evaluate the effect of dabrafenib and trametinib in patients with ALM in Asian countries. In light of the most recent advances in the treatment of BRAF mutation cutaneous melanoma, the study aims to evaluate the efficacy and safety of dabrafenib and trametinib in Asian subjects with either acral lentiginous or cutaneous melanoma pathology subtypes who have BRAF V600 mutation. This study will provide important scientific information to help to address the unmet medical needs in Asian melanoma patients.

Objective(s)

Primary Objective

- To determine the objective response rate (ORR) of dabrafenib and trametinib combination in subjects with BRAF V600 mutation-positive, unresectable or metastatic acral lentiginous or cutaneous melanoma.

Secondary Objectives

- To further evaluate the antitumor activity [progression free survival (PFS), duration of response, and overall survival (OS)]
- To assess exposure to dabrafenib, dabrafenib metabolites, and trametinib after a single dose (Chinese patients) and at steady-state and characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of dabrafenib and trametinib

- To evaluate the safety and tolerability of dabrafenib and trametinib combination therapy.

[redacted]

Study Design

This is a single-arm, open-label, multi-center, Phase II study to evaluate dabrafenib and trametinib combination therapy in BRAF V600 mutant unresectable or metastatic ALM or cutaneous melanoma. Subjects with histologically confirmed acral lentiginous or cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV will be screened for eligibility. Screening will include central testing of BRAF V600 mutation status. Eligible subjects must be BRAF V600 mutation positive. Subjects may have had prior systemic anti-cancer treatment in the adjuvant or metastatic setting, but should not have been exposed to MEK or BRAF inhibitor. Objective response rate will be assessed based on RECIST 1.1. Approximately 65 subjects will be enrolled and will receive dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily.

Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, or study completion. After treatment discontinuation, subjects will be followed for survival and disease progression as applicable.

Survival and new anti-cancer therapy follow-up will continue until study completion. The study completion is defined as:

- In case all subjects stop study treatment within 48 weeks after Last Subject First Visit(LSFV): the study is completed once the last subject has completed the 48 weeks survival follow-up or all subjects die or loss to follow-up, whichever comes first.
- In case some subjects are still on study treatment 48 weeks after LSFV: the study is completed once all subjects stop study medication, or all subjects who are still on study medication can have access to alternative supply of MEK/BRAF inhibitors, whichever comes first.

Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment.

Study Endpoints/Assessments

The primary endpoint for the study is ORR as determined by investigator assessment as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Duration of response, PFS, and OS endpoints will also be determined based on the investigator's assessment.

Safety Endpoints

Safety will be evaluated by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiograms (ECHO), eye exams, chemistry and hematology laboratory values, and adverse events (AEs).

Pharmacokinetic Endpoints

Noncompartmental PK parameters will include:

Trametinib, dabrafenib and dabrafenib metabolites Cmax, tmax, Ctrough, AUC(0-t), and AUC(0-8); AUC(0-12) (dabrafenib and dabrafenib metabolites only), AUC (0-24) (trametinib only) and the dabrafenib metabolite to dabrafenib ratio of AUC(0-12). For Chinese patients, the accumulation ratio will be calculated by using the pharmacokinetic parameters from Day 1 and Day 15. Population PK parameters will include: apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and absorption rate constant (Ka) for dabrafenib and trametinib.

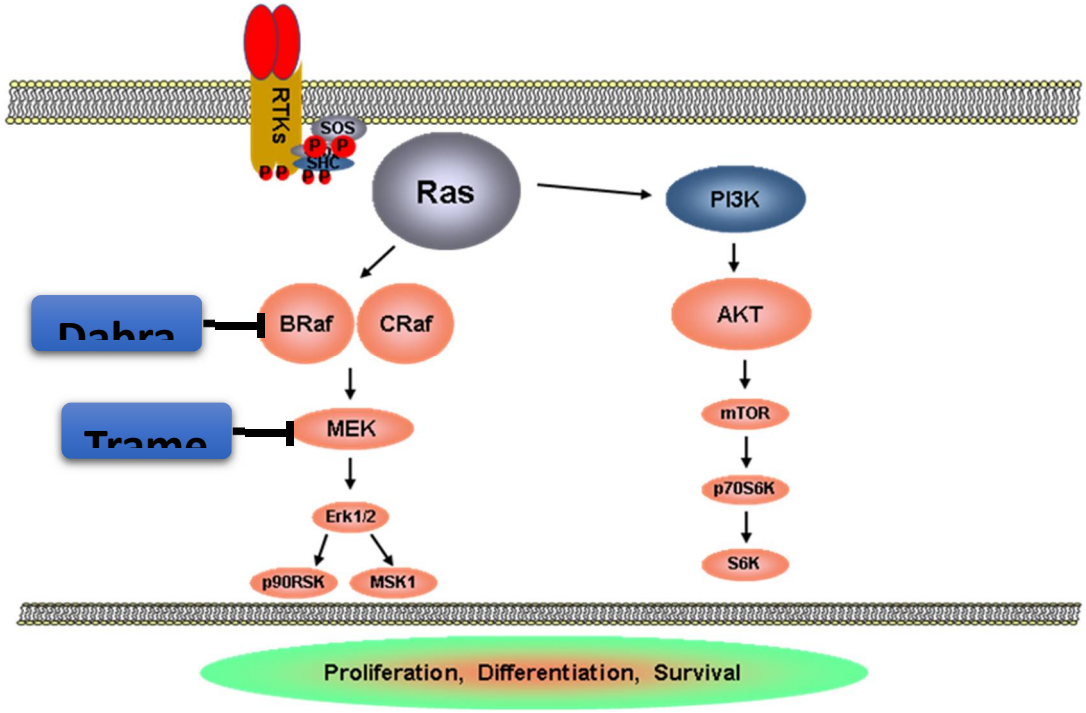
[redacted]

1 Introduction

1.1 Background

The RAS/RAF/MEK/ERK pathway (i.e., the MAP kinase pathway, Figure 1) is a critical proliferation pathway in many human cancers, including melanoma. Oncogenic mutations in both RAS and BRAF signal through MEK1 and MEK2 and this is an early event. Enzymes in this pathway, particularly BRAF and MEK, are therefore attractive anti-cancer targets. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 40% to 60% of melanoma [Davies H, 2002]. Cutaneous melanoma is the most aggressive form of all skin cancers, with approximately 232,000 new cases and approximately 55,000 disease-related deaths worldwide each year [GLOBOCAN, 2012]. This study will evaluate the combination of two, small-molecule, oral agents, dabrafenib and trametinib in ALM or cutaneous melanoma.

Figure 1 The RAS/RAF/MAP (Erk1/2) Signal Transduction Pathway



1.2 Current treatment options for melanoma

Due to early detection, a majority of melanoma patients with early-stage localized disease are cured with surgery alone. In contrast, those with unresectable or metastatic melanoma have a poor prognosis. Historically, the median survival time for subjects with Stage IV melanoma has been approximately 6 months with 26% of subjects alive at 1-year, and a median time to progression-free survival (PFS) at 1.7 months with 14.5% of subjects progression-free at 6 months [Korn EL, 2008]. With a median age at first diagnosis of 59 years, advanced and metastatic melanoma ranks second only to acute leukemia in terms of loss of years of potential life per death [NCCN, 2014].. Although, combination therapies of chemotherapeutic agents and cytokines such as interferon-alpha and interleukin-2 have resulted in an increase of

response rates, the overall survival (OS) of patients with unresectable melanoma has so far not been improved [Hodi FS 2010].

Since 2010, the therapeutic landscape of melanoma has rapidly changed with the regulatory approval of 3 targeted, small molecules (vemurafenib, dabrafenib, and trametinib), and 3 immunomodulators (ipilimumab, pembrolizumab, and nivolumab).

Dependence on MAPK signaling is a key feature of BRAF V600 mutant melanoma, as demonstrated by the clinical efficacy of vemurafenib, dabrafenib, and trametinib Phase III results [Chapman PB, 2011; Hauschild A 2012; Flaherty KT, 2012a]. While monotherapy with MAPK inhibitors represents a significant advance in the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma, approximately half of patients treated with a BRAF or MEK inhibitor as monotherapy will develop resistance and progress within 5 to 7 months of starting treatment [Sosman JA, 2012; Hauschild A, 2012; Flaherty KT, 2012b], therefore there is an unmet medical need for treatments that overcome or delay resistance and that improve survival.

Since both BRAF and MEK are in the MAPK pathway, and MEK is a substrate of activated BRAF, greater inhibition of the MAPK pathway may be achieved with the combination of BRAF and MEK inhibitors. Concomitant inhibition of BRAF and MEK may lead to greater response rates, provide more durable responses, and increase progression free survival and overall survival. Furthermore, hyperproliferative skin lesions, including cuSCC and keratoacanthoma, have been associated with paradoxical activation of the MAPK pathway by BRAF inhibition. Combining a MEK and BRAF inhibitor may attenuate these BRAF inhibitor-mediated hyperproliferative skin toxicities, thereby enhancing the benefit:risk ratio for the combination compared to BRAF inhibitor monotherapy.

The rationale to combine a MEK and BRAF inhibitor is supported by non-clinical and clinical data as outlined below:

Enhanced inhibition of the MAPK pathway can be achieved by the combination of dabrafenib and trametinib, which predicts a greater response to therapy. In vitro data demonstrate that the combination of dabrafenib and trametinib is either additive or synergistic in 15 BRAF inhibitor-sensitive cell lines [GlaxoSmithKline Document Number 2011N116395_00].

Concomitant inhibition of BRAF and MEK may prevent or delay resistance that arises through reactivation of the MAPK pathway. MAPK reactivation, or MAPK-dependent resistance, is the most common type of BRAF-inhibitor resistance. Importantly, MAPK reactivation predicts sensitivity to MEK inhibition Several mechanisms mediating resistance to BRAF inhibitors through MAPK pathway reactivation have been described, including the up-regulation of bypass pathways mediated by cancer Osaka thyroid (COT)-kinases [Johannessen CM, 2010], development of de novo NRAS or MEK mutations [Nazarian R 2010; Emery CM, 2009; Greger JG, 2012; Shi H, 2012 (b)], amplification of BRAF V600 [Shi H, 2012 (a)], and dimerization of variant splicing of mutant BRAF V600 [Poulikakos PI, 2011]. In preclinical studies, combining a BRAF inhibitor and a MEK inhibitor blocked the rebound pERK signaling in BRAF mutant melanoma cells and enhanced cell death [Paraiso KH, 2010]. Non-clinical data have also shown that the combination is more effective in BRAF inhibitor-sensitive BRAF mutant melanoma cell lines than in BRAF mutant melanoma cell lines that had acquired resistance to dabrafenib [GlaxoSmithKline Document Number

2011N116395_00]. Finally, the combination of dabrafenib and trametinib demonstrated prolonged tumor growth inhibition and delayed tumor outgrowth when compared to treatment with the single agents in mouse melanoma xenograft studies.

The addition of a MEK inhibitor to BRAF inhibitor therapy may decrease the frequency of secondary cuSCC and other hyperproliferative skin lesions caused by BRAF monotherapy. Hyperproliferative skin lesions, including cuSCC, have been associated with paradoxical activation of the MAPK pathway in BRAF wild type cells with pre-existing RAS mutations in the presence of a BRAF inhibitor. The addition of a MEK inhibitor could potentially block the paradoxical activation, thereby attenuating the frequency of hyperproliferative skin lesions. [Su F, 2012].

Overall, these data demonstrate that concomitant and more complete inhibition of the MAPK pathway at the level of the BRAF- and MEK -kinases could provide greater anti-tumor effect than administration of either monotherapy alone.

Based on the aforementioned hypothesis, the combination of BRAF and MEK inhibition, as compared with single-agent BRAF inhibition, was tested and demonstrated a delay of the emergence of resistance and decreased the incidence of cutaneous hyperproliferation. Long and colleagues reported the result of a randomized double blind phase III study which compared trametinib plus dabrafenib versus dabrafenib alone in metastatic melanoma patient who had BRAF V600 E or K mutation. The combined treatment significantly improved PFS (mPFS: 9.3 vs 8.8 months, HR=0.75, p=0.03), response rate (67% vs 51%, p=0.0002). At 6 months, the interim survival analysis also showed a improvement of survival (HR=0.63, p=0.02). The patients who received combined treatment experienced more frequent pyrexia, chill, diarrhea, hypertension, vomiting, peripheral edema, elevated liver enzyme, decreased left ventricular ejection fraction (LVEF), dermatitis acneiform, but less frequent cutaneous squamous-cell carcinoma, hyperkeratosis, skin papilloma, hand-foot syndrome, dry skin, pruritus and alopecia.[Long GV 2014] Similar efficacy results were confirmed by 2 independent randomized studies using trametinib plus dabrafenib versus vemurafenib [Robert C 2015] and cobimetinib plus vemurafenib versus vemurafenib [Larkin J 2014].

The AE profile of dabrafenib and trametinib given in combination was acceptable and was manageable with dose modifications and supportive care.

As of March, 2015, in United States, Australia, Canada and a few other countries, dabrafenib in combination with trametinib has been approved to treat metastatic melanoma with BRAF V600 mutation.

1.2.1 Dabrafenib

Dabrafenib (GSK2118436), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is a potent and selective inhibitor of B-RAF kinase activity with a mode of action consistent with adenosine triphosphate (ATP)-competitive inhibition. Dabrafenib has already demonstrated substantial clinical activity with an acceptable safety profile in Phase I, II and III studies and was approved in May 2013 by the US FDA in patients with unresectable or metastatic melanoma in adult patients with the BRAF V600E mutation. In the pivotal Phase III trial BRF113683 (BREAK-3), 250 subjects were randomly assigned to receive either dabrafenib (187 subjects) or dacarbazine (63 subjects). Median PFS was 5.1 months for dabrafenib and 2.7 months for dacarbazine, with a hazard ratio (HR) of 0.30 (95% CI 0.18-0.51; p<0·0001).

At data cutoff, 107 (57%) subjects in the dabrafenib group and 14 (22%) in the dacarbazine group remained on randomized treatment. Confirmed objective responses were reported by the independent review committee (IRC) in 93 (50%, 95% CI 42·4–57·1) of 187 patients randomly assigned to dabrafenib (6 [3%] had a complete response and 87 [47%] had a partial response), with a median time to response of 6·3 weeks (95% CI 6·1–6.3).Treatment-related adverse events (grade 2 or higher) occurred in 100 (53%) of the 187 patients who received dabrafenib and in 26 (44%) of the 59 patients who received dacarbazine. The most common adverse events with dabrafenib were skin-related toxic effects, fever, fatigue, arthralgia, and headache. The most common adverse events with dacarbazine were nausea, vomiting, neutropenia, fatigue, and asthenia. Grade 3-4 adverse events were uncommon in both groups [Hauschild A 2012].

The experience with dabrafenib as monotherapy was generally obtained in patients with melanoma. Common AEs include: fatigue, gastro-intestinal (GI) effects (diarrhea), rash, pyrexia, arthralgias, headaches, and skin effects. Among those common AEs, pyrexia has been noted in 27% of patients receiving dabrafenib. Most of these cases have been mild, self-limited, and have responded to anti-pyretic therapy. However, cases of complex pyrexia have been reported as serious adverse events (SAEs) in which patients have presented with high fever (up to 105 -106 degrees F), with severe rigors, and in some instances dehydration or hypotension. Most cases of pyrexia have presented within the first two months of therapy and guidelines for supportive care and dose modifications are provided in Section 5.8.5.1. A variety of skin effects have been noted in BRAF inhibitor treated patients including rash, hyperkeratosis, actinic keratosis, seborrheic keratosis, hand-foot skin reactions (HFSR) and cutaneous squamous cell carcinomas (SCC), papilloma or new primary malignant melanoma. Squamous cell cancers related to BRAF inhibitor therapy often have characteristics of keratoacanthoma type of SCC, which traditionally have a relatively benign prognosis. All reports of SCCs are captured as SAEs. These lesions are treated surgically without need for dose modification of dabrafenib (see Section 5.8.4.44) [Hauschild A 2012].

Among the rare AEs, renal insufficiency/failure was recently identified as a potential adverse drug reaction associated with dabrafenib. Most cases of renal insufficiency have been in the setting of dehydration and/or pyrexia; however there have been reports of acute renal failure suggestive of intrinsic renal disease (see Section 5.8.5.3). Dabrafenib, like the other BRAF inhibitor, has been associated with reports of uveitis, the frequency of which is being currently determined (likely 1-2%). The mechanism remains unclear, but may involve a possible immune mechanism.

1.2.2 Trametinib

Trametinib (GSK1120212), a pyrido-pyrimidine derivative, is a potent and highly selective allosteric i.e. non-ATP competitive inhibitor of MEK1 and MEK2 activation and kinase activity. Trametinib has demonstrated activity with an acceptable safety; [Gordon MS 2010; Kim K 2011; Kim KB 2013], and was approved in May 2013 by the US FDA in patients with unresectable or metastatic melanoma in adult patients with the BRAF V600E or V600K mutations.

In the pivotal Phase III study (NCT01245062), trametinib demonstrated significant improvement in both PFS and OS in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma compared with chemotherapy. Median PFS was 4.8 months in

the trametinib group and 1.5 months in the chemotherapy group (hazard ratio for disease progression or death in the trametinib group, 0.45; 95% CI, 0.33 to 0.63; p<0.001). At 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the chemotherapy group despite crossover (hazard ratio for death, 0.54; 95% CI, 0.32 to 0.92; P = 0.01). The confirmed response rate was 22% (95% CI, 17 to 28) in the trametinib group and 8% (95% CI, 4 to 15) in the chemotherapy group (p=0.01). The median duration of response was 5.5 months (95% CI, 4.1 to 5.9) in the trametinib group (in 47 subjects) and had not been reached in the chemotherapy group (in 9 subjects).

Trametinib has also been evaluated, as monotherapy, in well over 500 subjects [GlaxoSmithKline Document Number HM2009/00151/03]. Common AEs include rash, peripheral edema, and GI effects (diarrhea). In addition, a decrease left-ventricular ejection fraction (LVEF) has been observed in approximately 10% of subjects receiving trametinib. Most of these cases were associated with no symptoms. Consequently, strict monitoring has been in place along with guidelines on management of patients with decreased LVEF (see Section 5.8.3.1). Emerging data on blood pressure suggests that trametinib may be associated with increases in blood pressure and hypertension was reported as an adverse event in 15% of subjects in the Phase III study. Subjects enrolled in this study are expected to have well controlled blood pressure at baseline and guidelines for treatment related blood pressure management are provided in Section 5.8.3.2. Trametinib, like other MEK inhibitors, can be associated with visual changes including central serous retinopathy and rarely with retinal vein occlusion (RVO), the latter being the more severe event. Guidelines for the management of visual changes are provided in Section 5.8.5.4.

1.2.3 BRAF and MEK Inhibitors as Combination Therapy

Clinical evaluation of the dabrafenib 150 mg BID + trametinib 2 mg QD (150/2) combination treatment has shown efficacy in patients with V600 mutant melanoma. The results of the randomized Part C of Study BRF113220 in BRAF-inhibitor naïve subjects demonstrated an improved efficacy profile for the 150/2 combination treatment compared to dabrafenib monotherapy across all efficacy parameters tested.

BRF113220 was a Phase I/II study with 4 parts that include a randomized part (Part C) which investigated the clinical activity, durability of response, safety/tolerability and population PK parameters in the three different arms in subjects with BRAF-mutant melanoma (n=162). In Part C, a statistically significant (p=0.0264) increase in the confirmed overall response rate was observed in the 150/2 treatment arm (76%) when compared to the dabrafenib monotherapy arm (54%) [Flaherty KT 2012b]. Moreover, the rate of complete responses was higher in the 150/2-treatment arm (9% vs 4%) while early disease progression (i.e., no best response of disease progression (PD) at the first timepoint assessment), was absent (0 vs 6%) when compared to the dabrafenib monotherapy arm. Clinically more important, the investigator-assessed PFS was significantly prolonged for the 150/2 combination arm relative to the dabrafenib monotherapy arm (HR=0.39; p<0.0001) [Flaherty KT 2012b]. This benefit was sustained at 12 months, with a 12-month progression-free rate of 41% in the 150/2 arm vs 9% in the dabrafenib monotherapy arm. While a significant difference in PFS was also observed in the 150/1 combination therapy group compared to dabrafenib monotherapy (HR=0.56, p=0.0057), the benefit was lower at 12 months (12-month progression-free rate of 26%) [Flaherty KT 2012b].

Safety data reported from Part C showed that dose-limiting toxic effects were infrequently observed in subjects receiving combination therapy with 150 mg of dabrafenib and 2 mg of trametinib (combination 150/2). Cutaneous squamous-cell carcinoma was seen in 7% of subjects receiving combination 150/2 and in 19% receiving dabrafenib monotherapy (p = 0.09), whereas pyrexia was more common in the combination 150/2 group than in the monotherapy group (71% vs. 26%) [Flaherty KT 2012b].

MEK115306 study is a double blind randomized phase III study that recruited 423 previously untreated metastatic melanoma patients who had BRF V600E or V600K mutation. Eligible patients were randomized to receive dabrafenib 150mg bid plus trametinib 2mg qd, or dabrafenib 150mg bid plus placebo. The primary endpoint was PFS. The results showed the combination significantly improved PFS (median PFS: 9.3 vs 8.8 months, HR=0.75, p=0.03) and response rate (67% vs 51%, p=0.0002) . The interim OS analysis at 6 months showed the survival rate was 93% and 85% in the combination arm vs dabrafenib arm (HR=0.63, p=0.02). However, a pre-defined specific efficacy stopping boundary of OS (two-side p=0.00028) was crossed. So the survival follow-up is still on-going as of December 2014.

In this study, 9% patient from combination treatment arm and 5% from dabrafenib monotherapy arm permanently discontinued study medication before disease progression. In addition, dose reduction was required in 25% and 13% of patients receiving combination and dabrafenib monotherapy, respectively.

The adverse event profile of combination treatment was different from dabrafenib monotherapy. The patients who received combined treatment experienced more frequent pyrexia(51% vs 28%), chill(30% vs 16%), diarrhea(24% vs 14%), hypertension(22% vs 14%), vomiting(20% vs 14%), peripheral edema(14% vs 5%), elevated ALT (11% vs 5%) or AST (11% vs 3%), decreased left ventricular ejection fraction(LVEF)(4% vs 2%), dermatitis acneiform(8% vs 3%), but less frequent cutanenous squamous-cell carcinoma(2% vs 9%), hyperkeratosis(3% vs 32%), skin papilloma(1% vs 21%), hand-foot syndrome(5% vs 27%), dry skin(9% vs 13%), pruritus(8% vs 12%) and alopecia(7% vs 26%). [Long GV 2014]

MEK116513 study is an open label randomized phase III study that recruited 704 previously untreated metastatic melanoma patients who had BRF V600E or V600K mutation. Eligible patients were randomized to receive dabrafenib 150mg bid plus trametinib 2mg qd, or vemurafenib 960mg bid. The primary endpoint was overall survival. At a pre-planned interim analysis, this study demonstrated the combination of dabrafenib plus trametinib achieved significant OS improvement (12 months OS rate: 72% vs 65%, HR: 0.69, p=0.005) and this result crossed the pre-defined interim stopping boundary. Therefore this study was stopped because of the efficacy and the interim analysis was considered the final analysis. The combination treatment also significantly improved PFS (median PFS: 11.4 vs 7.3 months, HR: 0.56, p<0.001) and response rate (64% vs 51%, p<0.001).

Rates of study-drug discontinuations were similar in the two groups(13% in combination arm and 12% in vemurafenib arm). Adverse events leading to dose reduction was reported in 33% of patients in combination arm and 39% in the vemurafenib arm.

The most frequent adverse events in the combination-therapy group were pyrexia (53%), nausea (35%), diarrhea (32%), chills (31%), fatigue (29%), headache (29%), and vomiting (29%). In the vemurafenib group, the most frequent adverse events were arthralgia (51%), rash (43%), alopecia (39%), diarrhea (38%), nausea (36%), and fatigue (33%). Skin toxic effects were more frequent in the vemurafenib group than in the combination-therapy group,

in particular rash (43% vs. 22%), photosensitivity reaction (22% vs. 4%), hand–foot syndrome (25% vs. 4%), skin papillomas (23% vs. 2%), squamous-cell carcinomas and keratoacanthomas (18% vs. 1%), and hyperkeratosis (25% vs. 4%). Pyrexia was more frequent in the combination-therapy group than in the vemurafenib group (53% vs. 21%).Grade 3 or 4 adverse events occurred in 52% of the patients in the combination-therapy group and in 63% of those in the vemurafenib group. Three fatal events occurred in each group; all were deemed by the investigator to be unrelated to the study drug [Robert C 2015].

1.2.3.1 Dabrafenib and Trametinib in Acral Lentiginous Melanoma

Acral lentiginous melanoma is one of 4 major histological subtypes of cutaneous melanoma. It is characterized by lesions presenting on non-hair bearing skin including the palm, soles, and nail beds. Although ALM accounts for only 2% to 3% of all melanomas in Caucasians, ALM makes up a much higher proportion (40-50%) of cutaneous malignant melanomas in darker-skinned individuals (ie, blacks, Asians, and Hispanics) [Bradford PT 2009]. The frequency of BRAF mutations in melanoma varies with anatomical site and sun exposure patterns. BRAF mutations are less frequent (25 – 30%) in acral melanoma not associated with chronic sun-damage [Curtin JA 2006] [Curtin JA 2006]. In contrast, c-Kit mutations are more common in mucosal (39%) and acral melanomas (36%), which can also be accompanied by an increase in c-Kit copy numbers [Curtin JA 2006]. Thus far, very few patients with ALM have been treated with dabrafenib and trametinib combination since the vast majority subjects enrolled were Caucasians.

To date, approximately 14 subjects with acral lentiginous melanoma have been treated with dabrafenib or trametinib monotherapy, or combination therapy with both agents. In the dabrafenib BREAK-3(BRF113683) study, 5 subjects with ALM received dabrafenib either in the randomized study or after crossover. Exposure to dabrafenib ranged from 3 days (subject discontinued treatment due to adverse event) to 5 months. In addition, one subject with ALM was enrolled into the METRIC (MEK114267) study with trametinib monotherapy and was treated with trametinib for over 50 weeks.

In the BRF113220 study, 8 subjects received combination dabrafenib and trametinib therapy either in the randomized phase or after crossover from dabrafenib monotherapy. Exposure time ranged from 3 to 18 months, including 2 subjects with a partial response who are still ongoing on study treatment.

In Asian population, approximately 25.5% of all melanoma patients and 15.5% of ALM have BRAF V600 mutation [Lu S 2011]. There are no PK data in Chinese patients. Preliminary PK data obtained in Japanese patients showed there no major ethnic difference in the pharmacokinetic profile of trametinib or dabrafenib when administered in monotherapy [GlaxoSmithKline Document Number 2014N196180_00 and GlaxoSmithKline Document Number 2012N133089_00], however, exposure to dabrafenib and trametinib tended to be higher when administered in combination [GlaxoSmithKline Document Number 2014N196181_00].

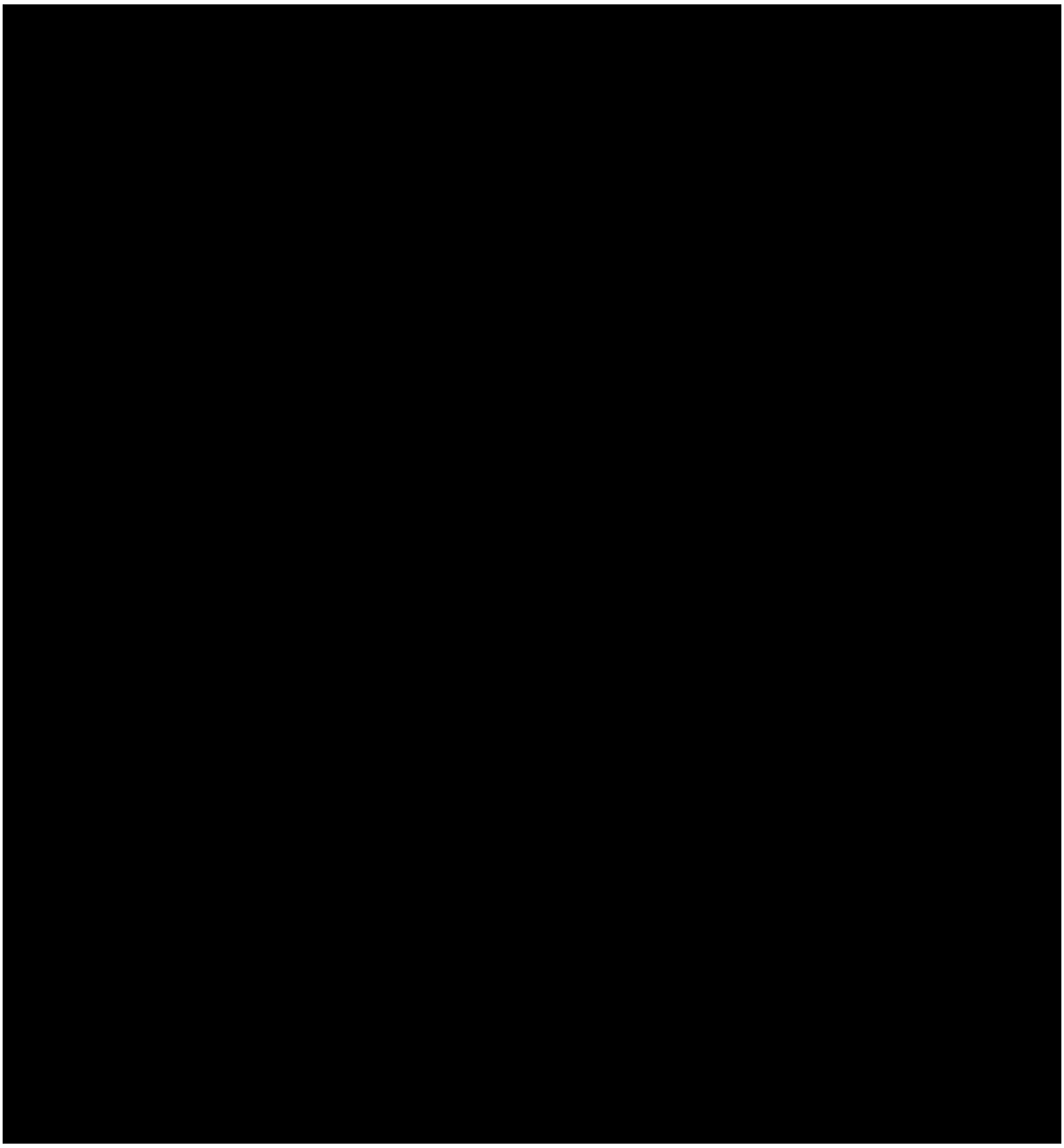
Data in subjects with acral lentiginous melanoma subtype or Asian population was limited and further exploration in these populations is warranted. This study was originally intended to enroll subjects with acral lentiginous melanoma. The eligibility criterion has been amended to include cutaneous melanoma in light of the advance in the management of metastatic melanoma with BRAF V600 mutation.

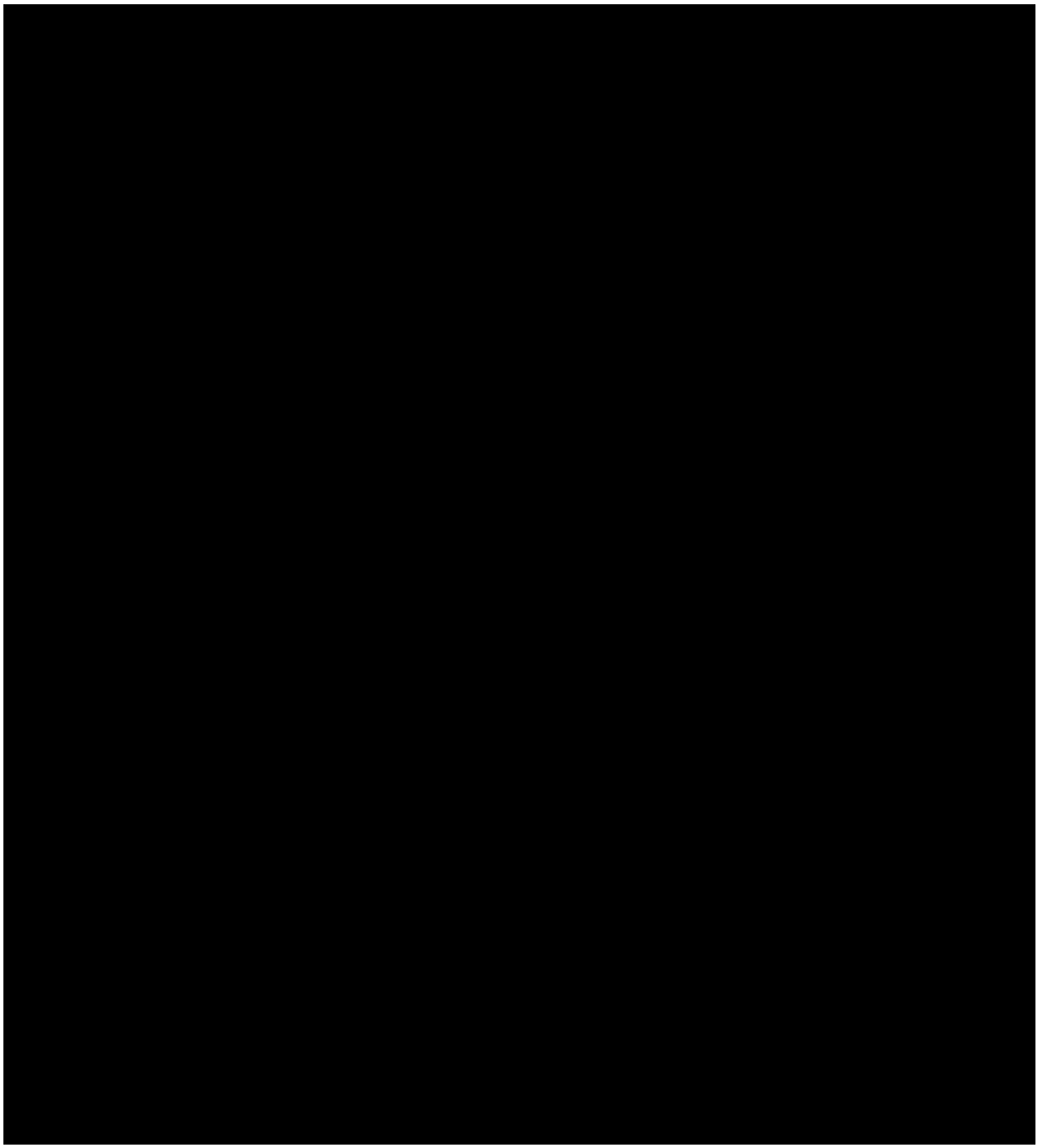
1.3 Rationale

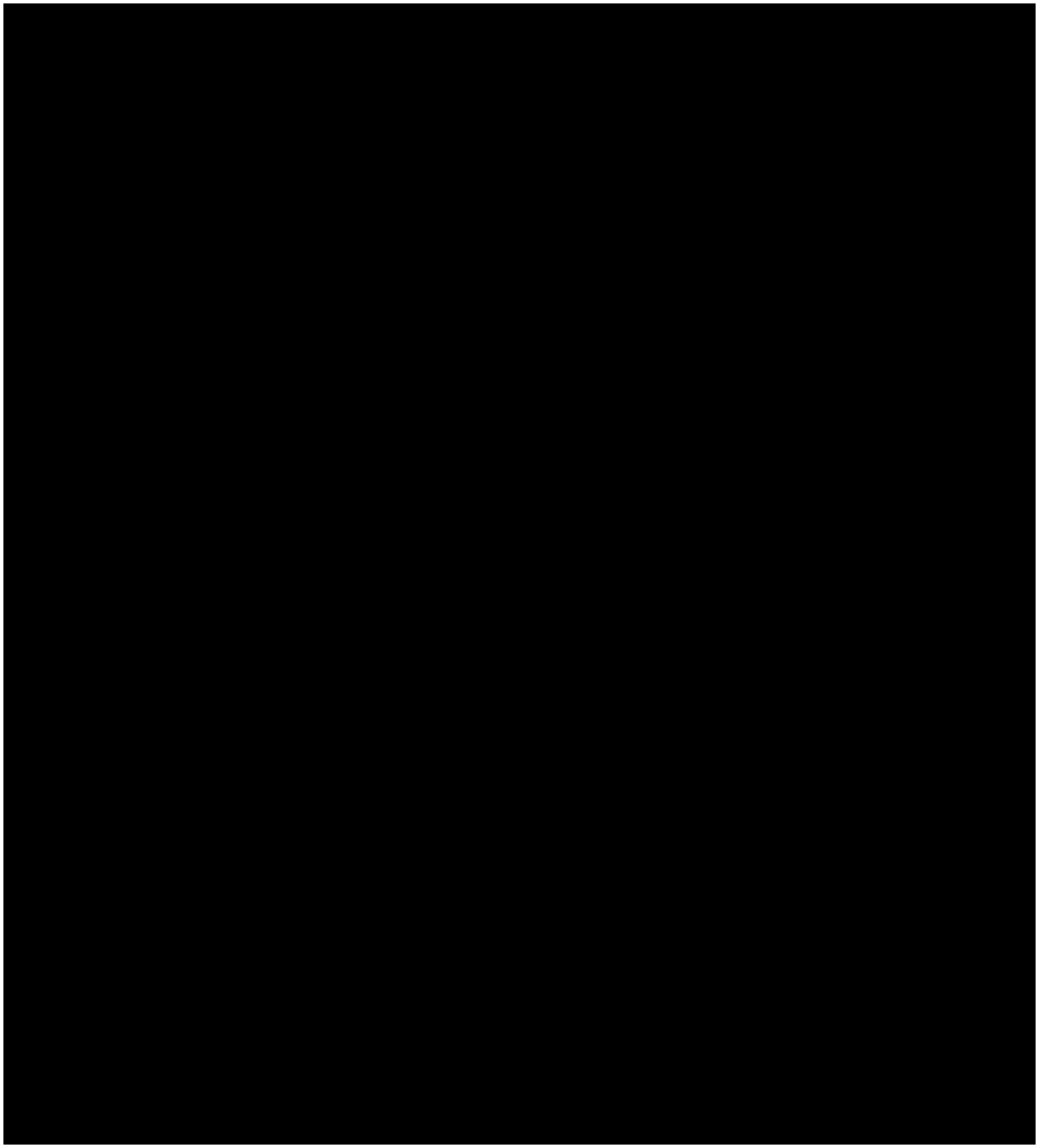
- Clinical studies for dabrafenib and trametinib monotherapies have demonstrated single-agent clinical activity in subjects with BRAF-V600-mutant melanoma.
- Preclinical studies and clinical data indicate that primary- and acquired resistance to a BRAF-inhibitor single-agent therapy may be addressed and potentially overcome by a combination of a BRAF- and MEK-inhibitor
- Data from the BRF113220 study (Part C) and 2 randomized phase III study evaluating the combination of dabrafenib and trametinib demonstrated promising clinical activity and an acceptable clinical safety profile of the dabrafenib and trametinib combination given at full single-agent dose
- Limited data are available in non-Caucasian populations and ALM.
- Limited pharmacokinetic data are available from Asian subjects, in whom melanoma sub-types such as ALM may be more prevalent compared to Caucasian subjects.

1.4 Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with dabrafenib and trametinib can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2011N126811_02]. The following section outlines the risk assessment and mitigation strategy for this protocol:







1.4.1 Benefit Assessment

Current research suggests that combination therapies of BRAF- and MEK-targeted agents can further improve the effect on survival currently achieved with BRAF inhibitor monotherapy [Long GV 2014; Robert C 2015] in metastatic melanoma patients with BRAF V600 mutation. Patients treated with combination of trametinib and dabrafenib can achieve a 6 months survival rate of 93% [Long GV 2014] and 12 months survival rate of 72% [Robert C 2015].

New treatments, like CTLA-4 antibody or anti-PD-1 antibodies, are not available in countries like China. Dacarbazine (DTIC), considered the most active of the agents currently available, is approved for metastatic melanoma [Huncharek M 2001] and widely used in clinical practice in Asian countries. The benefit of DTIC remains small, with median progression-free survival lasting approximately 2 months and median overall survival of approximately 7 months.

There are no PK data in Chinese patients. Preliminary PK data obtained in Japanese patients showed there no major ethnic difference in the pharmacokinetic profile of trametinib or dabrafenib when administered in monotherapy [GlaxoSmithKline Document Number 2014N196180_00 and GlaxoSmithKline Document Number 2012N133089_00] , however, exposure to dabrafenib and trametinib tended to be higher when administered in combination [GlaxoSmithKline Document Number 2014N196181_00]. Nevertheless, the planned dose of study medication is expected to be tolerable in the study population and bring clinical benefit.

Subjects enrolled into this study may benefit from receiving a combination of targeted agents which have demonstrated efficacy and tolerability in Caucasian populations.

1.4.2 Overall Benefit: Risk Conclusion

To date, >3000 subjects, of predominantly Caucasian ethnicity and with majority of BRAF V600 mutated melanoma have received this combination regimen in 5 phase I/II studies and 3 phase III studies. The complete list of these studies can be found in the IB.

As both agents target the MAP-kinase (MAPK) pathway, which is constitutively activated in V600 BRAF-mutation positive melanoma, a concomitant combination regimen may result in a more pronounced and prolonged anti-tumor efficacy as experimental data strongly suggests. This additive or synergistic activity is the result of a near-complete MAPK-pathway inhibition which addresses molecular mechanisms of primary resistance and delays the onset of secondary resistance to monotherapy treatment. Furthermore, in a relevant pre-clinical model of chemically induced skin carcinogenesis, inhibition of the MAPK-pathway at the two separate nodes of BRAF and downstream MEK abolished the paradoxical MAPK pathway activation induced by the BRAF inhibitor vemurafenib and resulted in an almost complete inhibition of cutaneous squamous cell carcinoma (cuSCC) development which is, a known side effect of monotherapy BRAF inhibition.

The safety profile for the combination treatment of dabrafenib 150 mg twice daily and trametinib 2 mg once daily in subjects with unresectable or metastatic melanoma with a BRAF V600 mutation is defined by the results of the pivotal Phase III Study MEK115306 and MEK116513 and supported by the BRF113220 pooled combination therapy population [GlaxoSmithKline Document Number 2011N126811_02].

The combination therapy has a higher rate of pyrexia, fatigue and nausea, while lower incidences of hyperkeratosis, alopecia and skin papilloma were observed compared with dabrafenib monotherapy. Relative to trametinib monotherapy, there was a higher incidence of fatigue, nausea, and vomiting observed but lower incidences of rash and diarrhea with combination therapy.

Overall, the addition of dabrafenib to trametinib does not appear to increase the frequency or severity of cardiac-related AEs, hypertension, hepatic disorders, diarrhea and pneumonitis, which previously were observed with trametinib monotherapy.

Similarly, the addition of trametinib to dabrafenib does not appear to increase the frequency or severity of palmar-plantar-erythrodysaesthesia syndrome (PPES) or treatment-emergent malignancies previously observed with dabrafenib monotherapy.

The risk-to-benefit ratio in this patient population remains favorable.

2 OBJECTIVE(S) and endpoints

Table 1 lists the study objectives and corresponding endpoints.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the objective response rate (ORR) of dabrafenib in combination with trametinib in subjects with BRAF V600 mutation-positive, unresectable or metastatic acral lentiginous or cutaneous melanoma	• ORR defined as the percentage of subjects with evidence of a confirmed complete response (CR) or partial response (PR) as per RECIST v1.1 [Eisenhauer EA 2009].
Secondary	
• To further evaluate the antitumor activity (progression-free survival (PFS), duration of response, and overall survival (OS)	• Duration of response is defined as the time from first documented evidence of CR or PR until the earliest date of documented radiological progression or death due to any cause among subjects who achieved a confirmed CR or PR. • PFS defined as the time from first dose of study treatment until the first date of either objective disease progression or death due to any cause. • OS defined as the interval from first dose of study treatment to the date of death, irrespective of the cause of death; subjects still alive will be censored at the date of the last contact.
• To assess exposures to dabrafenib, dabrafenib metabolites, and trametinib after a single dose (Chinese patients) and at steady-	• Trametinib, dabrafenib and dabrafenib metabolites concentrations by visit. Noncompartmental PK parameters include

Objectives	Endpoints
state, and characterize the population pharmacokinetics and pharmacodynamics of dabrafenib and trametinib	trametinib, dabrafenib and dabrafenib metabolites Cmax, tmax, Ctrough, AUC(0-t), and AUC(0-8); AUC(0-12) (dabrafenib and dabrafenib metabolites only), AUC (0-24) (trametinib only) and the dabrafenib metabolite to dabrafenib ratio of AUC(0-12). For Chinese patients, the accumulation ratio will be calculated by using the pharmacokinetic parameters from Day 1 and Day 15. Population PK parameters include, apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and absorption rate constant (Ka) for dabrafenib and trametinib.
• To evaluate the safety and tolerability of dabrafenib and trametinib	• 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]

3 Study design

3.1 Study Design

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This is an open-label, Phase IIA, multi-center study to evaluate the objective response rate of dabrafenib and trametinib combination therapy in subjects that have BRAF V600 mutation-positive ALM or cutaneous melanoma. Approximately 65 subjects will be enrolled to receive oral dabrafenib 150 mg twice daily in combination with oral trametinib 2 mg once daily. Dose modification guidelines for adverse events are provided in Section 5.8. Other measures of efficacy including duration of response, PFS and OS, as well as PK and PD properties, safety and tolerability of dabrafenib and trametinib will also be evaluated. Blood and tissue samples will be collected to determine possible mechanisms of drug response and resistance.

Subjects will continue study treatment until disease progression, death, unacceptable toxicity, withdrawal of consent, or study completion. After treatment discontinuation, subjects will be followed for survival and disease progression as applicable.

The study completion is defined as:

- In case all subjects stop study treatment within 48 weeks after Last Subject First Visit(LSFV): the study is completed once the last subject has completed the 48 weeks survival follow-up or all subjects die or loss to follow-up, whichever comes first.
- In case some subjects are still on study treatment 48 weeks after LSFV: the study is completed once all subjects stop study medication, or all subjects who are still on study medication can have access to alternative supply of MEK/BRAF inhibitors, whichever comes 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.

4 Subject selection and discontinuation/completion criteria

4.1 Subject Selection Criteria

4.1.1 Number of Subjects

Approximately 65 subjects will be enrolled. See 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 the Novartis investigational product or other study treatment that may impact subject eligibility is provided in the trametinib and dabrafenib and trametinib combination IB's.

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

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

1. Signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
2. ≥18 years of age,
3. Histologically confirmed acral lentiginous or cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600 mutation-positive by a central reference laboratory. Subjects with ocular or mucosal melanoma are not eligible.
4. Measurable disease (i.e., present with at least one measurable lesion) by RECIST version1.1 [Eisenhauer EA 2009] by investigator's assessment. Refer to Section 7.2.3 for the definition of a measurable lesion.
5. Performance status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale [Oken MM 1982].
6. All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 2) must be ≤ Grade 1 according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.0) at the time of enrolment [NCI 2009].
7. 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.
8. Women of child-bearing potential (see Section 7.3.7 for definitions) must have a negative serum pregnancy test within 14 days of first dose of study treatment and agree to use effective contraception, as stated in Section 7.3.7 from 14 days prior to enrolment, throughout the treatment period and for 4 months after the last dose of study treatment.
9. Adequate baseline organ function as defined in Table 2.
10. Subjects with East Asian origin.

Table 2 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic[a]	
ANC	≥ 1.2 × 10^9/L
Hemoglobin	≥ 9 g/dL
Platelet count	≥ 100 x 10^9/L
PT/INR[b] and PTT	≤ 1.5 x ULN
Hepatic	
Albumin	≥ 2.5 g/dL
Total bilirubin	≤ 1.5 x ULN[c]
AST and ALT	≤ 2.5 x ULN

Renal	
Calculated creatinine clearance[d]	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection Fraction (LVEF)[e]	≥ LLN by ECHO

ANC=absolute neutrophil count, PT=prothrombin time, INR=international normalized ratio, PTT=partial thromboplastin time, AST=aspartate aminotransferase, ALT=alanine aminotransferase, LLN=lower limit of normal

a. Laboratory values obtained without growth factors or transfusion support for at least 4 weeks

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

c. Total bilirubin < 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin < 3.0 x ULN or direct bilirubin < 1.5 x ULN.

d. Calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 2).

e. ECHO scans must be used throughout the study.

4.1.3 Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise 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. Primary mucosal or ocular melanoma.
2. Prior treatment with a BRAF inhibitor (including but not limited to dabrafenib, vemurafenib, LGX818, and XL281/BMS-908662) or a MEK inhibitor (including but not limited to trametinib, AZD6244, and RDEA119). Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biological anti-cancer therapy, or immunol anti-cancer therapy within 21 days prior to enrollment /or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to enrollment. . (Note: Ipilimumab, pembrolizumab and nivolumab treatment must have ended at least 8 weeks prior to enrollment).
3. Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to enrollment(Note: in case ipilimuamb, pembrolizmab and nivolumab are investigational drug in the regions and countries, and in case of PD-L1 antibody, these investigational treatment shall be ended at least 8 weeks prior to enrollment).
4. Current use of a prohibited medication (See Section 6.1).
5. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).
6. A history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (subjects with laboratory evidence of cleared HBV and/or HCV will be permitted, which is defined as HBs antigen negative and HBV DNA negative(≤1000 copies/mL) and HCV antibody is negative).

7. Leptomeningeal or brain metastases or metastases causing spinal cord compression that are: symptomatic or untreated or not stable for ≥3 months (must be documented by imaging before inclusion and compare with the latest brain scan prior to the one for the inclusion) or requiring corticosteroids. Subjects on a stable dose of corticosteroids >1 month, or on replacement dose only, or have been off of corticosteroids for at least 2 weeks can be enrolled with approval of the Novartis Medical Lead. Subjects must also be off of enzyme-inducing anticonvulsants for >4 weeks.

8. History of malignancy other than disease under study within 3 years, of study enrolment with exceptions below.

   Exception: Subjects with a history of completely resected non-melanoma skin cancer, or subjects with indolent second malignancies are eligible only after the approval of the sponsor's Medical Lead.

9. History of malignancy with confirmed activating RAS mutation at any time. Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

10. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.

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

a. Current LVEF < Institutional LLN

b. A QTc interval corrected for heart rate ≥480 msec (using Bazett's formula; see Appendix 3 for correction methods)

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

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

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

e. A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines (Appendix 4);

f. Patients with intra-cardiac defibrillators;

g. Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;

h. Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.

12. Uncorrectable electrolyte abnormalities (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia determined by blood chemistry), long QT syndrome or taking medicinal products known to prolong the QT interval.
13. A history or current evidence of retinal vein occlusion (RVO)
14. [Retired from protocol version 03]
15. [Retired from protocol version 03]
16. Pregnant or nursing females.
17. History of or current diagnosis of interstitial lung disease or pneumonitis.

4.2 Permanent Discontinuation from Study Treatment and Study Completion Criteria

4.2.1 Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death, or unacceptable AE, including hematologic or other non-hematologic toxicity, and/or meeting stopping criteria for liver chemistry defined in Section 5.9. Note: Subjects who are experiencing progression of disease (by RECIST, version 1.1) but are receiving clinical benefit based on the investigator's assessment, may be allowed to continue study treatment (see Section 4.2.2) with the agreement of sponsor's Medical Lead.

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

a. deviation(s) from the protocol
b. request of the subject or his/her proxy
c. investigator's discretion
d. subject is lost to follow-up, (defined as no contact with the subject after 3 telephone calls and one certified letter to the last known address, and documented in the patient's chart)
e. study is completed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

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

Note: If one study drug is permanently discontinued, administration of the other study drug may continue if appropriate (see Section 5.8), and subjects should be assessed as indicated in the Time and Events Table (see Section 7).

All subjects who permanently discontinue all study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the Time and Events Table (Table 20) and Section 7.

All subjects who permanently discontinue all study treatment without disease progression will be followed for progression according to the Time and Events Table (Table 20) until disease progression, death, or withdrawal of consent, whichever occurs first.

In addition, all subjects who permanently discontinue all study treatment will be followed for survival and new anti-cancer therapy according to the Time and Events Table (Table 20). Follow-up contact to assess survival and new anti-cancer therapy may be made via clinic visit, phone, or email.

Survival and new anti-cancer therapy follow-up will continue until study completion.

4.2.2 Continuation of Study Treatment after Disease Progression

Subjects may be eligible to continue study treatment after disease progression if they have:

- Achieved an objective response (partial or complete response) according to RECIST, version 1.1, or have had stable disease with imaging evidence of tumor reduction lasting at least 8 weeks prior to disease progression while receiving study treatment
- No treatment-related AEs of CTCAE grade 4 during the last four weeks of study treatment
- No signs and symptoms of clinical disease progression that decrease ECOG performance status to ≥ 2
- No severe clinical conditions that require immediate surgical or radiotherapeutical intervention. Note: subjects who require palliative radiation of bone lesions or limited surgical removal of isolated tumor lesions may be considered after completion of the procedure (radiotherapy or surgery) and review by the Novartis Medical Lead.

If all of the above conditions are met, the following steps must be implemented prior to continuation of study treatment:

- **The investigator must consult with and receive approval from the** Novartis Medical Lead
- **The subject must sign an informed consent that specifies alternative therapies (e.g., FDA-approved therapies) that the subject may be foregoing by continuing study treatment**

After a subject has been permitted to continue on study treatment:

- All study procedures, including tumor assessments, must be followed as scheduled (Table 20)
- After each tumor assessment, the investigators must confirm with the Novartis Medical Lead that the subject is still benefitting from study treatment and therefore can continue receiving study treatment.

4.2.3 Subject Completion Criteria

A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period. The cause of death will be documented in the eCRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to

follow-up or has withdrawn consent, or if the study is completed. The definition of study completion was described in protocol Section 3.1.

5 Study treatments

The term 'study treatment' is used throughout the protocol to describe any 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 Product and Other Study Treatment

5.1.1 Dabrafenib (GSK2118436)

Dabrafenib will be provided as 50 mg and 75 mg capsules. Each capsule will contain 50 mg or 75 mg of free base (present as the [redacted]).

Dabrafenib will be provided to sites by Novartis with the exception of sites in China where GSK will organize to provide supplies under GSK`s sponsorship. The contents of the label will be in accordance with all applicable regulatory requirements.

5.1.2 Trametinib (GSK1120212)

Trametinib study medication will be provided as 0.5 mg and 2.0 mg tablets. Each tablet will contain 0.5 mg or 2.0 mg of trametinib parent (present as the [redacted]).

Trametinib will be provided to sites by Novartis with the exception of sites in China where GSK will organize to provide supplies under GSK`s sponsorship. The contents of the label will be in accordance with all applicable regulatory requirements

5.2 Dosage and Administration

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

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

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

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

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

If a subject misses a trametinib dose, the subject may take the dose immediately if the next dose is scheduled for at least 12 hours later.

5.3 Handling and Storage of Study Treatments

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

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

5.4 Treatment Assignment

This is a single arm, open label study. All subjects enrolled will receive the combination of dabrafenib and trametinib.

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

All subjects will be registered into the My Access Program (MAP) system, by the investigator or authorized site staff.

MAP allows study sites to register subjects, and also is used in study treatment supply.

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

5.5 Blinding

This is an open-label, single-arm study.

5.6 Product Accountability

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

5.7 Treatment Compliance

Subjects will be instructed to return treatment bottles at each visit. Compliance with study treatment will be assessed by querying the subject and thorough pill count at each visit. Compliance will be documented in the source documents and the eCRF.

A record of the number of dabrafenib and trametinib 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 will also be recorded in the eCRF. The investigator will make every effort to bring non-compliant subjects into compliance.

5.8 Dose Modification Guidelines

The severity of adverse events will be graded utilizing the CTCAE v4.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in this section.

Dose modifications in response to adverse events are permitted. Dose modification guidelines include:

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

With the exceptions of pyrexia (likely related to dabrafenib) and LVEF (likely related to trametinib), the guidance suggests that both therapies be reduced simultaneously in response to toxicities that are considered by the investigator to be treatment related.

Table 3 Categories of Dose Modification Guidelines

Adverse Event	Dabrafenib	Trametinib	Section
General Guidelines for Clinically Significant Toxicities	X	X	5.8.2
Guidelines for Specific Adverse Events Cardiovascular Adverse Events			
LVEF		X	5.8.3.1
Hypertension	X	X	5.8.3.2
Prolonged QTc	X	X	5.8.3.3
Skin –Related Adverse Events (Except cuSCC)[a]			
Rash	X	X	5.8.4.1
Hand-Foot Skin Reaction	X	X	5.8.4.2
Other Adverse Events			
Pyrexia	X		5.8.5.1
Diarrhea	X	X	5.8.5.2
Renal Insufficiency	X	X	5.8.5.3
Visual Changes	X	X	5.8.5.4
Pneumonitis	X	X	5.8.5.5
Liver Chemistry Stopping Criteria	X	X	5.9.1

a. Refer to Section 5.8.4.4 for management of cuSCC

5.8.1 Dose Levels of dabrafenib and trametinib

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

Table 4 Dose Level Reduction Guidelines

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

Abbreviation: BID = twice daily

Re-escalation of dose levels is permitted if an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose.

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

If a dose reduction below1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib.

Note: Approval from the Novartis Medical Lead is required to restart study treatment after ≥21 days of interruption. Study drug must be discontinued permanently if any interruption goes beyond 26 weeks.

5.8.2 General Guidelines for Clinically Significant Toxicities

The below Table 5 presents general guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and which do not have specific guidelines listed in Table 3.

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

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

1. Adverse events assessed by clinical laboratory parameters, adverse events, cardiac parameters, and vital signs according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0).

5.8.3 Guidelines for Cardiovascular Adverse Events

Cardiovascular adverse events have been seen in subjects receiving either dabrafenib, trametinib or both in combination (see the trametinib, dabrafenib and combination IBs for additional information).

5.8.3.1 Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Time and Events Table (Table 20). 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 trametinib and repeat ECHO within 2 weeks[a b] • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) ○ Consult with the Novartis Medical Lead and request approval for restart ○ If approve, restart treatment with trametinib reduced by one dose level ○ Repeat ECHO at 2 , 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter • If repeat LVEF does not recover within 4 weeks ○ Consult with cardiologist ○ **Permanently discontinue trametinib** ○ **Report as SAE** ○ Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib[b]** • **Interrupt dabrafenib.[d]** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[b,d]

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

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.

b. If recurrent episodes of LVEF reduction occur in subjects receiving dabrafenib monotherapy, consult Novartis Medical Lead.

c. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

d. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with Novartis Medical Lead.

5.8.3.2 Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided in Section 5.8.3.2.1 and Section 5.8.3.2.2.

5.8.3.2.1 Monitoring of Hypertension

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

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

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

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the Time and Events Table (Table 20). Ideally, subsequent blood pressure assessments should be performed within one week.

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

5.8.3.2.2 Management of Hypertension

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below in Table 7.

Table 7 Management and Dose Modification Guidelines for Hypertension

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

BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;

a. Hypertension detected in two separate readings during up to three consecutive visits

b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.

c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

5.8.3.3 QT Prolongation

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

Table 8 Withholding and Stopping Criteria for QTc-Prolongation

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

Abbreviations: msec = milliseconds; QTc = QT interval on electrocardiogram corrected

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.

5.8.4 Guidelines for Skin-related Adverse Events

Cutaneous adverse events have been observed in subjects receiving dabrafenib, trametinib or both therapies in combination (see the Investigator Brochures for more information). Recommendations for supportive care and guidelines for dose modifications are provided (Section 5.8.4.1, Section 5.8.4.2, Section 5.8.4.3 and Section 5.8.4.44. The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the Novartis Medical Lead may be required. In addition, the Sponsor may require biopsies of any new skin lesions especially those suspicious of cuSCC for further study.

5.8.4.1 Rash

Rash is a frequent AE observed in subjects receiving trametinib, dabrafenib, or the combination of both therapies. Guidelines for rash management are based on experience with other MEK inhibitors and EGFR inhibitors [Balagula Y 2010; Lacouture ME 2008] and are provided below (Table 9 and Table 10).

Table 9 Guidelines for Supportive Care of Rash

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

BID = twice daily; SPF = skin protection factor

a. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

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

Table 10 Management and Dose Modification Guidelines for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures • Use moderate strength topical steroid[a] • Reassess after 2 weeks	• Continue study treatment • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce study treatment by one dose level[b]**
Grade 2	• Initiate prophylactic and symptomatic treatment measures • Use moderate strength topical steroid[a] • Reassess after 2 weeks	• **Reduce study treatment by one dose level** ○ If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level ○ If no recovery to ≤grade 1 within 2 weeks, interrupt study treatment until recovery to ≤grade 1 • **Restart study treatment at reduced dose level[b]**
Grade ≥3	• Use moderate strength topical steroids[a] PLUS oral methyl-prednisolone dose pack • Consult dermatologist	• Interrupt study treatment until rash recovers to grade ≤1 • **Restart[b] with study treatment reduced by one dose level[c]** • If no recovery to grade ≤2 within 4 weeks**, permanently discontinue study treatment**

CTCAE = Common Terminology Criteria for Adverse Events

a. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream

b. Approval of Novartis Medical Lead is required to restart study treatment after >21 days of interruption.

c. Escalation of study treatment to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

5.8.4.2 Severe Cutaneous Adverse Reactions (SCARs)

Cases of SCARs, including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib in combination with trametinib. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be permanently discontinued.

5.8.4.3 Guidelines for Hand-foot Skin Reactions (HFSR)

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

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

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

CTCAE = Common Terminology Criteria for Adverse Events

a. A full-body skin examination and a removal of pre-existing calluses and keratotic skin is recommended prior to initiation of study treatment

b. Life-style changes: (1)reduce exposure of hands and feet to hot water, (2) avoid traumatic activity including vigorous exercise especially in the first 4 weeks after start of study treatment, (3) avoid constrictive footwear, (4) avoid excessive friction on the skin, when applying topical treatments, (5) wear thick cotton socks and gloves, and shoes with padded insoles

c. Symptomatic Treatments: (1) use moisturizing creams frequently and especially on hands and feet (2) consider topical keratolytics: urea 20-40 % cream, or salicylic acid 6%, or tazarotene 0.1% cream, or fluorouracil 5% cream; (3) erythrematous areas: clobetasol propionate 0.05% ointment; (4) Pain: topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin

d. Approval of Novartis Medical Lead is required to re-start study treatment after ≥21 days of interruption.

e. Escalation of study treatment to the previous dose level is allowed if no HFSR is observed in the 4 weeks subsequent to dose reduction.

5.8.4.4 Guidelines for cuSCC

Cutaneous squamous cell carcinomas have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB). These treatment-related cuSCC should be surgically removed according to institutional practice. Dose modifications or interruptions of the study treatment are not required for cuSCC. Occurrence of cuSCC must be reported as an SAE. Submit cuSCC tumor tissue for analysis as directed in the SPM.

5.8.5 Guidelines for Other Adverse Events of Special Interest

5.8.5.1 Guidelines for Pyrexia

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

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics (e.g.- ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia (see Section 5.8.5.3).

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

Table 12 Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification
Pyrexia[a]	<u>All Events:</u> • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d] <u>1st Event[b]:</u> • Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration or hypotension[e] <u>2nd Event[f]</u> • Within 3 days of onset of pyrexia o Optimize anti-pyretic therapy o Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[f] <u>Subsequent Events</u>: • Within 3 days of onset of pyrexia: o Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f] o If corticosteroids have been tapered and pyrexia recurs, restart steroids o If corticosteroids cannot be tapered consult Novartis Medical Lead	<u>1st Event:</u> • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** <u>2nd Event:</u> • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** <u>Subsequent Events:</u> • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[g]** • If dabrafenib must be reduced to <75 mg BID, permanently **discontinue dabrafenib. Trametinib may be continued**

Table 12 Management and Dose Modification Guidelines for Pyrexia (Continued)

a. Pyrexia is defined as a body temperature equal to or above 38.5 Celsius or 101.3° Fahrenheit.
b. For subjects experiencing pyrexia, a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
e. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
f. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
g. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

5.8.5.2 Guidelines for Diarrhea

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

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

Table 13 Management and Dose Modification Guidelines for Diarrhea

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

Table 13 Management and Dose Modification Guidelines for Diarrhea (Continued)

CTCAE = Common Terminology Criteria for Adverse Events

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

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

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

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

5.8.5.3 Guidelines for Renal Insufficiency

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

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

Table 14 Management and Dose Modification Guidelines for Renal Insufficiency

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

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

NSAIDS = non-steroidal anti-inflammatory drugs

a. NSAIDs can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia Section 5.8.5.1.

b. Investigator may restart at either the same or a reduced dose level. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Consultation with Novartis Medical Lead is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

5.8.5.4 Guidelines for Visual Changes or Specified Ophthalmic Examination Findings

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

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

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

Table 15 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued.If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification Table 16 below; **report as SAE if diagnosed.** • If RVO: **Permanently discontinue study treatment**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued.	• If RPED and RVO excluded, restart trametinib at same dose level. • If RPED diagnosed, see RPED dose modification table below; **report as SAE.** • If RVO: **Permanently discontinue trametinib and report as SAE.**
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued.	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study Medical Lead • **If RVO or RPED diagnosed, permanently discontinue trametinib and report as SAE.**

Abbreviations: RPED = retinal pigment epithelial detachment; CTCAE = Common Terminology Criteria for Adverse Events;

RVO = retinal vein occlusion; SAE = serious adverse event

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

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

Table 16 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

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

a. Refers to CTCAE Version 4.0 'Retinopathy'

Ophthalmologic Exam

At certain time points in the trial (see Table 20) and if visual changes develop (as described in this section below), an eye exam is indicated. The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

For adverse events of uveitis, no dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, interrupt dabrafenib and hold until resolution of ocular inflammation. Then restart dabrafenib reduced by one dose level.

5.8.5.5 Guidelines for Pneumonitis

Pneumonitis has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in Table 17.

Table 17 Management and Dose Modification Guidelines for Pneumonitis

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

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

5.9 Monitoring, Interruption and Stopping Criteria for Hepatobiliary Events

5.9.1 Liver Chemistry Stopping Criteria

These liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.

Liver chemistry stopping criteria 1-5 are defined below and an algorithm is presented in Appendix 6**:**

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

   NOTE: If serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. ALT ≥ 8xULN
3. ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
4. ALT ≥ 3xULN if associated with the appearance or worsening of symptoms believed to be hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
5. 5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

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

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

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Withdraw the subject from the study treatment after completion of the liver chemistry monitoring as described below (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 is required following discontinuation from study treatment.
- Do not rechallenge with study treatment unless written approval for drug restart 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 CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM. **PK sampling will be discontinued 8 weeks after last patient first treatment.**
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia as relevant on the AE form. Please note that treatment with trametinib often associates with rash which is usually acneiform and affects the scalp, face, neck, chest, and upper back. Discuss with Novartis Medical Lead as needed.
- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.
- Record alcohol use on the liver event alcohol intake form.

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

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

- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, in subjects with definite or likely acetaminophen use in the preceding week. **NOTE: not required in China** [James LP 2009].
- 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) [Le Gal F 2005].

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 Section 12.6 for an algorithm of liver chemistry monitoring, stopping, and follow-up criteria.

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

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

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

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

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

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

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

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 anti-cancer therapies will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted, however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.While patients are on study treatment, palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline.

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

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

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

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

47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 18) 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 Medical Lead is required in these situations. The list may be modified based on emerging data. Refer to the SPM for the most current list.

Subjects should not receive palliative radiotherapy prior to documented disease progression while on treatment in this study.

Table 18 Prohibited Medications

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

*: topical use is allowed if clinically indicated.

6.2 Medications to be Used with Caution

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

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in the SPM.

- 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 the maximum peak concentration (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 19 Medications to be used with Caution

USE WITH CAUTION: : Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19 Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone
Antidiabetics	Glyburide, saxagliptin, tolbutamide
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
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan
Selective Aldosterone Blockers	Eplerenone

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

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

6.3 Treatment after Discontinuation from both Study Treatments or Withdrawal from/Completion of the Study

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

Post-study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non-protocol) anti-cancer therapy at the discretion of the treating physician. New anti-cancer therapy should be documented in the eCRF that includes new therapy onset and end dates if possible. Every effort should be made to complete the required follow-up evaluations prior to initiating new anti-cancer therapy. Subjects will 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 for survival and/or disease progression after permanently discontinuing both study treatments.

Upon study completion, if some subjects are still on study treatment and have not yet progressed, their follow-up treatment will be at the discretion of the attending physician.

6.4 Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (the highest dose tested in clinical studies to date), and/or a trametinib overdose, defined as administration of more than 3.0 mg once daily (the maximum tolerated dose defined in the MEK111054 Study), the investigator should contact the Novartis 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. Haemodialysis is not expected to enhance the elimination of either dabrafenib or trametinib as both are highly bound to plasma proteins.

Decisions regarding dose modifications or interruptions 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.

Re-screening of patients who failed to be enrolled (for other reasons than BRAF status) will be allowed. BRAF assay does not need to be repeated providing a positive result from the central lab is available.

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

testing, coagulation, hematology, clinical chemistry, and serum pregnancy are required for eligibility.

Refer to the Time and Events Table (Table 20) for the timing of all assessments. Assessments must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. Details on efficacy and safety assessments are presented in Section 7.2 and Section 7.3, respectively. [redacted] Further details of study procedures and assessments can be found in the SPM.

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

Table 20 outlines study assessments and their timing.

Table 20 Time and Events Table

STUDY PHASES[1]	SCREENING[2]	TREATMENT					FOLLOW-UP		
		Day 1	Day 15	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Treatment Discontinuation[27]	Contact	Conclusion
Visit Window (Days)	**(≤ 28 except where noted)[2]**		**(± 3)**	**(± 3)**	**(± 7)**	**(± 7)**	**(± 7)**	**(± 7)**	**N/A**
CLINICAL ASSESSMENTS[1]									
Informed consent[3]	X								
Demographic data	X								
Past and current medical conditions including cardiovascular medical history and risk factors	X	X[4]							
Family history (cardiac, cancer)	X								
Disease characteristics[5]	X								
Prior anti-cancer therapies	X								
Tumor tissue for BRAF V600 mutation testing (required for eligibility)[6]	X								
Brain MRI/CT[7]	X				X[7]				
Lesion assessment[8]	X	Week 8, and every 8 weeks through Week 56, then every 12 weeks thereafter (all ± 7 days) until disease progression							
Performance status (ECOG)	X	X[4]		X			X		
Enrollment		X							
SAFETY ASSESSMENTS[1]									
Physical examination[9]	X (Complete)	X[4]		X (Brief)			X (Complete)		
Dermatological examination (including skin lesion photography)[10]	X				X		X		
Ophthalmic examination[11]	X			X Only at week 4					
Vital signs[12]	X			X			X		
Adverse events[13]	X	X		X			X	X	X
Concomitant medications[14]	X	X		X			X	X	

STUDY PHASES[1]	**SCREENING**[2]	**TREATMENT**					**FOLLOW-UP**		
		Day 1	**Day 15**	**Every 4 Weeks**	**Every 8 Weeks**	**Every 12 Weeks**	**Treatment Discontinuation**[27]	**Contact**	**Conclusion**
Visit Window (Days)	**(≤ 28 except where noted)**[2]		**(± 3)**	**(± 3)**	**(± 7)**	**(± 7)**	**(± 7)**	**(± 7)**	**N/A**
ECG[15]	X (5 weeks)		X	X (only at Week 4, 8 and 12)		X (after week 12)	X		
ECHO[16]	X (5 weeks)			X (only at Week 4)		X			
Optional non-melanoma skin lesion biopsy		X (anytime if cutaneous squamous cell carcinoma or basal cell carcinoma develop during the study)							
STUDY TREATMENTS									
Dispensation of medication[17]		X		X					
Assessment of compliance[18]				X			X		
LABORATORY ASSESSMENTS[1]									
Chemistry and Hematology[19]	X	X[4]		X			X		
Serum pregnancy test[20]	X (≤ 14 days)								
Pharmacokinetics blood collection[21]		X	X						

[redacted]

STUDY PHASES[1]	SCREENING[2]	TREATMENT					FOLLOW-UP		
		Day 1	Day 15	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Treatment Discontinuation[27]	Contact	Conclusion
Visit Window (Days)	**(≤ 28 except where noted)[2]**		**(± 3)**	**(± 3)**	**(± 7)**	**(± 7)**	**(± 7)**	**(± 7)**	**N/A**
END OF STUDY									
Follow-up contact[25]								X	
Follow-up anti-cancer therapy[26]								X	
Subject completion or withdrawal									X

Abbreviations: [redacted]; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors; 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.
2. Screening procedures may be performed up to 28 days prior to enrollment. Screening procedures that have a different visit window are indicated in parentheses.
3. Informed consent will be obtained prior to performance of any study-related procedures. [redacted]
4. If done within 3 days before Day 1 , this assessment does not need to be repeated on Day 1.
5. Disease characteristics will include date of diagnosis and last recurrence, primary tumor type, histology, stage, biopsy details, and visceral/non-visceral disease.
6. Collection of archived tumor tissue or fresh tumor biopsies for determination of the subject's BRAF genetic status is required for enrolment (See Section 7.4.4 and SPM for details.); for those who consent, additional tumor genetic markers related to the activity of dabrafenib or trametinib may be analyzed. A BRAF V600 mutation test performed by the central lab does not need to be repeated if enrolment falls outside the screening window providing that the BRAF V600 test result was positive. In case the first sample sent to the central laboratory for BRAF testing does not fulfil all quality requirements, the site may send an additional sample obtained from archived tumor tissue or new biopsy to confirm the BRAF mutation status as appropriate by clinical judgement and with the agreement from Novartis Medical Lead.
7. Baseline MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain must be performed on all subjects to rule out current leptomeningeal metastases, brain metastases, or spinal cord compression secondary to metastasis. Post-baseline scans should be performed in all subjects with documented CNS metastases at baseline and as clinically indicated (e.g., symptoms suggestive of CNS progression).
8. Lesion assessment must be done for chest, abdomen, pelvis, and any area of known disease. Lesion assessment by contrast CT (preferred) or MRI must be performed at the times indicated until disease progression, death, or withdrawal of consent, whichever occurs first. (See Section 7.2.2 for instructions regarding chest X-Rays and CT assessment). Target and non-target lesions must be identified at the time of screening and the same lesions must be reassessed at each time point in a consistent manner according to RECIST, version 1.1. Superficial skin lesions must be assessed as target/non-target lesions by digital color photography with the scale ruler. The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate each lesion. Direct lesion measurements will be taken using ruler or calipers. If the last assessment was >8 weeks prior to study withdrawal and disease progression had not been documented, a disease assessment should be obtained. Disease

assessment should continue in follow up phase for all subjects who discontinue treatment without documented RECIST 1.1 progression and for those who have consented to continue study treatment after documented progression.

9. A complete physical examination will be performed at Screening and treatment discontinuation; brief physical examinations will be performed at all other time points as indicated. Pelvic and rectal exams will be performed at screening and treatment discontinuation and periodically during treatment as clinically indicated; they do not need to be repeated at screening if they had been performed within 24 weeks of enrollment. Refer to Section 7.3.14 for details.
10. A full skin exam will be done every 8 weeks. Photographic images are required to assess hyperproliferative skin diseases. Upon study treatment discontinuation, a final skin exam is required within 8 weeks of the last dose of study treatment.
11. An ophthalmic examination will be performed at Screening and week 4; after week 4, additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.3.12 for details.
12. Refer to Section 7.3.13 for details regarding vital sign measurements.
13. 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 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), or study treatment which must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
14. All medications the subject takes 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 27.
15. At each time point listed, 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.
16. See Section 5.8.3.1 for LVEF guidelines for study drug management and requirements for ECHO scans.
17. A 4-week supply of study medication should be dispensed at each scheduled study visit as of Day 1; Dosing instructions must be provided. Subjects should start treatment as soon as possible after enrolment but no later than 72 hours post-enrolment.
18. Subjects should be instructed to return study drug at each visit; compliance will be assessed by querying the subject and counting tablets/capsules. Dose modifications and interruptions must be recorded.
19. Analysis of clinical chemistry and hematology samples will be performed by a central laboratory
20. Serum pregnancy test is required at Screening. Subsequent tests may be urine tests, and should be performed as clinically indicated.
21. Blood samples for PK analysis will be drawn on Day 15 at predose (within 30 minutes prior to dosing) and 1, 2, 4, 6, and 8 hours after dosing. For subjects in China, PK blood samples will be drawn on Day 1 at predose (within 30 minutes prior to dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 (pre dose on Day 2) hours and on Day 15 at predose (within 30 minutes prior to dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 (pre dose on Day 16) hours after dosing. Refer to section 7.5 and 5.9.1.1 for details on pharmacokinetics blood sampling including liver PK sampling.
22. [redacted]

[redacted]

25. Follow-up contact will include clinic visits, telephone contacts, and e-mail communications. The date of contact must be recorded. After treatment discontinuation, subjects should be contacted for follow-up every 12 weeks ± 7 days until death.
26. After treatment discontinuation, any new anti-cancer therapy initiated will be recorded until study completion/withdrawal/lost to follow-up, or death.
27. The treatment discontinuation visit should be performed within 30 days of the subject's last dose. If a subject discontinues study treatment at a scheduled visit, the assessments performed at that visit can be used to fulfil the treatment discontinuation visit requirements. Laboratory assessments and other required assessments do not need to be repeated at the discontinuation visit if they were performed within 14 and 30 days, respectively, of the discontinuation visit. If the last disease assessment was >8 weeks prior to study withdrawal and disease progression had not been documented, a disease assessment should be obtained.

7.1 Critical Baseline Assessments

Efficacy assessments conducted at baseline are described in Section 7.2.2, and tumor tissue [redacted] assessments are described in Section 7.4.2. 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 V600 Mutation-positive Melanoma

Subjects with histologically confirmed unresectable or metastatic acral lentiginous or cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV 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 V600 mutation, indicating their eligibility for the study. Formalin fixed paraffin embedded (FFPE) specimens reflective of the metastatic disease setting is preferred for the mutation testing. Tumor mutation status will be determined in a Novartis designated central lab. Only if clinical outcome data warrants, a companion diagnostic assay may need to be developed for regulatory submission and approval. Additional BRAF mutation testing may be conducted on the screening tissue to support the development of the companion diagnostic assay.

Further details on tissue requirement for BRAF mutation will be provided in the SPM.

7.1.2 Baseline Documentation of Target and Non-target Lesions

All baseline lesion assessments, including brain MRI/CT to rule out brain metastases, must be performed within 4 weeks prior to enrolment.

- Lymph nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with a short axis of < 15 mm but ≥ 10 mm are considered non-measurable.
- Pathological lymph nodes with a short axis of ≥ 15 mm are considered measurable and can be selected as target lesions. Lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (i.e., lesions with the longest diameter) and their suitability for accurate repeated measurements (i.e., either by imaging techniques or clinically).

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

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

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans,

fluorodeoxyglucose positron emission tomography (FDG-PET) scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

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

7.2 Efficacy

7.2.1 Efficacy Endpoints

7.2.1.1 Primary Efficacy Endpoint

The primary endpoint for this study is objective response rate of dabrafenib in combination with trametinib in subjects with BRAF V600 mutation-positive, unresectable or metastatic acral lentiginous or cutaneous melanoma (ALM). Objective response rate is defined as the percentage of subjects with evidence of confirmed complete response (CR) or partial response (PR) as per RECIST v1.1 [Eisenhauer EA 2009].

7.2.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Duration of response, defined as the time from first documented evidence of CR or PR until the earliest date of documented radiological progression or death due to any cause among subjects who achieve a confirmed response (i.e. confirmed CR or PR)
- PFS, defined as the time from first dose of study treatment until the first date of either objective disease progression or death due to any cause.
- OS, defined as the interval between the treatment start date and the date of death due to any cause.

7.2.2 Efficacy Assessments

Disease progression and response evaluations will be determined according to the definitions established in RECIST, version 1.1 [Eisenhauer EA 2009].

Refer to the Time and Events Table (Table 20) 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 assessments, a window of ±7 days is permitted to allow for flexible scheduling.

- The following scans/assessments are required at baseline: contrast CT (preferred method) of chest/abdomen/pelvis or MRI of abdomen/pelvis and any area of known disease, skin lesion photography, and clinical disease assessment for palpable lesions. Exception: If a chest CT cannot be performed, chest X-ray can be used only to document **the absence of disease** (no tumor lesions) or the **presence of new lesions**. If lesions are detected at baseline by chest X-ray, chest CT must be done to properly document these lesions at baseline and in follow-up tumor assessments. At each post-baseline assessment, evaluations of the sites of disease identified by these scans are required.

- A baseline brain scan is required for all subjects. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression). For subjects with CNS disease at baseline, a brain scan is required every 8 weeks or as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed 1 week prior to the 1st set of images showing CR to 4 weeks after the next protocol specified assessment.
- If clinically indicated, a contrast enhanced CT or MRI scan of affected bone areas will be required at baseline. Bone lesions, if present as non-target lesions, will continue to be followed consistently throughout the study until disease progression, death, or withdrawal of consent.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than four weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

Scans will be assessed by investigators and will be collected and stored. Details related to disease assessment acquisition and image transfer to be applied to baseline and all subsequent imaging will be provided in the SPM.

7.2.2.1 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate lesions. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose-positron emission tomography (FDG-PET) is generally not suitable for ongoing assessments of disease. It can, however, be useful in confirming new sites of disease when a positive FDG-PET scan 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. Fluorodeoxyglucose (FDG)-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If positron emission tomography/computed tomography (PET/CT) is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT in the eCRF.

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

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

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are at least 20 mm and clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer EA 2009].

Brain Scan: Contrast enhanced MRI is preferable to contrast enhanced CT for assessment of brain lesion(s).

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

Note: Positron emission tomography (PET; FDG or fluoride) may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

7.2.2.2 Follow-up Assessments for Subjects Permanently Discontinued from both Study Treatments

Refer to Section 4.2.1 Permanent Discontinuation from Study Treatment and Time and Events Schedule (Table 20) for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinue from study treatment.

All subjects who permanently discontinue both study treatments without disease progression will have radiographic disease assessments performed on the same assessment schedule noted in the Time and Events Table (Table 20) until disease progression, death, starting of another anti-cancer treatment(including radiotherapy), or withdrawal of consent, whichever is documented first.

In addition, all subjects who permanently discontinue both study treatments will be followed for survival and new anti-cancer therapy according to the Time and Events Table (Table 20). Follow-up contact to assess survival and new anti-cancer therapy may be made via clinic visit, phone, or email; follow-up will continue until study completion/withdrawal/lost to follow-up or death, whichever occurs first.

7.2.2.3 Assessment at Subject Completion

If the last radiographic assessment was more than 8 weeks prior to study withdrawal and progressive disease had not been documented, a disease assessment should be obtained at the time of withdrawal.

7.2.3 Guidelines for Evaluation of Disease

7.2.3.1 Measurable and Non-measurable Definitions

Measurable lesion(s):

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

- ≥10 mm with MRI or CT when the scan slice thickness is ≤ 5 mm. If the slice thickness is >5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if:

- The short axis measures ≥ 15 mm when assessed by CT or MRI (the slice thickness is recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer EA 2009].

Non-measurable lesion(s):

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

Measurable disease:

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

Non-measurable only disease:

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

7.2.4 Response Criteria

7.2.4.1 Evaluation of Target Lesions

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

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must have a short axis of <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (i.e., percent change from baseline).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD).
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (i.e., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of >5 mm.
- Not Evaluable (NE): Cannot be classified by one of the 5 preceding definitions.

Note:

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

7.2.4.2 Evaluation of Non-target Lesions

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

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (i.e., a short axis of <10 mm).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline with a short axis of ≥10 mm.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the 4 preceding definitions.

Note:

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

7.2.4.3 New Lesions

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

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

7.2.4.4 Evaluation of Overall Response

Table 21 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 21 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

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

Abbreviations: CR = complete response; NA = not applicable; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Note:

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

recommended that the residual lesion be investigated (e.g., fine needle aspirate/biopsy) to confirm the CR.

7.2.4.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression, death, or withdrawal of consent, whichever occurs first. Best overall response will be determined programmatically by Novartis based on the investigator's assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after enrollment for a minimum of 49 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered NE.

Confirmation Criteria:

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

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, chemistry and hematology laboratory values, and AEs will be monitored and evaluated. AEs will be graded by the investigator according to the NCI CTCAE, version 4.0.

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 7.3.2.1 and Section 7.3.2.2 respectively.

7.3.2.1 Definition of an AE

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

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

Events meeting the definition of an AE include:

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

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

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that 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 is any untoward medical occurrence that, at any dose:

a. Results in death

   NOTE: Death due to disease under study is to be recorded on the Death CRF form and does not need to be reported as an SAE

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-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

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

g. Protocol-specific SAEs:

- All events of possible drug-induced liver injury with hyperbilirubinemia 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 and new primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.

- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance (Section 5.8.3.1)

- Retinal pigment epithelial detachment (RPED) or retinal vein occlusion (RVO)

7.3.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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

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.

Any new primary cancer must be reported as an SAE.

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.

7.3.4 Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

7.3.5 Death Events

In addition, all deaths that occur whether or not they are considered SAEs will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

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

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE.

Death due to disease under study is to be recorded on the Death eCRF form and does not need to be reported as an SAE.

If however, the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and disease progression, then this must be reported as an SAE.

7.3.7 Pregnancy Testing, Prevention and Reporting

7.3.7.1 Pregnancy Testing and Prevention

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

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

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

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

If a female subject is of childbearing potential, she must have a serum β-human chorionic gonadotropin (HCG) pregnancy test performed within 14 days of first dose of study treatment. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below throughout the treatment period and for 16 weeks after stopping treatment with trametinib or 2 weeks after stopping treatment with dabrafenib monotherapy, whichever is longer.

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

- Placement of a hormonal or non-hormonal intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
- Sterilization (at least 6 months prior to screening) for male partners. The vasectomized male partner should be the sole partner for that subject.
- Total abstinence (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.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Notes:

- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository) are not considered highly effective methods of contraception.
- Hormonal-based methods (e.g., oral contraceptives) are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib and/or trametinib.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Female subjects who are lactating must discontinue nursing prior to enrollment and must refrain from nursing throughout the treatment period and for 30 days after the last dose of study treatment.

Male contraception

Dabrafenib may cause infertility in males, which may be irreversible.
Adverse effects of trametinib on male reproductive organs have been seen in animals. Male patients (including those that have had a vasectomy) taking the dabrafenib and trametinib combination therapy must use a condom during intercourse, and for 16 weeks after stopping treatment, and should not father a child during these periods.

7.3.7.2 Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

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

7.3.8 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.

Adverse events (AEs) will be collected from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment regardless of initiation of a new anti-cancer therapy or transfer to hospice. In China, SAEs will be recorded from the time the consent form is signed. For all other countries, SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy), will 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 7.3.10.

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

7.3.9 Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

"How are you feeling?"

"Have you had any (other) medical problems since your last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.10 Prompt Reporting of Serious Adverse Events 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 that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy notification form	2 weeks	Pregnancy follow-up form
Cardiovascular or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Liver Chemistry Abnormalities:				
ALT ≥ 3 x ULN **PLUS** total bilirubin ≥ 2 x ULN (> 35% direct) or ALT ≥ 3 x ULN and INR > 1.5, if INR measured[a]	24 hours[b]	SAE data collection tool, liver event eCRF form, and liver imaging and/or biopsy eCRFs, if applicable[c]	24 hours	Updated SAE data collection tool and updated liver event eCRF form[c]
ALT ≥ 5 x ULN; ALT ≥ 3 x ULN with hepatitis or rash **or** ≥ 3 x ULN that persists ≥ 4 weeks	24 hours[b]	Liver event eCRF form[c]	24 hours	Updated liver event eCRF form[c]
ALT ≥ 3 x ULN and < 5 x ULN, **PLUS** total bilirubin < 2 x ULN	24 hours[b]	Liver event eCRF form does not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[c]		

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

a. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

b. Novartis to be notified at onset of liver chemistry elevations to discuss subject safety.

c. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

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

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to Novartis are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

7.3.10.1 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, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.3.11 Other Safety Outcomes

Laboratory Assessments

All protocol-required laboratory assessments must be performed by the central laboratories. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule (Table 20).

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and they result in a change in patient management (for example SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of sample to avoid duplicate and/or additional blood draws.

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

Clinical chemistry and hematology parameters to be tested are listed in Table 22. Female subjects will have a serum pregnancy test at Screening; urine pregnancy testing may be done during study treatment, if necessary.

Table 22 Clinical Chemistry and Hematology Parameters

Clinical Chemistry Parameters
Albumin Alkaline Phosphatase Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT) Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT) Gamma-Glutamyl Transpeptidase (GGT) Bicarbonate Blood Urea Nitrogen (BUN) or urea Calcium Chloride Creatinine[c] Glucose (random) Lactate Dehydrogenase (LDH) Magnesium Phosphate Potassium Sodium Total Bilirubin[b] Total Protein
Hematology Parameters
White Blood Cell (WBC) Count Hemoglobin Hemoglobin A1C Hematocrit International Normalized Ratio (INR; at Screening only)[a] Platelet Count Prothrombin Time (PT; at Screening only)[a] Partial Thromboplastin Time (PTT; at Screening only)[a] Automated WBC Differential (expressed as Gl/L): Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Other tests
Amylase and lipase [monitor via local laboratory where appropriate to evaluate certain AEs (i.e., abdominal pain, pancreatitis, etc.)]
serum β-hCG (human chorionic gonadotrophin)
For subjects with a history of chronic HBV and/or HCV, the following tests will be performed at Screening: • Viral hepatitis serology (HBs Antigen, HBc Antibody, HBs Antibody, HCV Antibody); • HBV DNA • Hepatitis C RNA

a. Coagulation panel to be done at Screening only.

b. Bilirubin fractionation is recommended if total bilirubin is > 2 x the upper limit of normal (ULN).

c. .If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockcroft-Gault formula (Appendix 2).

7.3.12 Ophthalmic Examination

Subjects are required to have a standard ophthalmic examination performed by an ophthalmologist at baseline, at week 4 and as clinically warranted per protocol's guidance (Section 5.8.5.4). The exam will include indirect fundoscopic examination, visual acuity (with

correction), visual field examination, and tonometry, with special attention to retinal abnormalities that are predisposing factors for RVO or CSR. Direct fundoscopy may be performed but is not required.

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

7.3.13 Vital Signs

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

See Section 5.8.3.2.1 for details on monitoring of hypertension.

7.3.14 Physical Examinations

Complete physical examination will include assessments of eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease, and of the head, neck, ears, nose, mouth, throat, thyroid, lymph nodes, extremities, and a full skin exam to assess cutaneous malignancies and proliferative skin diseases. Complete physical examinations will also include thorough genitourinary (pelvic) and rectal exams to assess secondary malignancies. In females the pelvic exam must visualise the cervix. (Pap smear and colposcopy are not required unless clinically indicated). Rectal exam must include digital rectal exam and visual inspection of the anus and perianal area. Brief physical examinations will include assessment of head, neck, eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease. Refer to the Time and Events Table (Table 20) for when to perform a complete or a brief physical examination.

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

7.3.14.1 Dermatological Exams

A full skin exam is required at screening and every 8 weeks to assess cutaneous malignancies and proliferative skin diseases. Upon study treatment discontinuation, a final skin exam is required within 8 weeks of the last dose of study treatment. Medical photographs should be taken for patients with such skin abnormalities.

Dermatologic skin exams may be referred to a dermatologist, if needed. If possible, the same physician should perform each examination for the duration of the study to ensure consistency between evaluations.

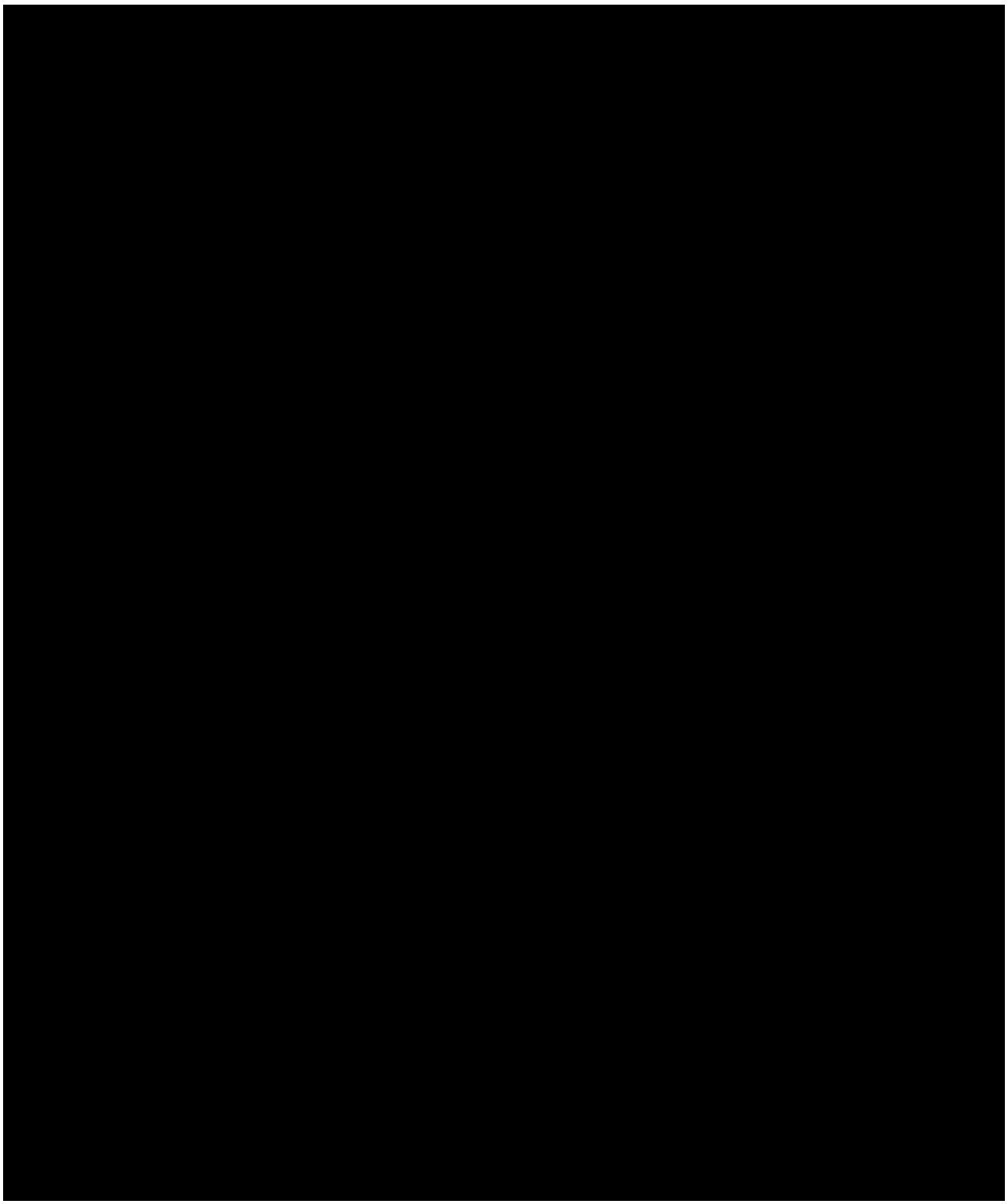
7.3.15 Electrocardiograms (ECG)

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.

7.3.16 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 will be centrally collected for review. Collection details will be provided in the SPM.



7.5 Pharmacokinetics

7.5.1 Blood Sample Collection

Blood samples (2 mL) for pharmacokinetic analysis of dabrafenib and metabolites (hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib) and trametinib will be collected at the time points indicated in the Time and Events table (Table 20). The actual date and time of each blood sample collection will be recorded.

7.5.2 Sample Analysis

Plasma analysis will be performed under the control of PK Sciences, the details of which will be included in the Study Procedures Manual. Concentrations of carboxy-dabrafenib will be determined in plasma samples using a separate assay using the currently approved analytical methodology while the other two metabolites are quantified together with dabrafenib in one assay. Raw data will be stored in the Good Laboratory Practice (GLP) Archives.

Once the plasma has been analyzed for dabrafenib and its metabolites and trametinib, any remaining plasma may be analyzed for other compound-related metabolites and the results reported.

8 Data management

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

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

Clinical data management will be performed in accordance with applicable Novartis standards and data cleaning procedures to ensure the integrity of the data, e.g., resolving errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom drug dictionary. An appropriate medical dictionary that covers all approved drugs in studies where Japan is participating will be referenced.

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 study will pursue an estimation strategy rather than formal hypothesis testing. This is reasonable given the proven performance of the combination therapy and the desire to estimate efficacy and safety in the Asian population. Since estimation is the goal, there are no formal hypotheses to be tested. The minimal effect to be excluded from the lower end of the confidence interval for ORR will be 25%.

9.2 Study Design Considerations

9.2.1 Sample Size Assumptions

Approximately 65 subjects will be enrolled. This sample size was deemed to be sufficient to assess efficacy, safety and tolerability of dabrafenib in combination with trametinib in Asian patients with BRAF V600 Mutation-Positive Melanoma.

9.2.2 Sample Size Sensitivity

Sample size sensitivity has been illustrated in Table 23 of Section 9.2.1.

9.2.3 Sample Size Re-estimation

Sample size re-estimation is not planned.

9.3 Data Analysis Considerations

Data will be listed and summarized according to Novartis integrated data standards library (IDSL) reporting standards where applicable. Complete details will be provided in the Statistical Analysis Plan (SAP).

9.3.1 Analysis Populations

The All Treated Subjects (ATS) Population will consist of all subjects that receive at least one dose of study treatment. Safety and efficacy data will be evaluated based on this population.

The PK Population will consist of those subjects in ATS population for whom a PK sample is obtained and analyzed.

9.3.2 Analysis Data Sets

The primary dataset for efficacy and safety will be comprised of the ATS population defined in Section 9.3.1.

9.3.3 Treatment Comparisons

9.3.3.1 Primary Comparisons of Interest

The primary objective will be supported by the calculation of objective response rate using the ATS population. The final analysis of ORR will be performed after 65 subjects have been treated for 16 weeks or have otherwise discontinued study treatment.

Subjects will continue to be followed for survival until death, lost to follow-up, or study completion. The definition of study completion is described in Section 3.1.

9.3.3.2 Other Comparisons of Interest

Safety, PK, PD, duration of response, PFS, OS, [redacted] will be listed and summarized in tabular and graphic formats as data warrant. There are no other formal comparisons of interest.

Since there is a single primary endpoint (ORR), supported by secondary endpoints, the nominal level of significance for the primary analysis will not be affected by multiplicity.

9.3.4 Interim Analysis

Not applicable

9.3.5 Key Elements of Analysis Plan

Data will be listed and summarized according to Novartis reporting standards, where applicable. Complete details will be documented in the SAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final study report and will not require a protocol amendment.

As it is anticipated that accrual will be spread thinly across study sites, summaries of data by study site would not be informative. Data from all participating study sites will therefore be pooled prior to analysis.

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

As treatment duration 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.

Details on the determination of tumor response are given in Section 7.2.4.

Additional details on efficacy analyses (Section 9.3.5.1) and safety analyses (Section 9.3.5.2) are provided.

9.3.5.1 Efficacy Analyses

9.3.5.1.1 Primary Efficacy Analyses

Anti-tumor activities will be calculated based on RECIST 1.1 [Eisenhauer EA 2009]. The ORR is defined as the percentage of subjects among all subjects who have enrolled and received at least one dose of investigational product, who have a confirmed complete response or a partial response. Subjects with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage. No imputation will be performed for missing lesion assessments or tumor response data.

95% confidence limits for objective response rate will be calculated. . An exact binomial confidence interval will be calculated Clopper and Pearson 1934.

9.3.5.1.2 Secondary Efficacy Analyses

Progression-Free Survival(PFS)

PFS will be defined as the time from first dose until the first date of either objective disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of radiological or photographic disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment or first dose for subjects without any adequate post baseline assessments. In addition, subjects with an extended loss to follow-up or who start new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Progression free survival will be summarized descriptively using Kaplan-Meier medians and quartiles.

Further details on censoring rules will be outlined in the SAP.

Overall Survial (OS)

OS is defined as the time from first dose until death due to any cause. For subjects who have not died, time to death will be censored at the last date of known contact

OS will utilize all -cause mortality and censoring will be performed using the date of last known contact for those who are alive at the time of analysis. OS will be summarized descriptively using Kaplan-Meier medians and quartiles.

Duration of Response

If data permits (i.e. a sufficient number of subjects with confirmed CR or PR), duration of response will be summarized descriptively using Kaplan-Meier medians and quartiles . Duration of Response for the subset of subjects with a confirmed CR or PR is defined as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause. Censoring rules for duration of response will follow the rules for PFS and will be outlined in detail in the SAP.

9.3.5.2 Safety Analyses

Safety endpoints are described in Section 2 and Section 7.3.1.

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

9.3.5.2.1 Extent of Exposure

The number of subjects administered study treatment will be summarized for subjects in the ATS population according to exposure and duration of therapy.

9.3.5.2.2 Adverse Events

Adverse events will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the NCI CTCAE, version 4.0.

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

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

Any AEs of special interest (including SCC and other proliferative diseases) will be summarized as detailed in the SAP.

The incidence of death 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 (v4.0). The proportion of values lying outside the reference range will also be presented for laboratory tests which are not graded because there are no associated NCI CTCAE criteria (v4.0). Summaries by visit will include data from scheduled assessments only and all data will be reported according to the nominal visit for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in 'worse case post baseline' summaries which will be capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the SAP.

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 by visit will include data from scheduled assessments only. All data will be reported according to the nominal visit for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in the 'worst 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 SAP.

9.3.5.3 Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling & Simulation (CPMS) department within Novartis. Plasma dabrafenib and metabolites including hydroxy- , desmethyl-, and carboxy-dabrafenib and trametinib concentration-time data will be analyzed by standard noncompartmental methods in subjects from whom the full PK blood sample scheme were collected. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined for dabrafenib and metabolites and trametinib, as data permit:

Steady-state (all subjects) - trough concentration at steady-state (Ctrough), Cmax, tmax, AUC(0-t), AUC(0-8), (AUC(0-12); dabrafenib and metabolites only), AUC (0-24) (trametinib only)), and apparent terminal phase half-life ($t_{1/2}$) for trametinib and dabrafenib and metabolites. The metabolite to parent ratio for AUC(0-12) will be calculated for each metabolite of dabrafenib. AUC(0-12) on Day 15 will be estimated for dabrafenib and metabolites by setting the plasma concentration 12 hours after dosing equal to the predose concentration. The AUC(0-24) on Day 15 will be estimated for trametinib by setting the plasma concentration 24 hours after dosing equal to the predose concentration.

[redacted]

Noncompartmental pharmacokinetic parameters will be listed and summarized by day. Separate summaries will be created for parameters calculated with the dense blood sampling scheme and the sparse blood sampling scheme. No formal statistical analysis of the pharmacokinetic parameters is planned.

9.3.5.4 Pharmacokinetic/Pharmacodynamic Analysis

[redacted]

10 Study CONDUCT CONSIDERATIONS

10.1 Posting of Information on Publicly Available Clinical Trial Registers

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

10.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

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

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

The study will be conducted in accordance with ICH 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 favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

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

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

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., [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 Novartis personnel or designated CRO 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, GCP, and all applicable regulatory requirements.

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

10.4 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5 Study and Site Closure

The study will be close when it is completed, as defined in Section 3.1.

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

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

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

10.6 Records Retention

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

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

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 aims to post a results summary to the Novartis Clinical Trial Results website (www.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 (www.novartisclinicaltrials.com) for a summary of the trial results.

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GlaxoSmithKline Document Number 2014N196181_00 Study ID MEK116885 A Japanese open-label Phase I/II study to assess the safety, tolerability, pharmacokinetics and efficacy of GSK2118436 and GSK1120212 combination therapy in subjects with BRAF V600E/K mutation positive advanced solid tumors (Phase I part) and BRAF V600E/K mutation positive cutaneous melanoma (Phase II part). Report date 05-Feb-2015

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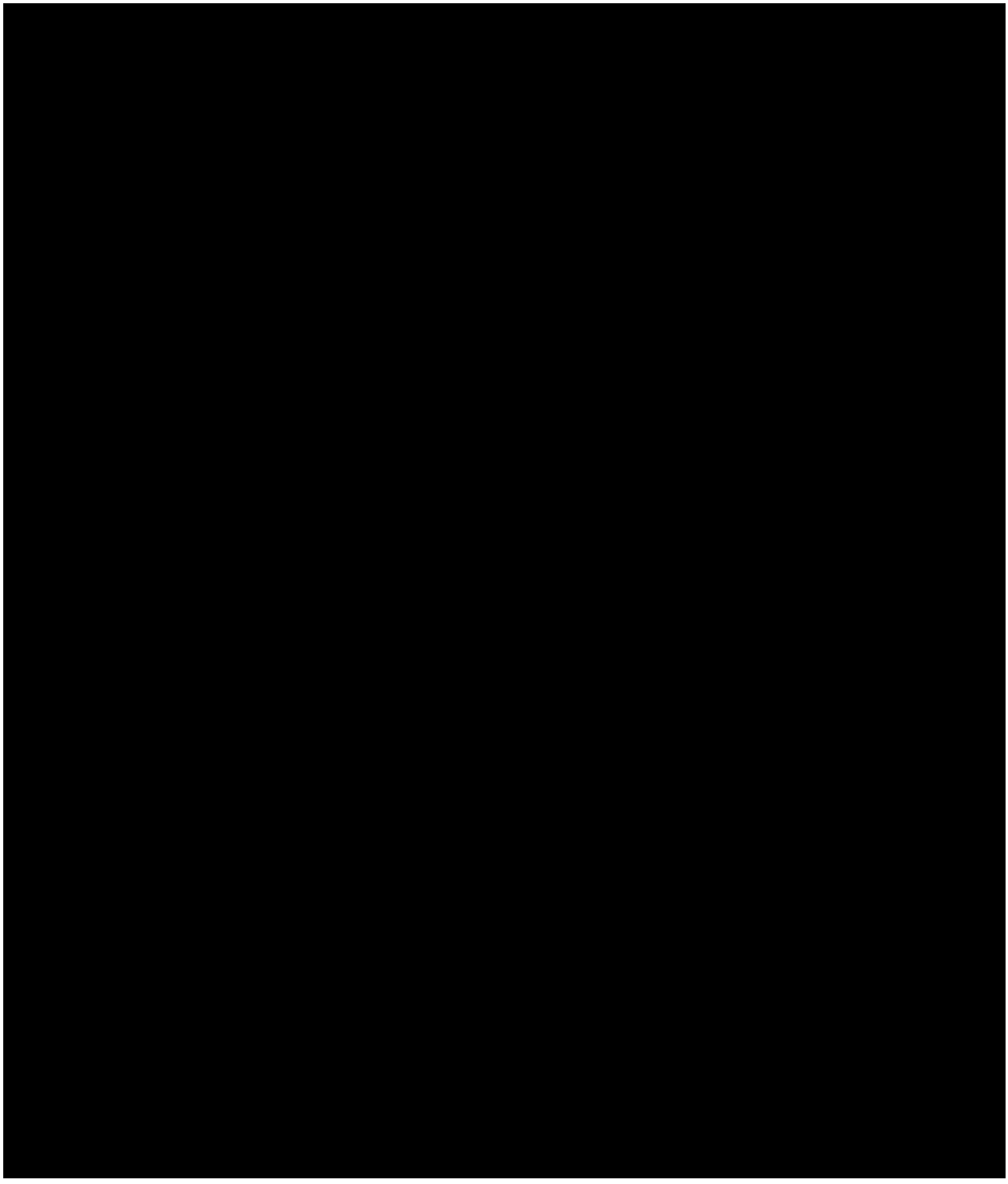
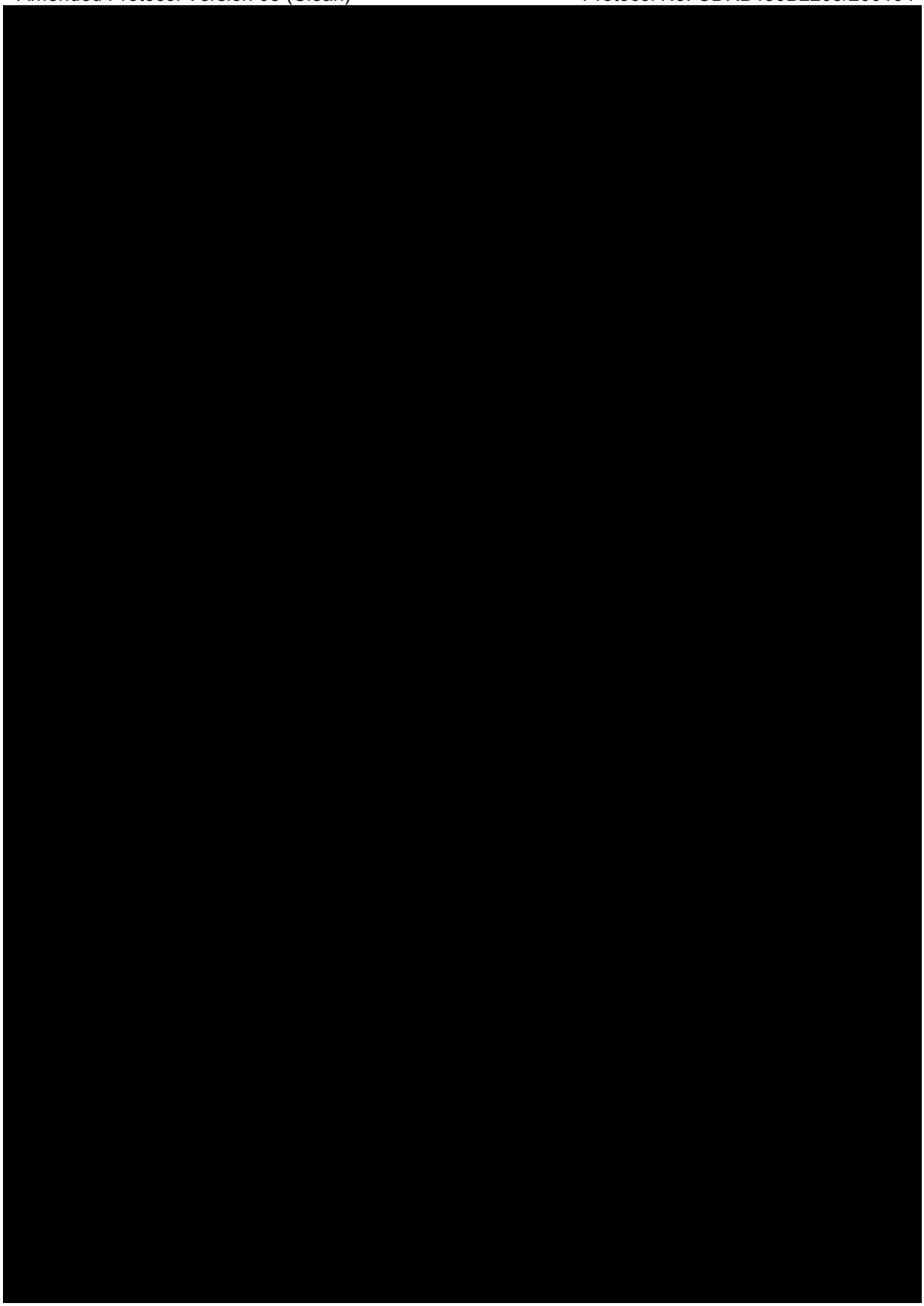
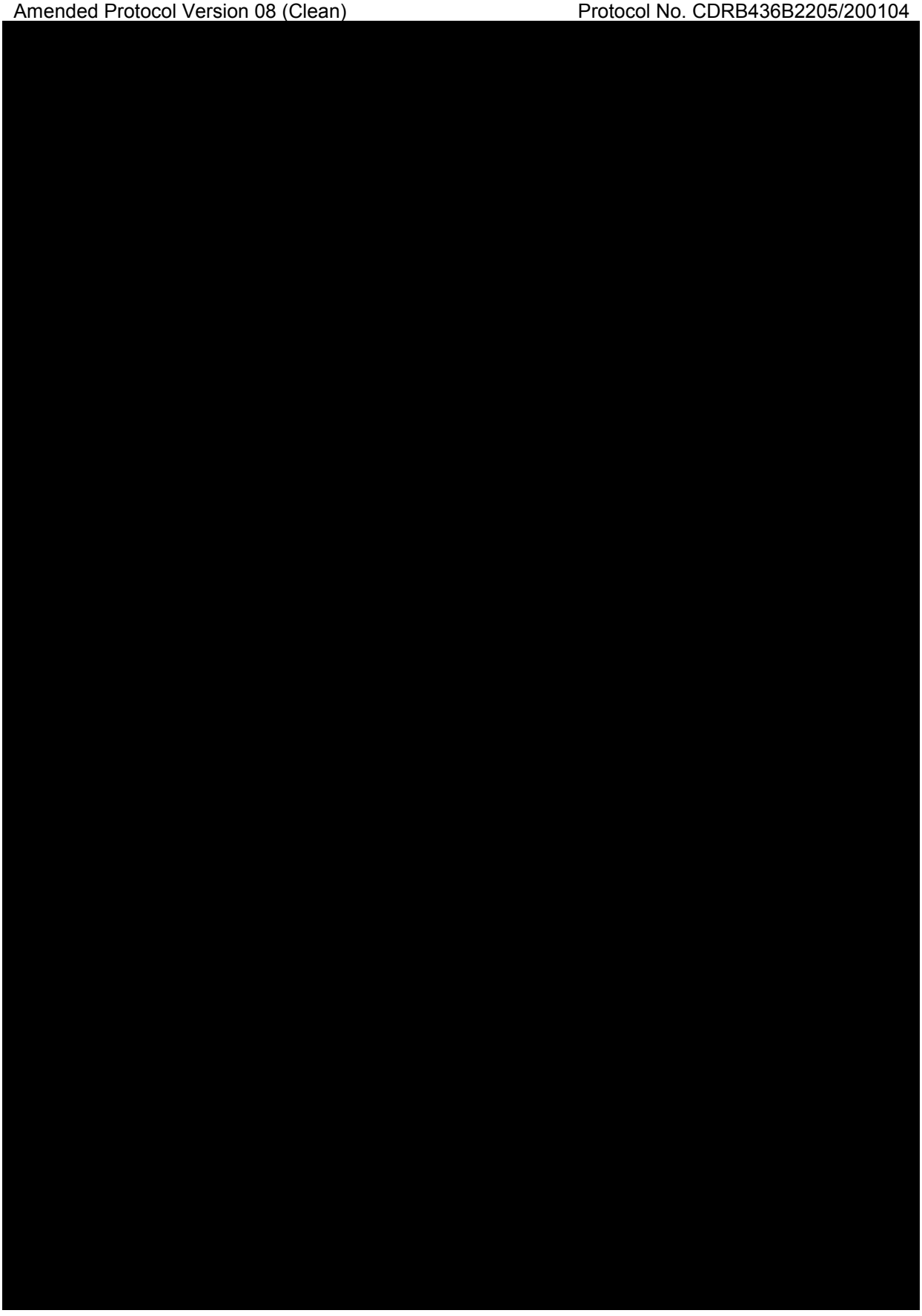
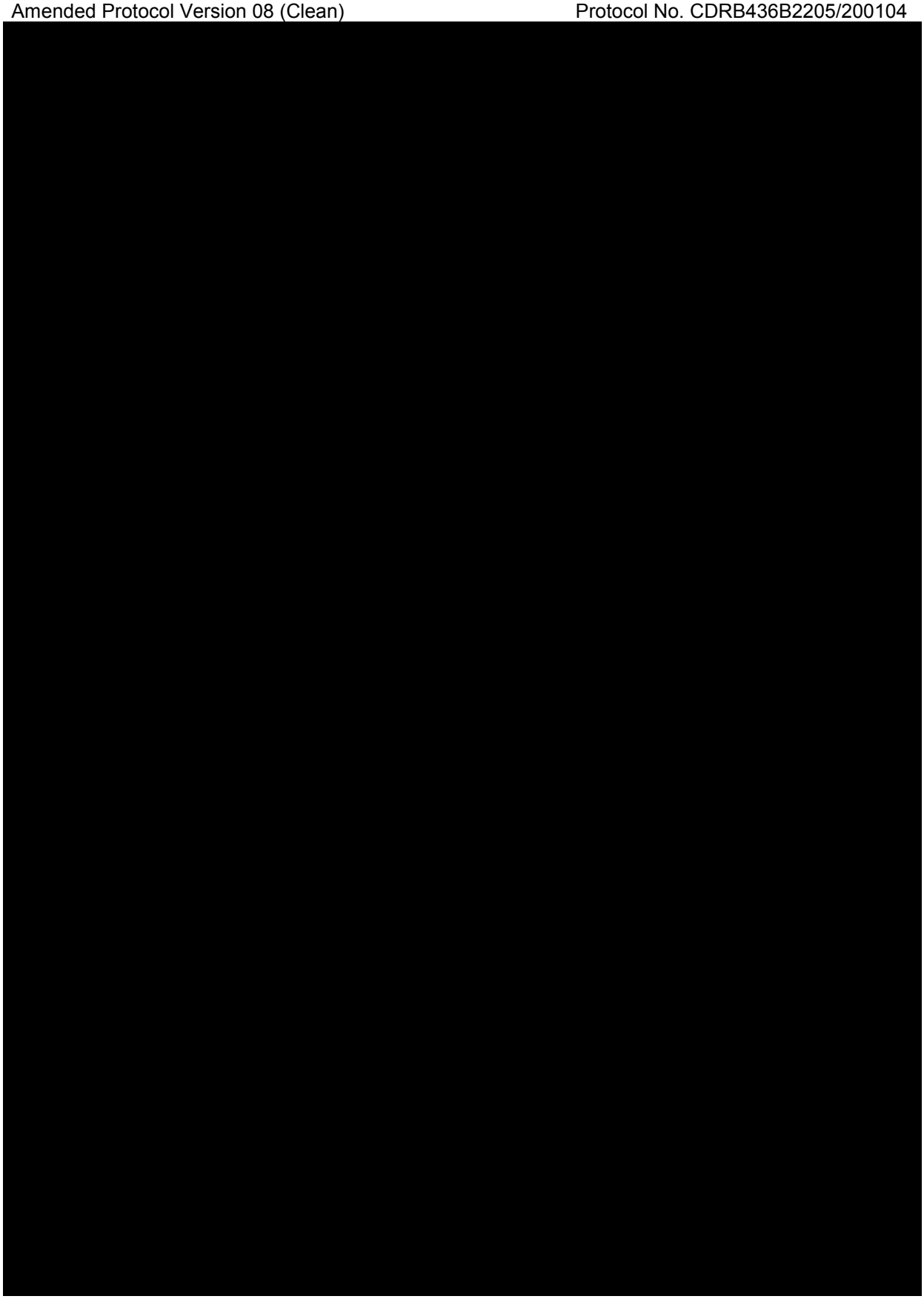
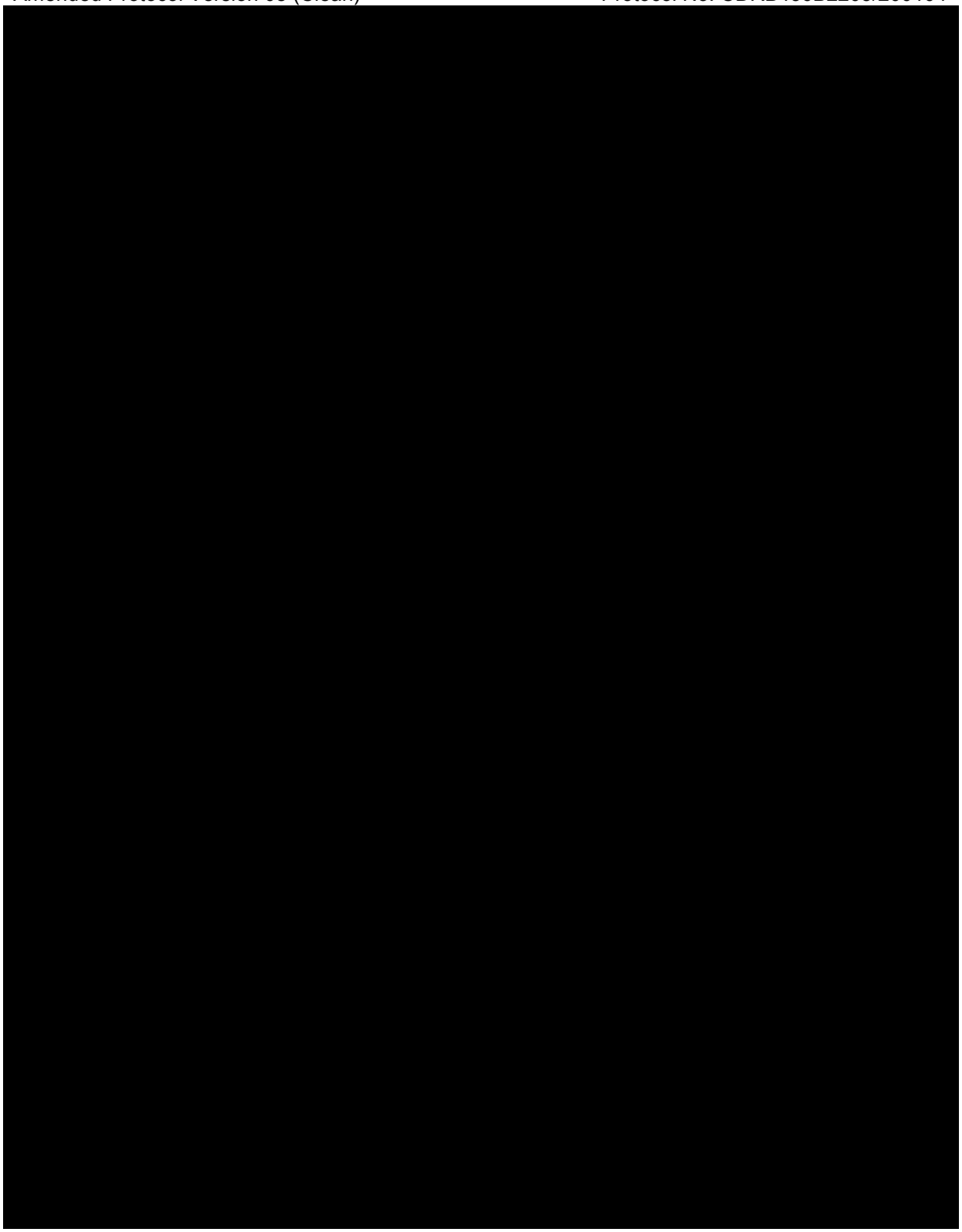
12 Appendices











12.2 Appendix 2: Cockcroft-Gault

The Cockcroft-Gault formula is a commonly-used surrogate marker for actual creatinine clearance and employs creatinine measurements and a subject's weight (kg) to predict the clearance [Cockcroft, 1976].

CrCl (mL/min)=	Q x (140-age [years]) X actual body weight (kg)[a]
	72 X serum creatinine (mg/dL)
CrCL=creatinine clearance Q=0.85 for females Q=1.0 for males	

OR

CrCl (mL/min)=	K x (140-age [years]) X actual body weight (kg)
	serum creatinine (μmol/L)
K=1.04 for females K=1.23 for males	

If the subject is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimate CrCl.

a. Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]

Male subjects:	
	50.0 kg + (2.3 kg x each inch over 5 feet) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Female subjects:	
	45.5 kg + (2.3 kg x each inch over 5 feet) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)

For example:

For a male subject with actual body weight = 90.0 kg, and height = 68 inches, the calculation would be as follows:

Ideal body weight= 50.0 + (2.3) (68-60) = 68.4 kg

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

References

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Devine BJ. Case Number 25 Gentamicin Therapy: Clinical Pharmacy Case Studies. Drug Intelligence and Clinical Pharmacy. 1974; 8:650-655.

12.3 Appendix 3: QT interval on electrocardiogram corrected using the Bazett's formula (QTcB)

The correction method must be collected for ECG machines with a QT correction method programmed by the manufacturer. For purposes of data analysis, QTcB will be used.

If the ECG machine does not calculate QTc using Bazett's formula, QTcB should be calculated manually and entered on the eCRF.

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*.

References

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

12.4 Appendix 4: 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.

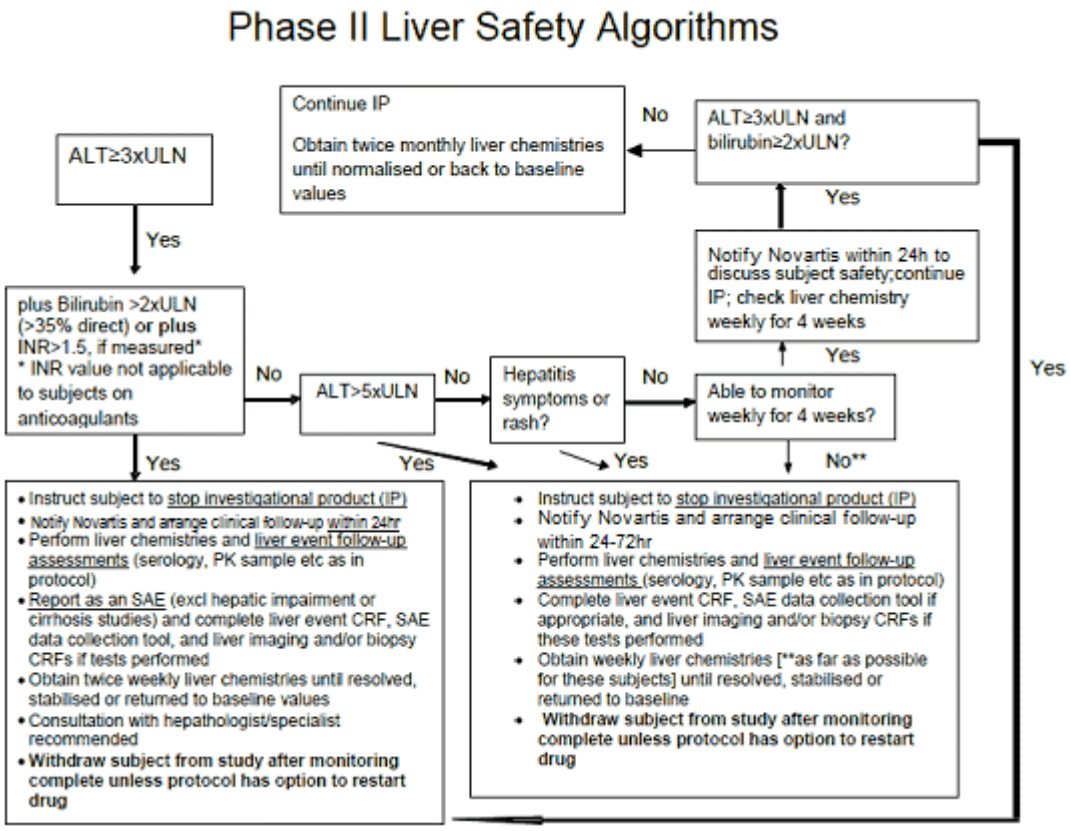
Reference:

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.

12.5 Appendix 5: Country Specific Requirements

No country-specific requirements exist.

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



12.7 Appendix 7: Liver Safety Drug Restart or Rechallenge Guidelines

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

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

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

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

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

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

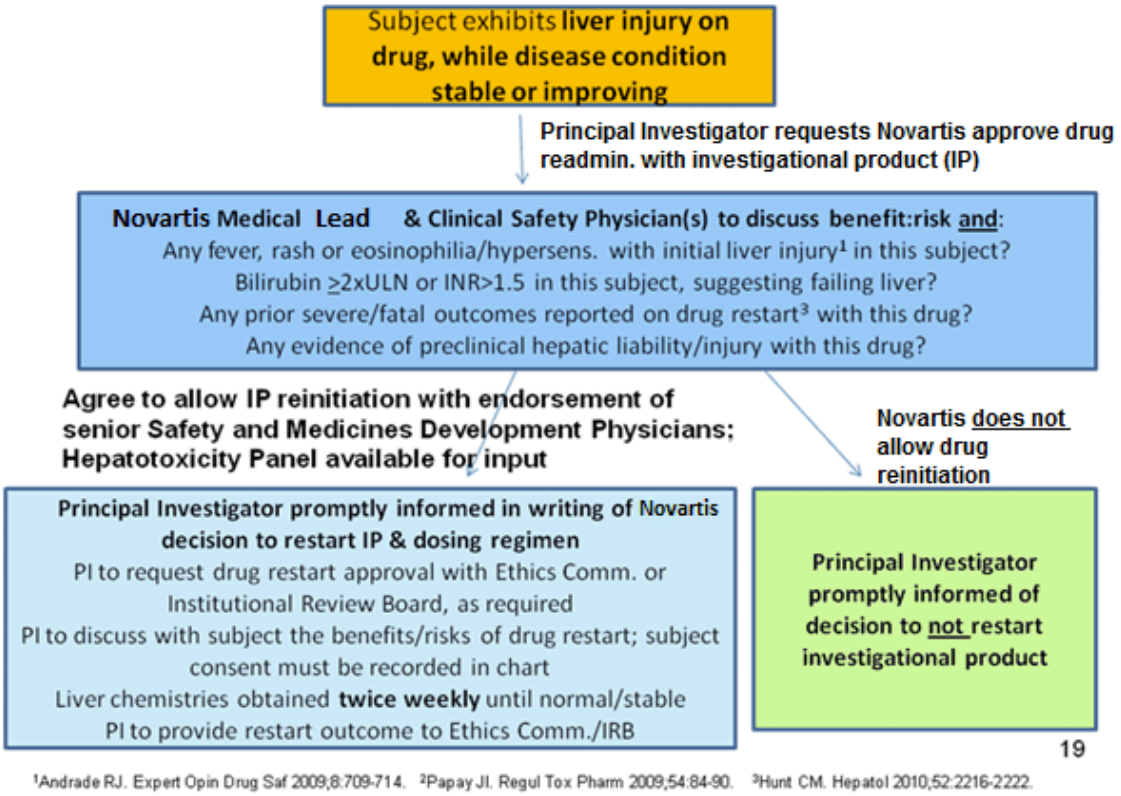
- Novartis Medical Lead & Clinical Safety Physician to review the subject's restart/ rechallenge risk factors & complete checklist (Table 1).

Table 1. Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)		
	Yes	**No**
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug restart/rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
○ fever, rash, eosinophilia, or hypersensitivity		
○ or bilirubin>2xULN (direct bilirubin >35% of total)		
• Subject currently exhibits ALT >3xULN, bilirubin ≥ 2xULN (direct bilirubin >35% of total, if available), or INR ≥ 1.5		
• Severe or fatal restart/rechallenge has earlier been observed with IP **If yes, please provide brief explanation**:		
• IP associated with known preclinical hepatic liability/ injury		

Principal Investigator (PI) Actions:

- The PI must obtain Ethics Committee or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the possible benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.
- The drug must be reinitiated at Novartis-approved dose(s).
- Liver chemistries should be followed twice weekly until stable.
- The Ethics Committee or Institutional Review Board must be informed of the subject's outcome, as required.
- Novartis to be notified of any adverse events, as per Section 7.3.2-Section 7.3.3.

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



References:

1. Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

2. Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

3. Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Drug Restart Guidelines

Novartis Decision Process for Drug Restart Approval or Disapproval (also see Figure 3)

- Principal Investigator (PI) requests consideration of drug reinitiation for a subject stable or improving on investigational product (IP), who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and resolves.
- Novartis Medical Lead & Clinical Safety Physician to review the subject's diagnosis, restart risk factors & complete checklist (Table 2).

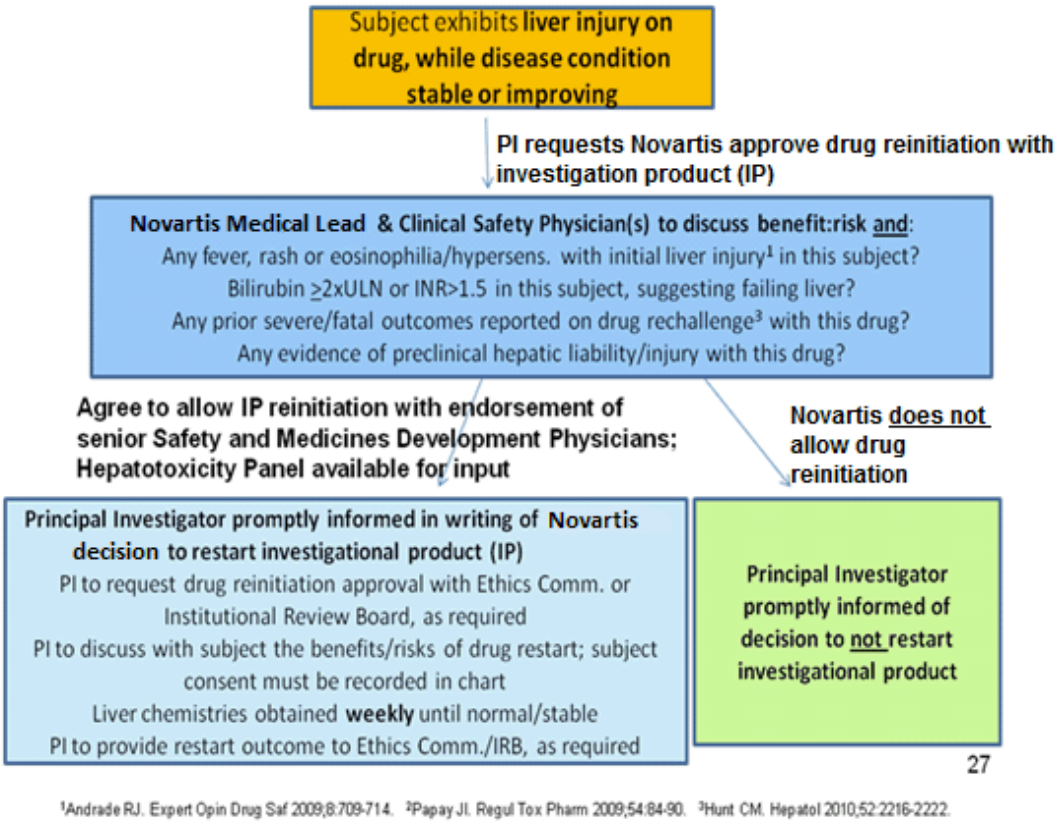
Table 2. Checklist for Phase III drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, CHF, acute viral hepatitis), liver chemistries improving to normal, or ≤1.5x baseline and ALT<3xULN.

	Yes	No
Is subject stable or improving on the investigational product (IP)?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• IP associated with liver injury and an HLA genetic marker (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		

Principal Investigator (PI) Actions

- The PI must obtain Ethics Comm. or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.
- Liver chemistries should be followed weekly until stable.
- The Ethics Committee or Institutional Review Board must be informed of the patient's outcome, as required.
- Novartis to be notified of any adverse or serious adverse events, as per Section 7.3.2-Section 7.3.3

Figure 3 Novartis process for drug restart approvals



References:

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

12.8 Appendix 8: Protocol Amendment Changes

Amendment 1 (27-Mar-2015) from the Original Protocol (08-July-2013)

This amendment applies to all investigator sites participating in this study. The summary of rationale for this amendment is provided below:

Summary of Amendment Changes with Rationale

- In Asian population approximately 25.5% of all melanoma patients and 15.5% of ALM have BRAF V600 mutation. The study was originally intended to enroll subjects with acral lentiginous melanoma and it was less than 5% population eligible. To explore the target population, it is decided to enroll subjects with BRAF V600E/K mutation positive melanoma, and not limited to acral lentiginous melanoma only. The changes broader data in Asian acral and cutaneous melanoma.
- A recently reported phase II study concluded that patients pre-treated with 1 regimen of chemotherapy or interleukin-2 (IL-2) in metastatic setting with BRAF V600 mutation was allowed to be recruited. As a result, 19% (21/162) of these patients had received prior chemo or IL-2 in metastatic setting. Literature also showed the efficacy of BRAF inhibitor was similar prior or after immunotherapy.
- In approved label, it did not specify the combination of trametinib and dabrafenib treatment shall only be used as 1st line treatment in metastatic setting.
- There are two other China alone PK studies were approved. It is no longer needed to collect single dose (Chinese subjects only) PK data from this study.

Given the clinical considerations described above, the inclusion criteria and sample collection time point was modified. In addition, there are some changes to meet specific country regulatory requirement and the safety information is updated based on most recent studies data.

Revised Text is captured in the format strikethrough=deleted text; underline=new text

12.8.1 List of Specific Changes:

Rationale for change(s): Change in Study team members

Title page

REVISED TEXT

Title:	Protocol 200104: An Open-Label, Multi-Center Study to Investigate the Objective Response Rate of Dabrafenib in Combination with Trametinib in Subjects with BRAF V600 E/K Mutation-Positive ~~Acral Lentiginous~~ Melanoma

Rationale for change(s): Change in Study team members

Revised text:

Author (s): [redacted]

SPONSOR SIGNATORY

[redacted], MD [redacted] ~~, MD PhD~~ Date
[redacted]

SPONSOR INFORMATION PAGE

Rationale for Change: The sponsor information was updated based on internal GSK team personnel changes.

REVISED TEXT

Sponsor Serious Adverse Events (SAE) Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GlaxoSmithKline (GSK) Address
Primary Medical Monitor	[redacted] ~~, MD, PhD~~ [redacted]	[redacted]	Cell: [redacted]	[redacted]	~~GlaxoSmithKline~~ ~~1250 South Collegeville Road~~ ~~Mailstop UP 4340~~ ~~Collegeville, PA 19426,~~ ~~USA~~ [redacted] GlaxoSmithKline China No.1, 917 Long, Halei Road Zhangjiang High Tech Park Shanghai China 201203 [redacted]
Secondary Medical Monitor	[redacted] MD [redacted] ~~, MD, PhD~~	[redacted]	Cell: [redacted] ~~Cell:~~ [redacted]	[redacted]	GlaxoSmithKline 1250 South Collegeville Road Mailstop UP 4400 Collegeville, PA 19426, USA [redacted]

~~Tertiary Medical Monitor~~	[redacted] ~~MD, PhD~~	[redacted]	~~Cell:~~ [redacted]	[redacted]	~~GlaxoSmithKline 1250 South Collegeville Road Mailstop UP 4340 Collegeville, PA 19426, USA~~ [redacted]

Regulatory Agency Identifying Number(s):

Investigational New Drug (IND) Number	[redacted]

PROTOCOL SUMMARY

Rationale for change(s): Update as per the most recent study results and clarifying the need for amendment.

REVISED TEXT

Paragraph 3

However, much has changed in the treatment landscape of melanoma ~~in 2011 with~~since the ~~regulatory approval of two new agents which have demonstrated a significant survival benefit in well-controlled Phase III trials.~~past 5 years. The immunotherapy as anti-cancer treatment in melanoma has significantly advanced. Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen or CTLA-4, was approved by the US-Food and Drug Administration (FDA) for unresectable or metastatic melanoma ~~based on a significant prolongation of OS (hazard ratio [HR] 0.68, p=0.003) compared to gp100 tumor vaccine [Hodi, 2010] . In addition, ipilimumab in combination with standard dacarbazine (DTIC) significantly improved the OS of previously untreated metastatic melanoma patients as compared to DTIC alone (HR 0.72, p<0.001). While ipilimumab was approved for the clinical use in unselected patients,~~in 2011. 2 immune check-point therapy, Programmed Death (PD) receptor-1 antibody (pembrolizumab and nivolumab) were also approved in 2014 for the treatment of metastatic melanoma following the standard treatment. The selective small molecule BRAF ~~V600-mutant-~~kinase inhibitor ~~vemurafenib received FDA-approval in August of 2011,~~ demonstrated significant clinical benefit as ~~the first molecular-targeted agent for unresectable or metastatic melanoma harboring BRAF V600 mutations. In the pivotal Phase III study BRIM-3 treatment with vemurafenib resulted in a significant improvement of progression-free survival (PFS) (HR 0.26, p<0.001) and overall survival (HR 0.37, p<0.001) in the interim data analysis compared to DTIC [Chapman, 2011]. At 6 months, overall survival was 84% (95% CI, 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group.~~monotherapy in metastatic melanoma patients with V600 mutation. However the efficacy of ~~vemurafenib. It is widely believed, that combination therapies of targeted agents can further improve the effect on survival currently achieved with ipilimumab- and vemurafenib- single agent-therapies [Eggermont, 2011]. However, the recent study report~~

~~of hepatotoxicity highlighted the risk of concurrent administration of vemurafenib and ipilimumab [Ribas, 2013]. For the approximately 50% of melanoma patients whose tumor harbour a BRAF V600-activating mutation, a combination of a selective and potent BRAF- and a MEK-~~BRAF inhibitor ~~is favoured to address specific molecular mechanisms of intrinsic and acquired resistance to a~~ was not durable In addition, BRAF-inhibitor ~~monotherapy [Nissan , 2011].~~ induced paradoxical activation of the MAPK pathway.

~~In multiple dabrafenib or trametinib trials as a monotherapy, the confirmed overall response rate was about 50% and 25%, respectively. Emerging data from the ongoing Phase I/II study BRF113220 suggest that the small-molecule BRAF V600-inhibitor dabrafenib (known as GSK2118436) can be safely combined with the small molecule MEK-inhibitor trametinib (known as GSK1120212). The rate of complete or partial response with combination 150 mg dabrafenib/2 mg trametinib (150/2) therapy was 76%, as compared with 54% with dabrafenib monotherapy (p = 0.03)~~ [Single agent MEK inhibitor trametinib has proved to improve survival in metastatic melanoma with BRAF mutation and not associated with paradoxical activation of MAPK pathway [Flaherty, 2012]~~. In addition, the anti-tumor activity of the combination of both agents given continuously and at full-single-agent dose appears to be superior as compared with single-agent dabrafenib. Currently, multiple randomized phase III trails are ongoing with dabrafenib and trametinib combination therapy in patients with malignant melanoma.~~

July].

Combination of MEK and BRAF inhibitor was tolerable and delayed the emergence of resistance and decreased the incidence of cutaneous hyperproliferation. This was confirmed by 3 randomized phase III studies. In September 2014, Long and colleagues reported in New England Journal of Medicine the result of COMB-D study. In this study , combination treatment of MEK and BRAF inhibitor (dabrafenib and trametinib) compared with BRAF inhibitor (dabrafenib) alone, significantly improved progression free survival in previously untreated patients who had metastatic melanoma with BRAF V600E or V600 K mutations[Long, 2014]. In the same issue of New England Journal of Medicine, another phase III study in the similar population reported same result using a different combination of MEK and BRAF inhibitor (cobimetinib and vermurafenib)[Larkin, 2014]. Not long after that, also in New England Journal of Medicine, a third phase III study was published, which demonstrated the combination of trametinib and dabrafenib significantly improved overall survival compared with vemurafenib in metastatic melanoma with BRAF V600 mutation [Robert, 2014]. These 3 studied included more than 1,600 patients in total.

In United States and Australia, dabrafenib in combination with trametinib has been approved to treat metastatic melanoma with BRAF V600 mutation.

However, the above mentioned randomize phase III studies were mainly conducted in Caucasian population. The efficacy and safety of trametinib plus dabrafenib need to be evaluated in Asian melanoma patients.

Paragraph 8

The original objective of the study was to evaluate the effect of dabrafenib and trametinib in patients with ALM in Asian countries. In light of the most recent advances in the treatment of BRAF mutation cutaneous melanoma, the study aims to evaluate the efficacy and safety of dabrafenib and trametinib in Asian subjects with either acral lentiginous and cutaneous melanoma pathology subtype who have BRAF V600 E/K mutation. This study will provide

important scientific information to help to address the unmet medical needs in Asian melanoma patients.

Objective(s)

Primary Objective

- To determine the objective response rate (ORR) of dabrafenib and trametinib combination in subjects with BRAF V600 E/K mutation-positive, unresectable or metastatic acral lentiginous ~~metastatic~~or cutaneous melanoma.

Secondary Objectives

- To assess ~~single dose (Chinese subjects only) and~~ steady state ~~(all subjects)~~ exposure to dabrafenib, dabrafenib metabolites, and trametinib and characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of dabrafenib and trametinib

Study Design

This is a single-arm, open-label, multi-center, Phase II study to evaluate dabrafenib and trametinib combination therapy in BRAF V600-E/K mutant ALM~~.~~ or cutaneous melanoma. Subjects with histologically confirmed acral lentiginous or cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV will be screened for eligibility. Screening will include central testing of BRAF V600 mutation status. Eligible subjects must be BRAF V600E/K mutation positive. Subjects ~~who~~may have had prior systemic anti-cancer treatment in the ~~advanced~~adjuvant or metastatic setting ~~will~~, but should not ~~be eligible. Prior adjuvant systemic treatment is permitted.~~have been exposed to MEK or BRAF inhibitor. Objective response rate will be assessed using a 2-stage Green-Dahlberg design. Approximately 35 subjects (20 subjects in stage 1 and additional 15 subjects in stage 2) will be enrolled and will receive dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily.

Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, or study ~~closure~~completion. After treatment discontinuation, subjects will be followed for survival and disease progression as applicable.

Survival and new anti-cancer therapy follow-up will continue until ~~70% of the total enrolled population has died or been lost to follow-up. At such time the study will be closed.~~study completion. The study completion is defined as:

- In case all subjects stop study treatment within 48 weeks after Last Subject First Visit(LSFV): the study is completed once the last subject has completed the 48 weeks survival follow-up or all subjects die or loss to follow-up, whichever comes first.
- In case some subjects are still on study treatment 48 weeks after LSFV: the study is completed once all subjects stop study medication, or all subjects who are still on study medication can have access to alternative supply of MEK/BRAF inhibitors, whichever comes first.

Study Endpoints/Assessments

Noncompartmental PK parameters will include:

~~Single dose (Chinese subjects only) - maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC) from 0 to the time of the last quantifiable concentration (AUC(0-t)), AUC from 0 to 8 hours (AUC(0-8)), AUC from 0 to 12 hours (AUC(0-12); dabrafenib and metabolites only), AUC from 0 to 24 hours (AUC (0-24) :trametinib only)), AUC from 0 to infinity (AUC(0-(), and apparent terminal phase half-life (t1/2) for trametinib and dabrafenib and metabolites as data permit. The metabolite to parent ratio for AUC(0-t) will be calculated for each metabolite of dabrafenib.~~

Section 1. Introduction

Rationale for change(s): Updating as per the most recent study results and describing the scenario of amendment needed.

REVISED TEXT

Section 1.1. Background

The RAS/RAF/MEK/ERK pathway (i.e., the MAP kinase pathway, Figure 1) is a critical proliferation pathway in many human cancers, including melanoma. Oncogenic mutations in both RAS and 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 in ALM or cutaneous melanoma.

Section 1.2. Current treatment options for melanoma

Much has changed in the treatment landscape of melanoma since the past 5 years. The immunal anti-cancer treatment in melanoma had significantly advanced. Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen or CTLA-4, was approved by the US-Food and Drug Administration (FDA) for unresectable or metastatic melanoma in 2011. 2 immunal check-point therapy, Programmed Death (PD) receptor-1 antibody (pembrolizumab and nivolumab) were also approved in 2014 for the treatment of metastatic melanoma following the standard treatment.

BRAF inhibitor demonstrated significant clinical benefit compared to chemotherapy in metastatic melanoma patients with V600 mutation. ~~in the treatment landscape of melanoma in 2011 with the regulatory approval of two new agents which have demonstrated a significant survival benefit in well-controlled Phase III trials. Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen or CTLA-4, was approved by the US-Food and Drug Administration (FDA) for unresectable or metastatic melanoma based on a significant (p=0.003) improvement of OS [Hodi, 2010].~~ However the efficacy of BRAF inhibitor was not durable, as the PFS of vemurafenib or dabrafenib monotherapy was only 5.1- 5.3 months.[Hauschild, 2012; Chapman, 2011] In addition, BRAF-inhibitor–induced paradoxical activation of the MAPK pathway[Hatzivassiliou, 2010] can result in secondary cancers,

including cutaneous squamous-cell carcinoma, and may reactivate RAS-mutant tumors[Callahan, 2012].

Single agent MEK inhibitor trametinib has proved to improve survival in metastatic melanoma with BRAF mutation and not associated with paradoxical activation of MAPK pathway [Flaherty, 2012].

Combination of MEK and BRAF inhibitor was tolerable. The combination of BRAF and MEK inhibition, as compared with single-agent BRAF inhibition, delayed the emergence of resistance and decreased the incidence of cutaneous hyperproliferation. Long and colleagues reported the result of a randomized double blind phase III study which compared trametinib plus dabrafenib versus dabrafenib alone in metastatic melanoma patient who had BRAF V600 E or K mutation. The combined treatment significantly improved PFS (mPFS: 9.3 vs 8.8 months, HR=0.75, p=0.03), response rate (67% vs 51%, p=0.0002). At 6 months, the interim survival analysis also showed a improvement of survival (HR=0.63, p=0.02) . The patients who received combined treatment experienced more frequent pyrexia, chill, diarrhea, hypertension, vomiting, peripheral edema, elevated liver enzyme, decreased left ventricular ejection fraction(LVEF), dermatitis acneiform, but less frequent cutanenous squamous-cell carcinoma, hyperkeratosis, skin papilloma, hand-foot syndrome, dry skin, pruritus and alopecia. [Long, 2014] Similar efficacy results were confirmed by 2 independent randomized studies using trametinib plus dabrafenib versus vemurafenib[Robert, 2015], and cobimetinib plus vemurafenib versus vemurafenib [Larkin, 2014].

In United States and Australia, dabrafenib in combination with trametinib has been approved to treat metastatic melanoma with BRAF V600 mutation. ~~While ipilimumab was approved for the clinical use in unselected patients, the selective small molecule BRAF-inhibitor vemurafenib received FDA-approval in August of 2011, as the first molecular-targeted agent for unresectable or metastatic melanoma harbouring BRAF V600E mutations. In the pivotal Phase III study BRIM-3 treatment with vemurafenib resulted in a significant improvement of PFS and OS compared to DTIC [Chapman, 2011]. The BRIM-3 update on OS analysis at 12.5 months follow-up for vemurafenib and 9.5 months follow-up for DTIC showed significantly longer survival with vemurafenib (13.6 months) vs DITC (9.7 months) with an HR of 0.70 (95% CI: 0.57 – 0.87; p < 0.001).~~

~~Despite this major initial progress in the clinical management of unresectable melanoma, severe immune-mediated toxicities and the lack of a validated biomarker for patient selection may restrict the use of ipilimumab while the onset of acquired drug resistance limits the efficacy of vemurafenib. It is widely believed that combination therapies of targeted agents can further improve the effect on survival currently achieved with ipilimumab- and vemurafenib- single agent-therapies [Eggermont, 2011]. However, the recent study report of hepatotoxicity highlighted the risk of concurrent administration of vemurafenib and ipilimumab [Ribas, 2013]. For the approximately 50% of melanoma patients whose tumor harbor a BRAF-V600-activating mutation, a combination of a selective and potent BRAF- and a MEK-inhibitor is favoured to address specific molecular mechanisms of intrinsic and acquired resistance to a BRAF-inhibitor monotherapy [Nissan , 2011].~~

Section 1.2.3. BRAF and MEK Inhibitors as Combination Therapy

Paragraph 4

MEK115306 study is a double blind randomized phase III study that recruited 423 previously untreated metastatic melanoma patients who had BRF V600E or V600K mutation. Eligible patients were randomized to receive dabrafenib 150mg bid plus trametinib 2mg qd, or dabrafenib 150mg bid plus placebo. The primary endpoint was PFS. The results showed the combination significantly improved PFS (median PFS: 9.3 vs 8.8 months, HR=0.75, p=0.03) and response rate (67% vs 51%, p=0.0002) . The interim OS analysis at 6 months showed the survival rate was 93% and 85% in the combination arm vs dabrafenib arm (HR=0.63, p=0.02). However, a pre-defined specific efficacy stopping boundary of OS (two-side p=0.00028) was crossed. So the survival follow-up is still on-going as of December 2014.

In this study, 9% patient from combination treatment arm and 5% from dabrafenib monotherapy arm permanently discontinued study medication before disease progression. In addition, dose reduction was required in 25% and 13% of patients receiving combination and dabrafenib monotherapy, respectively.

The adverse event profile of combination treatment was different from dabrafenib monotherapy. The patients who received combined treatment experienced more frequent pyrexia(51% vs 28%), chill(30% vs 16%), diarrhea(24% vs 14%), hypertension(22% vs 14%), vomiting(20% vs 14%), peripheral edema(14% vs 5%), elevated ALT (11% vs 5%) or AST (11% vs 3%), decreased left ventricular ejection fraction(LVEF)(4% vs 2%), dermatitis acneiform(8% vs 3%), but less frequent cutanenous squamous-cell carcinoma(2% vs 9%), hyperkeratosis(3% vs 32%), skin papilloma(1% vs 21%), hand-foot syndrome(5% vs 27%), dry skin(9% vs 13%), pruritus(8% vs 12%) and alopecia(7% vs 26%). [Long, 2014]

MEK116513 study is an open lable randomized phase III study that recruited 704 previously untreated metastatic melanoma patients who had BRF V600E or V600K mutation. Eligible patients were randomized to receive dabrafenib 150mg bid plus trametinib 2mg qd, or vemurafenib 960mg bid. The primary endpoint was overall survival. At an pre-planned interim analysis, this study demonstrated the combination of dabrafenib plus trametinib achieved significant OS improvement (12 months OS rate: 72% vs 65%, HR: 0.69, p=0.005) and this result crossed the pre-defined interim stopping boundary. Therefore this study was stopped pre-maturely because of the efficacy. The combination treatment also significantly improved PFS (median PFS: 11.4 vs 7.3 months, HR: 0.56, p<0.001) and response rate (64% vs 51%, p<0.001).

Rates of study-drug discontinuations were similar in the two groups(13% in combination arm and 12% in vemurafenib arm). Adverse events leading to dose reduction was reported in 33% of patients in comintation arm and 39% in the vemurafenib arm.

The most frequent adverse events in the combination-therapy group were pyrexia (53%), nausea (35%), diarrhea (32%), chills (31%), fatigue (29%), headache (29%), and vomiting (29%). In the vemurafenib group, the most frequent adverse events were arthralgia (51%), rash (43%), alopecia (39%), diarrhea (38%), nausea (36%), and fatigue (33%). Skin toxic effects were more frequent in the vemurafenib group than in the combination-therapy group, in particular rash (43% vs. 22%), photosensitivity reaction (22% vs. 4%), hand–foot syndrome (25% vs. 4%), skin papillomas (23% vs. 2%), squamous-cell carcinomas and keratoacanthomas (18% vs. 1%), and hyperkeratosis (25% vs. 4%). Pyrexia was more frequent in the combination-therapy group than in the vemurafenib group (53% vs.

21%).Grade 3 or 4 adverse events occurred in 52% of the patients in the combination-therapy group and in 63% of those in the vemurafenib group. Three fatal events occurred in each group; all were deemed by the investigator to be unrelated to the study drug.[Robert, 2015],

Section 1.2.3.1. Dabrafenib and Trametinib in Acral Lentiginous Melanoma

Paragraph 4

In conclusion, currently available treatments for melanoma (all types) including ipilimumab, pembrolizumab, nivolumab, vemurafenib, dabrafenib, and trametinib are effective monotherapy treatments. Combination of MEK and BRAF inhibitor has become the standard treatment for metastatic melanoma with BRAF V600 mutation. ~~Combination therapy with ipilimumab and vemurafenib may not provide an optimal risk/benefit ratio due to potential hepatotoxicity. Exploration of other combinations, such as dabrafenib and tramentinib, is warranted. In Part C of the BRF113220 study, statistically significant and clinically meaningful improvements in PFS were observed.~~

In Asian population, approximately 25.5% of all melanoma patients and 15.5% of ALM have BRAF V600 muataion [Lu, 2011]. There are no PK data in Chinese patients. Preliminary PK data obtained in Japanese patients showed there no major ethnic difference in the pharmacokinetic profile of trametinib or dabrafenib when administered in monotherapy (Study BRF116056 and MEK114784), however, exposure to dabrafenib and trametinib tended to be higher when administered in combination [Study MEK116885 COMBO-IB].

~~Limited d~~ Data in subjects with acral lentiginous melanoma subtype or Asian population was limited and further exploration in these populations is warranted. ~~also showed promise in extending survival. This study aims to further evaluate the efficacy and safety of dabrafenib and trametinib in acral lentiginous melanoma, which represents an unmet medical need in non-Caucasians.~~

This study was originally intended to enroll subjects with acral lentiginous melanoma. ~~however based on a lower than expected BRAF v600 E/K mutation rate in this population, t~~ The eligibility criterion has been amended to include cutaneous melanoma in light of the advance in the management of metastatic melanoma with BRAF V600 mutation.

Section 1.3 Rationale

Point no. 3

Data from the ongoing BRF113220 study (Part C) and 2 randomized phase III study evaluating the combination of dabrafenib and trametinib demonstrated promising clinical activity and an acceptable clinical safety profile of the dabrafenib and trametinib combination given at full single-agent dose

Point no. 4

Limited data are available in non-Caucasian populations ~~where cutaneous melanoma sub-types such as~~ ALM ~~may be more prevalent~~.

~~Early safety and efficacy data, together with limited data in ALM subjects enrolled in dabrafenib and trametinib clinical trials, support the rationale and design of this Phase II study of the combination of dabrafenib and trametinib in unresectable V600E- and V600K-BRAF-mutant acral lentiginous melanoma subjects.~~

Section 1.4.1. Benefit Assessment

Current research suggests that combination therapies of BRAF- and MEK-targeted agents can further improve the effect on survival currently achieved with BRAF inhibitor monotherapy [Long, 2014, Robert 2015] in metastatic melanoma patients with BRAF V600 mutation. Patients treated with combination of trametinib and dabrafenib can achieve a 6 months survival rate of 93% [Long, 2014] and 12 months survival rate of 72% [Robert, 2015]. ~~ipilimumab- and vemurafenib- single agent-therapies [Eggermont, 2011]. For the approximately 50% of melanoma patients whose tumor harbor a BRAF V600-activating mutation, a combination of a selective and potent BRAF- and a MEK-inhibitor is favored to address specific molecular mechanisms of intrinsic and acquired resistance to a BRAF-inhibitor monotherapy [Nissan, 2011].~~

Dacarbazine (DTIC), considered the most active of the agents currently available, is approved for metastatic melanoma ~~and widely used in clinical practice~~ [Huncharek, 2001] and widely used in clinical practice in Asian countries. The benefit of DTIC remains small, with median progression-free survival lasting approximately 2 months and median overall survival of approximately 7 months.

There are no PK data in Chinese patients. Preliminary PK data obtained in Japanese patients showed there no major ethnic difference in the pharmacokinetic profile of trametinib or dabrafenib when administered in monotherapy (Study BRF116056 and MEK114784), however, exposure to dabrafenib and trametinib tended to be higher when administered in combination (Study MEK116885). However, ~~In Asian patients there was no pharmacokinetic difference observed with trametinib, dabrafenib or the combination, compared with Caucasian patients. Therefore,~~ the planned dose of study medication is expected to be tolerable in the study population and bring clinical benefit.

Section 1.4.2. Overall Benefit: Risk Conclusion

Paragraph 1

To date, over 1000 subjects, of predominantly Caucasian ethnicity and with majority of BRAF V600 mutated ~~metastatic~~ melanoma have received this combination regimen in 5 phase I/II studies and 3 phase III studies. The complete list of these studies can be found in the IB. ~~the completed Phase I/II study BRF113220 and the ongoing Phase III combination clinical trials. The Phase I/II Study BRF113220 is a 4-part study that included a randomized Phase II component (Part C). Part C of this study allowed for a direct comparison of the safety profile of combination therapy relative to dabrafenib monotherapy in a metastatic melanoma population. In addition, comprehensive safety data dabrafenib or trametinib as a monotherapy regimen enabled a comparison between the specific safety profile of the combination regimen and the individual components. Dabrafenib and trametinib have independently demonstrated~~

~~significant clinical benefit in randomized Phase III trials extending the progression-free survival of subjects with metastaticV600 BRAF-mutation positive melanoma as compared to standard chemotherapy.~~

Paragraph 3

The safety profile for the combination treatment of dabrafenib 150 mg twice daily and trametinib 2 mg once daily in subjects with unresectable or metastatic melanoma with a BRAF V600 mutation is defined by the results of the pivotal Phase III Study MEK115306 and MEK116513 and supported by the BRF113220 pooled combination therapy population.

Paragraph 4

The combination therapy has a higher rate of pyrexia, fatigue and nausea, while lower incidences of hyperkeratosis, alopecia and skin papilloma were observed compared with dabrafenib monotherapy. Relative to trametinib monotherapy, there was a higher incidence of fatigue, nausea, and vomiting observed but lower incidences of rash and diarrhea with combination therapy.

The risk-to-benefit ratio in this patient population remains favorable.

~~The dabrafenib/trametinib combination may decrease the frequency or severity of some toxicities previously observed with trametinib monotherapy such as skin-related toxicities (e.g., rash and dermatitis acneform). The safety profile of the combination therapy is primarily impacted by the emergence of a higher rate of pyrexia. While fatigue and nausea occur at a higher frequency relative to dabrafenib monotherapy, lower incidences of hyperkeratosis, alopecia, and skin papilloma are observed. Relative to trametinib monotherapy, there was a higher incidence of fatigue, nausea, and vomiting observed but lower incidences of rash and diarrhea with combination therapy. AEs resulting in dose reduction or interruption occurred more frequently with combination treatment. Despite this, the incidence of permanent discontinuation remained consistent with trametinib monotherapy suggesting that tolerability can be managed effectively with proper guidance to the prescribing physician. The incidence of serious adverse events (SAEs), which included all cases of pyrexia, was 2 to 3 fold higher in combination compared with either drug alone, primarily due to the inclusion of pyrexia cases regardless if they met the formal definition of SAE. Fatal SAEs remain infrequent with combination therapy. AEs of special interest were identified independently for both dabrafenib and trametinib based on the frequency and the potential association with the mode of action of BRAFand MEK- inhibitors. An extensive review of skin-related events, cardiac-related events, hepatic events, pneumonitis, ocular events, hypertension, and diarrhea appeared to be consistent with the known AE profiles of either dabrafenib or trametinib. The incidence of treatment-emergent malignancies and new primary melanoma observed in melanoma subjects receiving the dabrafenib and trametinib combination therapy was consistent with what has been observed so far in the dabrafenib safety population. No additional AEs of special interests were identified for the combination regimen. The most notable finding in the combination study was the reduced frequency of hyperproliferative skin diseases including keratoacanthoma and cuSCC noted in subjects treated with the dabrafenib and trametinib combination regimen compared to subjects treated with dabrafenib alone.~~

~~Thus, the non-clinical hypothesis that addition of trametinib abrogates the paradoxical MAP-kinase pathway excerted by BRAF-inhibitors such as dabrafenib in keratinocytes harboring upstream pathway activation has been substantiated. Pyrexia, a commonly noted AE associated with BRAF inhibition, occurred more frequently in combination compared with dabrafenib monotherapy. Most cases were of mild to moderate severity and occurred early during combination treatment. While temporary dosing modifications and supportive therapy led to a resolution of pyrexia, hospitalization was required in a number of cases due to additional complicating events including acute renal failure.~~

~~In conclusion, the combination of dabrafenib 150 mg two times a day and trametinib 2 mg once daily offers a unique treatment combination that has a predictable safety and tolerability profile that is based on the known profiles of each drug. Some commonly expected toxicities occur more frequently when these drugs are combined but appear to be managed clinically in a manner consistent with recommendations associated with monotherapy treatment. In addition, nonclinical and clinical data indicate that the combination also attenuates an important safety concern with the administration of BRAF inhibitors; namely the induction of hyperproliferative effects such as cutaneous squamous cell carcinoma.~~

Section 2. Objectives and endpoints

Rationale for change(s):

China is running the regulatory required China alone PK studies. The data from those studies are sufficient and it is no need to process additional single dose PK testing in this study.

REVISED TEXT

Objectives	Endpoints
Primary	
• To determine the objective response rate (ORR) of dabrafenib in combination with trametinib in subjects with BRAF V600E/K mutation-positive, unresectable or metastatic acral lentiginous <u>or cutaneous</u> melanoma ~~(ALM)~~	• ORR defined as the percentage of subjects with evidence of a confirmed complete response (CR) or partial response (PR) as per RECIST v1.1 [Eisenhauer, 2009].
Secondary	
1. To assess ~~single dose (Chinese subjects only) and~~ steady state (all subjects) exposures to dabrafenib, dabrafenib metabolites, and trametinib, and characterize the population pharmacokinetics and pharmacodynamics of dabrafenib and trametinib	• Trametinib, dabrafenib and dabrafenib metabolites concentrations by visit. Noncompartmental PK parameters include trametinib, dabrafenib and dabrafenib metabolites Cmax, tmax, Ctrough, AUC(0-t), and AUC(0-8); AUC(0-12) (dabrafenib and

Objectives	Endpoints
	dabrafenib metabolites only), AUC (0-24) (trametinib only) and the dabrafenib metabolite to dabrafenib ratio of AUC(0-12). Population PK parameters include, apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and absorption rate constant (Ka) for dabrafenib and trametinib.

Section 3 Study Design

Rationale for change(s):

To well-define the definition of study completion and avoid confusion caused.

REVISED TEXT

Section 3.1 Study Design

Paragraph 2

This is an open-label, Phase II, multi-center study to evaluate the objective response rate of dabrafenib and trametinib combination therapy in subjects that have BRAF V600E/K mutation-positive ALM or cutaneous melanoma.

Subjects will continue study treatment until disease progression, death, unacceptable toxicity, withdrawal of consent, or study ~~closure~~ completion closure. After treatment discontinuation, subjects will be followed for survival and disease progression as applicable.

The study completion is defined as:

- In case all subjects stop study treatment within 48 weeks after Last Subject First Visit(LSFV): the study is completed once the last subject has completed the 48 weeks survival follow-up or all subjects die or loss to follow-up, whichever comes first.
- In case some subjects are still on study treatment 48 weeks after LSFV: the study is completed once all subjects stop study medication, or all subjects who are still on study medication can have access to alternative supply of MEK/BRAF inhibitors, whichever comes first.

~~The study will be closed once 70% of the total enrolled study population has died or been lost to follow-up.~~

Section 4 Subject selection and discontinuation/completion criteria

Rationale for change(s):

1. Changing the criteria to meet local regulatory requirement in certain country (eg. In certain countries, legal adult age is greater than 20 years).
2. Specified the method of BRAF mutation testing and updating the wordings to be in line with asset required language.

REVISED TEXT

Section 4.1.2 Inclusion criteria

Inclusion criteria No. 2

≥18 years of age (or of legal adult age in countries where legal adult age is greater than 18 years),

Inclusion criteria No. 3

Histologically confirmed acral lentiginous or cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E/K mutation-positive~~. Note: BRAF V600E/K mutation status for study eligibility should be determined using direct sequencing or PCR method.~~ [redacted]. The ~~test~~assay will be conducted ~~at~~ by a ~~GSK designated~~ central reference laboratory. ~~If data warrants the development of a companion diagnostic assay, the screening tissue may be subject to additional testing of BRAF mutations.~~ Subjects with ocular or mucosal melanoma are not eligible.

Inclusion criteria No. 8

Women of child-bearing potential (see Section 7.3.7 for definitions) must have a negative serum pregnancy test within ~~7~~ 14 days of first dose of study treatment and agree to use effective contraception, as stated in Section 7.3.7 from 14 days prior to enrollment, throughout the treatment period and for 4 months after the last dose of study treatment.

Table 2 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
Platelet count	≥ ~~75~~ 100 x 10^9/L

b. Except subjects with known Gilbert's syndrome.

Section 4.1.3 Exclusion criteria

Exclusion criteria No. 1

Known non-acral lentiginous cutaneous,primary mucosal or ocular melanoma.

Exclusion criteria No. 2, 3 and 4 merged as Exclusion criteria No.2

Prior treatment with a BRAF inhibitor (including but not limited to dabrafenib, vemurafenib, LGX818, and XL281/BMS-908662) or a MEK inhibitor (including but not limited to trametinib, AZD6244, and RDEA119). ~~(Note: Ipilimumab treatment must end at least 8 weeks prior to enrollment.)~~ Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, ~~biologic~~biological anti-cancer therapy, or ~~immunotherapy~~immunol anti-cancer therapy within 21 days prior to enrollment /or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to enrollment. . (Note: Ipilimumab, pembrolizumab and nivolumab treatment must ended at least 8 weeks prior to enrollment).

Exclusion criteria No. 3 (Amended)

Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to enrollment (Note: in case ipilimuamb, pembrolizmab and nivolumab are investigational drug in the regions and countries, and in case of PD-L1 antibody, these investigational treatment shall be ended at least 8 weeks prior to enrollment).

Exclusion criteria No. 6 (Amended)

~~Known Human Immunodeficiency Virus (HIV),~~ A history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (subjects with ~~the exception~~ laboratory evidence of ~~chronic or~~ cleared HBV and/or HCV ~~infection which~~ will be permitted).

Exclusion criteria No. 7 (Amended)

Leptomeningeal or brain metastases or metastases causing spinal cord compression that are: symptomatic or untreated or not stable for 3 months (must be documented by imaging) or requiring corticosteroids. Subjects on a stable dose of corticosteroids >1 month or who have been off of corticosteroids for at least 2 weeks can be enrolled with approval of the GSK medical monitor. Subjects must also be off of enzyme-inducing anticonvulsants for >4 weeks.

~~Brain metastasis are excluded unless:~~

1. ~~All known lesions have been definitively treated with surgery or stereotactic surgery (whole-brain radiation may be given as adjuvant treatment), OR~~
2. ~~Brain lesion(s), if still present, must be confirmed stable (i.e., no increase in lesion size) for ≥ 12 weeks prior to enrollment (stability must be confirmed with two consecutive magnetic resonance image (MRI) or computed tomography (CT) scans with contrast, separated by >6 weeks~~

~~AND~~

- ~~Asymptomatic with no corticosteroid requirements for ≥ 4 weeks prior to enrollment, AND~~
- ~~No enzyme inducing anticonvulsants for ≥ 2 weeks prior to enrollment~~

~~In addition, for subjects that had brain metastases but currently have no evidence of disease (NED), NED for ≥12 weeks is required and must be confirmed by two consecutive scans, separated by ≥6 weeks, prior to randomization.~~

Exclusion criteria No. 8 (Amended)

History of ~~another~~ malignancy other than disease under study within 3 years, of study enrolment with exceptions below. Exception: Subjects ~~who have been disease-free for 3 years, (i.e.~~with a history of completely resected non-melanoma skin cancer, or subjects with indolent second malignancies are eligible.

Exclusion criteria No. 9 (Amended)

History of malignancy with confirmed activating RAS mutation at any time. Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

Exclusion criteria No.10 (Amended)

Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.

Exclusion criteria No.11 (Amended)

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

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

Clarification ~~**Exception:**~~ Subjects with atrial fibrillation controlled for > 30 days prior to dosing ~~enrollmen~~t are eligible.

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

e. A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines (Appendix 3);

f. Patients with intra-cardiac defibrillators;

g. Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;

~~h. Subjects with intra-cardiac defibrillators or permanent pacemakers;~~

~~i. Known cardiac metastases;~~

Exclusion criteria No.17 (Amended)
Interstitial lung disease or pneumonitis.

Section 4.2.1. Permanent Discontinuation from Study Treatment

Paragraph 1
Note: Subjects who are experiencing progression of disease (by RECIST, version 1.1) but are receiving clinical benefit based on the investigator's assessment, may be allowed to continue study treatment (see Section 4.2.2).) with the agreement of sponsor's medical monitor.

Paragraph 8
Survival and new anti-cancer therapy follow-up will continue until ~~70% of the total enrolled study population has died or been lost to follow-up.~~ study completion.

Section 4.2.3. Subject Completion Criteria
A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period. The cause of death will be documented in the eCRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, or has withdrawn consent, ~~at the investigator's discretion is no longer being followed~~ or if the study is ~~closed or terminated~~ completed. The definition of study completion was described in protocol Section 3.1.

Section 5 Study Treatments

Rationale for change(s):
1. To further clarify how to take study treatment properly and to update wordings to be in line with asset required language.
2. Changing typo in the original protocol.
3. Updating dose adjustment processed based on results of recent reported studies.

REVISED TEXT
Section 5.2. Dosage and Administration
- Dabrafenib, 150 mg, BID;
- Trametinib, 2.0 mg, once daily.

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

Paragraph 4

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

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

~~Subjects should start treatment as soon as possible after enrollment but no later than 7 days post-enrollment.~~

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

Section 5.3. Handling and Storage of Study Treatments

~~Under normal conditions of handling~~ Dabrafenib and ~~administration, investigational product is not expected to pose significant safety risks to site staff. Material Safety Data Sheet (MSDS) describing the occupational hazards~~ trametinib must be dispensed and ~~recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.~~

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

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

Section 5.8.1. Dose Levels of dabrafenib and trametinib

Paragraph 2

A dose reduction below 50~~75~~ mg BID for dabrafenib or below 1 mg once daily for trametinib is not allowed. If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued but these subjects will be allowed to continue trametinib.

Section 5.8.3.1. Left Ventricular Ejection Fraction (LVEF)

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 trametinib~~study treatment~~ and repeat ECHO within 2 weeks[a] • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) o Consult with the GSK medical monitor and request approval for restart o If approve, r~~R~~estart treatment with trametinib reduced by one dose level ~~o Restart dabrafenib at previous dose level~~ o Repeat ECHO at 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 o Consult with cardiologist o Permanently discontinue trametinib o Report as SAE o Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution ~~Consult with GSK medical monitorc~~
Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• Permanently discontinue ~~study treatment~~ tramatinib[b] • Interrupt dabrafenib.[d] • Report as SAE • Consult with cardiologist • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[b,d]

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

b. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.

c. If recurrent episodes of LVEF reduction occur in subjects receiving dabrafenib monotherapy, consult medical monitor.

~~a.~~

b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

c. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.~~Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.~~

Section 5.8.3.3. QT Prolongation

Table 8. Withholding and Stopping Criteria for QTc-Prolongation

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

Abbreviations: msec = milliseconds; QTc = QT interval on electrocardiogram corrected

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

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

Section 5.8.5. 1. Guidelines for Pyrexia

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy , and is increased in incidence and severity in subjects receiving dabrafenib~~or~~ in combination with trametinib [GlaxoSmithKline Document Number CM2010/00010/03 and GlaxoSmithKline Document Number 2011N126811_02]. In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

~~Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE as per Section 7.3.10.~~

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

~~rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully.~~ \

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

Table 12 Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification

Pyrexia[a]	All Events: • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d] 1st Event[b]: • ~~Clinical evaluation for infection and hypersensitivityc~~ • ~~Laboratory work-upc~~ • ~~Hydration as requiredd~~ • ~~Blood sample for cytokine analysise~~ • Administer anti-pyretic treatment as~~if~~ clinically indicated and initiate ~~continue~~ prophylactic treatment if associated with rigors, renal failure, dehydration or hypotension[e f] 2nd Event[f~~g~~] • ~~Clinical evaluation for infection and hypersensitivityc~~ • ~~Laboratory work-upc~~ • ~~Hydration as requiredd~~ • ~~Blood sample for cytokine analysise~~ • Within 3 days of onset of pyrexia o Optimize anti-pyretic therapy o Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[f~~g~~] Subsequent Events: • ~~Clinical evaluation for infection and hypersensitivityc~~ • ~~Laboratory work-upc~~ • ~~Hydration as requiredd~~ • ~~Blood sample for cytokine analysise~~ • W~~w~~ithin 3 days of onset of pyrexia: o Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f~~g~~] o If corticosteroids have been tapered and pyrexia recurs, restart steroids o If corticosteroids cannot be tapered consult medical monitor	1st Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** 2nd Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]** Subsequent Events: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[g~~h~~]** • If dabrafenib must be reduced to <50~~75~~ mg BID, permanently **discontinue dabrafenib. Trametinib may be continued**

Adverse Event	Adverse Event Management	Action and Dose Modification

~~e.~~ ~~Blood sample for cytokine analysis should be taken immediately at the first occurrence of fever (i.e. when the subject visits the clinic) and after the fever has disappeared (i.e. during the next routine visit), samples must be sent to the central laboratory.~~

ef. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia

fg. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.

g~~h~~. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

Section 5.8.5.4. Guidelines for Visual Changes or Specified Ophthalmic Examination Findings

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

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

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

Table 15 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	1. Consult ophthalmologist within 7 days of onset ~~Exclude CSR or RVO~~ ~~Consult retinal specialist in case of CSR or RVO~~ ~~Report RVO as SAE~~ ~~Continue follow up examination(s) by retinal specialist for CSR and RVO~~	~~2. Continue study treatment at the same dose level until ophthalmologic examination can be conductedb~~ ~~3. If ophthalmologic examination cannot be performed within 7 days of onset, interrupt study treatment until CSR and RVO can be excluded and symptoms resolve~~ ~~4. Restart study treatment at same dose level~~ ~~5. CSR: Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution~~ ~~6. Restart with study treatment reduced by one dose level~~ ~~7.~~ If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued. ~~8.~~ If RPED and RVO excluded, continue (or restart) trametinib at same dose level ~~9.~~ If RPED suspected or diagnosed: see RPED dose modification table Y below; **report as SAE if diagnosed.** ~~10.~~ If RVO: **Permanently discontinue study treatment**
Grade 2 and Grade 3	11. Consult ophthalmologist immediately 1. Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued. ~~Exclude CSR and RVO~~ ~~Consult retinal specialist in case of RVO or CSR for follow-up exam~~ ~~Report RVO as SAE~~ ~~Continue follow up examination(s) by retinal specialist for CSR and RVO~~	~~2. Interrupt study treatment until signs and symptoms have resolved to baseline~~ ~~3. Restart with study treatment reduced by one dose level~~ 4. ~~CSR: Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution Restart study treatment reduced by one dose level~~ 5. If RPED and RVO excluded, restart trametinib at same dose level. **12.** If RPED diagnosed, see RPED dose modification table below; **report as SAE.** **13.** If RVO: **Permanently discontinue ~~study treatment~~trametinib and report as SAE.**

Grade 4	14. Consult ophthalmologist immediately 15. Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued. ~~16. Exclude CSR and RVO~~ ~~17. Report RVO as SAE~~ 18. ~~Continue follow up examination(s) by retinal specialist for CSR and RVO~~	**19.** If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor **20. If RVO or RPED diagnosed, p~~P~~ermanently discontinue ~~study treatment~~trametinib and report as SAE.**

Abbreviations: RPED = retinal pigment epithelial detachment; ~~CSR = central serous retinopathy;~~ CTCAE = Common Terminology Criteria for Adverse Events;

RVO = retinal vein occlusion; SAE = serious adverse event

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

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

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

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	6. Interrupt trametinib 7. Retinal evaluation monthly 8. If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

d. Refers to CTCAE Version 4.0 'Retinopathy'

Ophthalmologic Exam

At certain time points in the trial and if visual changes develop, an eye exam is indicated. (Refer to Section 5.8.5.4 for visual changes stopping criteria). The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

Table 16 Management and Dose Modification Guidelines for Pneumonitis

In Action and Dose modification column "Study Treatment" was replaced by "Trametinib".

Section 6. Concomitant Medications and Non-Drug Therapies

Rationale for change(s): Update of wordings to be in line with asset required language.

REVISED TEXT

Section 6.1. Permitted Medications and Non-drug Therapies

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment ~~with the exception of new anti-cancer therapy, if taken after study treatment discontinuation; these will be documented until study completion/withdrawal or death.~~ Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted, however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.~~provided that INR is monitored in accordance with local institutional practice.~~

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

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

Section 6.3. Treatment after Discontinuation from both Study Treatments or Withdrawal from/Completion of the Study

Paragraph 4

Upon study ~~closure~~ completion, if some subjects are still on study treatment and have not yet progressed, their follow-up treatment will be at the discretion of the attending physician. ~~subjects who are still receiving study treatment will have the option to transition to BRF114144, in which they may continue to receive study treatment.~~

Section 6.4. Treatment of Study Treatment Overdose

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

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

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

Table 19. Time and Events Table

STUDY PHASES[1]	SCREENING 2	TREATMENT					FOLLOW-UP		
		Day 1	Day 15	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Treatment Discontinuation[28]	Contact	Conclusion
Visit Window (Days)	**(≤ 28 except where noted)[2]**		**(± 3)**	**(± 3)**	**(± 7)**	**(± 7)**	**(± 7)**	**(± 7)**	**N/A**
SAFETY ASSESSMENTS[1]									
Dermatological examination (including skin lesion photography)[10]	X				X		X		
Pharmacokinetics blood collection[21]		~~X~~	X						
~~Blood sample for cytokine analysis24~~		~~X~~		~~X24~~					

Point No.10. A full skin exam will be done every 8 weeks. Photographic images are required to assess hyperproliferative skin diseases. Upon study treatment discontinuation, a final skin exam is required within 8 weeks of the last dose of study treatment.

Point No. 21. Blood samples for PK analysis will be drawn on Day 15 at predose (within 30 minutes prior to dosing) and 1, 2, 4, 6, and 8 hours after dosing. For subjects in China, PK blood samples will be drawn at predose (within 30 minutes prior to dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after dosing on Day ~~1 and Day~~ 15. Refer to Section 7.5 for details on pharmacokinetic blood sampling.

Point No. 24. ~~A blood sample for potential analysis of cytokines is mandatory at Screening and at week 4. Subsequent cytokine samples should also be collected if indicated (See Section 5.8.5.1 Management Guidelines for Pyrexia and Table 12).~~.

Point No. 27. After treatment discontinuation, any new anti-cancer therapy initiated will be recorded until study completion/withdrawal /lost to follow-up, or death.

Section 7. Study Assessments and Procedures

Rationale for change(s):

Adding cutaneous melanoma to reflect the criteria change. Wordings are changed according to data and conclusion from the current reported studies. Specifying the country specific requiment of SAE reporting.

REVISED TEXT

Section 7.2.1. Efficacy Endpoints

Section 7.2.1.1. Primary Efficacy Endpoint

The primary endpoint for this study is objective response rate of dabrafenib in combination with trametinib in subjects with BRAF V600E/K mutation-positive, unresectable or metastatic

acral lentiginous or cutaneous melanoma (ALM). Objective response rate is defined as the percentage of subjects with evidence of confirmed complete response (CR) or partial response (PR) as per RECIST v1.1 [Eisenhauer, 2009]

Section 7.2.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoint of this study are:

- Duration of response, defined as the time from first documented evidence of CR or PR until the earliest date of documented radiological progression or death due to any cause among subjects who achieve a confirmed response (i.e. confirmed CR or PR)
- PFS, defined as the time from first dose of study treatment until the first date of either objective disease progression or death due to any cause.
- OS, defined as the interval between the treatment start date and the date of death due to any cause.
- ~~PFS, defined as the time from first dose of study treatment until the first date of either objective disease progression or death due to any cause.~~
- ~~OS, defined as the interval between the treatment start date and the date of death due to any cause.~~

Section 7.2.2.2. Follow-up Assessments for Subjects Permanently Discontinued from both Study Treatments

Paragraph 2

All subjects who permanently discontinue both study treatments without disease progression will have radiographic disease assessments performed on the same assessment schedule noted in the Time and Events Table 19 until disease progression, death, starting of another anti-cancer treatment(including radiotherapy), or withdrawal of consent, whichever is documented first.

Section 7.2.4. Response Criteria

Section 7.2.4.1. Evaluation of Target Lesions

Point No.5

- ~~Not Applicable (NA): No target lesions at baseline.~~

Section 7.3.2.2. Definition of an SAE

Point No. g. Protocol-specific SAEs:

- All events of possible drug-induced liver injury with hyperbilirubinemia 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 and new primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator. ~~Any new malignancy with a histology different from the primary tumor, including cutaneous squamous cell carcinoma, basal cell carcinoma and new primary malignant melanoma.~~
- ~~Laboratory abnormalities as referenced in Section 7.3.3.~~
- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance (Section 6.8.3.1)
- ~~LVEF that meets stopping criteria Section 5.8.3.1~~
- Retinal pigment epithelial detachment (RPED) or retinal vein occlusion (RVO)
- ~~CSR or RVO~~
- ~~Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills~~

Section 7.3.7. Pregnancy Testing, Prevention and Reporting

Section 7.3.7.1. Pregnancy Testing and Prevention

Paragraph 5

If a female subject is of childbearing potential, she must have a serum β-human chorionic gonadotropin (HCG) pregnancy test performed within ~~14 days prior to enrollment~~7 days of first dose of study treatment. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below throughout the treatment period and until 6 months after the last dose of study treatment.

Section 7.3.8. Time Period and Frequency of Detecting AEs and SAEs

Paragraph 2

Adverse events (AEs) will be collected from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment regardless of initiation of a new anti-cancer therapy or transfer to hospice. In China, SAEs will be recorded from the time the consent form is signed. For all other countries, SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.

Section 7.3.11. Other Safety Outcomes

Table 21. Clinical Chemistry and Hematology Parameters

Hematology Parameters
White Blood Cell (WBC) Count Hemoglobin Hemoglobin A1C Hematocrit International Normalized Ratio (INR; at Screening only)[a] Platelet Count Prothrombin Time (PT; at Screening only)[a] Partial Thromboplastin Time (PTT; at Screening only)[a] Automated WBC Differential (expressed as Gl/L%): Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Other tests
Amylase and lipase [monitor via local laboratory where appropriate to evaluate certain AEs (i.e., abdominal pain, pancreatitis, etc.)]
serum β-hCG (human chorionic gonadotrophin)
For subjects with a history of chronic HBV and/or HCV, the following tests will be performed at Screening: • Viral hepatitis serology; • Hepatitis B surface antigen and Hepatitis B core antibody (IgM); and/or • Hepatitis C RNA

a. Coagulation panel to be done at Screening only.

b. Bilirubin fractionation is recommended if total bilirubin is > 2 x the upper limit of normal (ULN).

c. .If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockcroft-Gault formula (Appendix 2).

Section 7.5.2. Sample Analysis

Plasma analysis will be performed under the control of GSK Platform Technology and Science (PTS)-Drug Metabolism and Pharmacokinetics (DMPK)/Scinovo, the details of which will be included in the Study Procedures Manual. Concentrations of carboxy-dabrafenib will be determined in plasma samples using a separate assay using the currently approved analytical methodology. ~~Concentrations of dabrafenib and its metabolites (hydroxy- and desmethyl -dabrafenib) and trametinib will be determined in plasma samples using the currently approved analytical methodology.~~ Raw data will be stored in the Good Laboratory Practice (GLP) Archives, GlaxoSmithKline.

Section 9. Data Analysis and Statistical Considerations

Rationale for change(s):

Even though the study target population is explored from acral melanoma to both acral or cutanous melanoma, the study hypothesis is remaining the same as the efficacy expected would remain the same.

REVISED TEXT

Section 9.1. Hypotheses

The primary objective is to determine the objective response rate (ORR) of dabrafenib in combination with trametinib in BRAF V600E/K mutation-positive unresectable or metastatic acral lentiginous or cutaneous melanoma subjects.

Paragraph 5

Even though, in the protocol amendment 1, the study population was extended to both acral and cutanenous melanoma, the hypothesis (Ho:25% & Ha: p=50%) will remain the same, because the expected efficacy of study medication in the new population is similar as the previous assumption.

Section 9.3.3.1. Primary Comparisons of Interest

The primary objective will be supported by the calculation of objective response rate using the ATS population. The final analysis of ORR will be performed after 35 subjects have been treated for 16 weeks or have otherwise discontinued study treatment.

Subjects will continue to be followed for survival until ~~70% of the total enrolled population has~~ death, ~~died or been~~ lost to follow-up, or study completion. The definition of study completion is described in Section 3.1.

Section 9.3.5.1.2. Secondary Efficacy Analyses

Progression-Free Survival (PFS)

~~Progression free survival and overall survival will be summarized descriptively using Kaplan-Meier medians and quartiles.~~

PFS will be defined as the time from first dose until the first date of either objective disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of radiological or photographic disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment or first dose for subjects without any adequate post baseline assessments. In addition, subjects with an extended loss to follow-up or who start new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Progression free survival will be summarized descriptively using Kaplan-Meier medians and quartiles.

-Further details on censoring rules will be outlined in the RAP.

Overall Survial (OS)

OS is defined as the time from first dose until death due to any cause. For subjects who have not died, time to death will be censored at the last date of known contact

OS will utilize all cause mortality and censoring will be performed using the date of last known contact for those who are alive at the time of analysis. OS will be summarized descriptively using Kaplan-Meier medians and quartiles.

Duration of Response

If sample size permits (i.e. a sufficient number of subjects with confirmed CR or PR) duration of response will be summarized descriptively using Kaplan-Meier medians and quartiles. ~~Only the subset of subjects who show a confirmed complete or partial tumor~~

~~response will be included.~~ Duration of Response for the subset of subjects with a confirmed CR or PR is defined as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause. Censoring rules for duration of response will follow the rules for PFS and will be outlined in detail in the RAP.

Section 10. Study Conduct Considerations

Rationale for change(s):

To well-define the definition of study completion and avoid confusion caused.

REVISED TEXT

Section 10.5. Study and Site Closure

The study will close when it is completed, as defined in Section3.1 ~~considered closed when 70% of the total enrolled study population has died or been lost to follow-up, which is estimated to be approximately 3 years after the start of the study~~.

Amendment 2 (Country-Specific Amendment for the Korea)

Rationale for change(s):

According to the safety data update, it was discussed and agreed to remove ophthalmic exclusion criteria, with the exception of the exclusion criterion for patients with a history of RVO, which will remain in place.

Korean regulatory authority commented the exclusion criteria xiii has to clarify not only a history of retinal vein occlusion (RVO) subjects should be excluded, but subjects with current RVO should be excluded.

Protocol Change(s):

Section 4.1.3 Exclusion Criteria Revised Text:

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

Amendment 3 (04 -MAR-2016) from the Amendment 02 (17-Sep-2015)

No	Proposed Change	Sections Affected	Rationale for Change
1	Refer to BRAF V600 mutation instead of BRAF V600 E/K throughout the protocol.	Title, Protocol Summary, Section 1.3, Table 1, Section 3.1, Section 4.1.2, Table 20, Section 7.1.1, Section 7.2.1	To be consistent will other protocols on the program.
2	Update Sponsor Signatory	NA	Sponsor signatory changed
3	Update Sponsor Serious Adverse Events (SAE) Contact Information	NA	Contact information changed
4	Addition of information in study rationale.	Protocol Summary	More information about unmet medical need became available.
5	Addition of reference to protocol numbers and acronyms	Section 1.2.3.1	To clarify the studies listed in the background and to be consistent throughout the protocol
[redacted]			

7	Increase sample size and remove 2 stage study design	Section 4.1.1	Increased sample size to fulfil the regulatory needs in China
8	Remove GlaxoSmithKline reference IB version numbers.	Section 4.1.2, Section 5.8.3, Section 5.8.4, Section 5.8.5, Section 9.3.5.4	The most current IB versions have to be used. Therefore, the version number have been removed.
9	Broaden inclusion criteria 3	Section 4.1.2	Remove the requirement to use the [redacted]
10	Addition of inclusion criteria 10: Subjects with East Asian origin.	Section 4.1.2	Specify the race of patients to be enrolled.
11	Adding the definition of Gilbert's syndrome.	Section 4.1.2,	The change is made to further clarify the function limitation for subjects with Gilbert's syndrome.
12	Adding definition of HBV/HCV negative in exclusion criteria 6.	Section 4.1.3	The change is to indicate the definition of HBV/HCV negative to avoid confusion caused.
13	Remove the duplicated exclusion criteria 14 and 15.	Section 4.1.3	Deleting duplicated criteria to avoid being redundant.
14	Clarifying the exclusion criteria 13 related to retinal vein occlusion.	Section 4.1.3	The change in protocol amendment 2 specific to Korea is now implemented to all countries.
15	Clarifying all subjects should be registered in RAMOS regardless of their screening status.	Section 5.4	To clarify that all subjects should be recorded in RAMOS, and not only those who complete the screening requirement.
16	Addition of instructions on how to handle adverse event of uveitis.	Section 5.8.5.4	In ophthalmologic exam, the instruction of handling uveitis is added per program updates.
17	Correcting the sequence number.	Section 5.9.1	The correct sequence number in the list of liver chemistry stopping criteria.

18	Remove the duplicate sentence.	Section 5.9.1	Deleting duplicate criteria to avoid being redundant.
19	Allow re-screening of patients.	Section 7	Allow patients to be re-screened and clarify that there is no need to repeat the BRAF mutation test if the positive results have been confirmed by the central lab.
20	Relevant cardiac and cancer family history should be recorded at screening.	Table 20	Typo correction.
21	Allow sites to resend tumor sample for BRAF testing.	Table 20	The sites would be allowed to re-send the tissue sample for mutation testing in case the samples are not fulfill quality requirement.
22	Remove Day 15 time point for optional tumor tissue sample collection and corresponding footnote 22 updated.	Table 20	Based on pharmacodynamic data available from previous studies the decision to prioritize the progression tumor sample was taken
23	Remove details regarding the assay to be used.	Section 7.1.1	Assay detail is not required.
24	Correcting the duration of contraception after last dose.	Section 7.3.7.	The inconsistent information should be corrected.
25	Remove the contraception duration requirement to the male subjects with a female partner of childbearing potential.	Section 7.3.7.1	To be aligned with the asset specific protocol language.
26	Remove pharmacodynamics section.	Section 7.4.3	[redacted]

			[redacted]
27	Update the study hypotheses and remove 2 stage design.	Section 9.1	The study is pursuing an estimation strategy.
28	Increase sample size.	Section 9.2	The target enrolment number is increased to 65 to fulfil registration purposes.
29	Increase sample size.	Section 9.3.3.1	The final analysis of ORR will be performed on the increased number of patients.
30	Remove the need for an interim analysis	Section 9.3.4	The section is no longer applicable since two stages of analysis was removed.

Amendment 4 (25-Oct-2016) from the Amendment 03 (04-Mar-2016)

No	Proposed Change	Sections Affected	Rationale for Change
1	Revise secondary objectives and endpoints in relation with the updated PK schedule	Section 2 – Table 1	Addition of PK samples in Chinese patients only to assess PK profile after a single dose.
2	Clarify the requirements for enrolment of patients with a history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection	Section 4.1.3	Provide clarity around Exclusion criterion#6 and consistency with Table 22.
3	Addition of the optional non-melanoma skin biopsy	Table 20	Correct the omission in previous protocol versions,
4	Add additional PK timepoints on Day 1 and Day 15 in Chinese patients only	Table 20 – footnote 21	Addition of PK samples in Chinese patients only to assess PK profile after a single dose and at steady state.
5	Addition of contraception	Section 7.3.7.1	New language at program level.

	requirements in male participants.		
6	Clarify the lab parameters to be tested at screening in patients with a history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection	Table 22	Provide clarity around the lab parameters to be tested at screening.

Amendment 05 (16-Dec-2016) from the Amendment 04 (25-Oct-2016)

This amendment applies to all investigator sites participating in this study except those in China.

Global Changes

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

Section(s)	Change	Rationale
Multiple	Make administrative changes	To align with the change of sponsorship from GSK to Novartis.
Appendices	References to GSK in figures changed to Novartis	To align with the change of sponsorship from GSK to Novartis.

Revised Text is captured in the format strikethrough=deleted text; underlined=new text.

List of Specific Changes:

Rationale for changes: Change in study sponsorship from GSK to Novartis

List of Abbreviations

The following abbreviation was deleted:

RAMOS	Registration and Medication Ordering System

The following abbreviation has been added:

CRO	Clinical Research Organization

Section '**Trademark Information**' has been deleted

5.1. Investigational Product and Other Study Treatment

REVISED TEXT

5.1.1. Dabrafenib (GSK2118436)

Dabrafenib will be provided as 50 mg and 75 mg capsules. Each capsule will contain 50 mg or 75 mg of free base (present as the [redacted]).

Dabrafenib will be provided to sites by ~~GSK~~ Novartis, with the exception of sites in China where GSK will organize to provide supplies under GSK`s sponsorship. The contents of the label will be in accordance with all applicable regulatory requirements.

5.1.2 Trametinib (GSK1120212)

Trametinib study medication will be provided as 0.5 mg and 2.0 mg tablets. Each tablet will contain 0.5 mg or 2.0 mg of trametinib parent (present as the [redacted]).

Trametinib will be provided to sites by ~~GSK~~ Novartis, with the exception of sites in China where GSK will organize to provide supplies under GSK`s sponsorship. The contents of the label will be in accordance with all applicable regulatory requirements.

5.4. Treatment Assignment

REVISED TEXT

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

~~RAMOS~~ MAP allows study sites to register subjects, and also is used in study treatment supply.

Detailed ~~RAMOS~~ MAP user instructions, worksheets, and telephone contact numbers will be provided to the study site ~~in the SPM~~.

7.3.7.2. Pregnancy Reporting

REVISED TEXT

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to ~~GSK~~ Novartis within ~~2 weeks~~ 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.

7.3.10. Prompt Reporting of Serious Adverse Events and Other Events to ~~GSK~~ Novartis

REVISED TEXT

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	~~2 weeks~~ 24 hours	Pregnancy notification form	2 weeks	Pregnancy follow-up form
Cardiovascular or death event	Initial and follow up reports to be completed within one week of when the cardiovascular	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable

8 Data Management

REVISED TEXT

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

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

Clinical data ~~M~~management ~~of clinical data~~ will be performed in accordance with applicable ~~GSK~~ standards and data cleaning procedures to ensure the integrity of the data, e.g., ~~removing~~ resolving errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and ~~an internal~~ a custom ~~validated medication~~ drug dictionary~~, GSKDrug~~. An appropriate medical

dictionary that covers all approved drugs in studies where Japan is participating will be referenced.

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

~~In all cases, subject initials will not be collected or transmitted to GSK in accordance with GSK policy.~~

10.3 Quality Control (Study Monitoring)

The following modifications were made:

In accordance with applicable regulations, GCP, and ~~GSK~~ Novartis procedures, Novartis personnel (or designated Clinical Research Organization [CRO]) will contact the site ~~will be contacted~~ prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ~~GSK~~ Novartis requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow ~~the monitor~~ Novartis personnel (or designated CRO) 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.

10.5. Study and Site Closure

REVISED TEXT

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

10.6.Records Retention

The following paragraph was deleted:

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

And replaced with the following:

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.

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

REVISED TEXT

~~The results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer-reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.~~

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

Novartis aims to post a results summary to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) and other publicly available registers no later than 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 (www.novartisclinicaltrials.com) for a summary of the trial results.

Amendment 6 (22-Mar-2018) from the Amendment 05 (16-Dec-2016)

No	Proposed Change	Sections Affected	Rationale for Change
1	Update Study Sponsor information	Study Sponsor information	Section updated following team member changes.
2	Remove duplicate sentence about PK endpoints	Protocol Summary	Remove duplicate sentence.
3	Correct the lowest allowed dose in case of pyrexia	5.8.5.1. Guidelines for Pyrexia Table 12	Correct typo from previous version of protocol. According to general dose reduction guideline, a dose reduction below 75 mg BID for dabrafenib is not allowed.
4	Clarify that liver PK samples collection will be discontinued 8 weeks after last patient first treatment.	5.9.1.1 Liver event follow up assessments	Clarify the liver PK samples will not be collected 8 weeks after last patient first treatment.
5	Adding 'Refer to section 7.5 and 5.9.1.1 for details on pharmacokinetics blood sampling including liver PK sampling.'	Table 20, footnote 21	The liver PK sampling clarification is added in the assessment procedure.
6	Extend the duration of contraceptive for male participants from 12 weeks to 16 weeks after	7.3.7.1. Pregnancy Testing and Prevention	The contraception requirement for male participants has been increased from 12 to 16 weeks in the period following stopping of study treatment. A re-evaluation of the existing pre-clinical data and the

	stopping study treatment.		application of the Novartis contraception guidance for clinical trials resulted in this change to the Investigator Brochures Edition 9.0.
7	Replace RAP by SAP.	All	Updated to use the Novartis terminology rather than the GSK one.
8	Remove the calculation of 95% Confidence Interval for vaious observed ORRs.	9.2.1 Sample Size Assumptions	The 95% confidence interval will be calculated based on the actual treated subjects, and an exact binomial method will be applied to calculate the confidence interval.
9	Clarify that an exact binomial confidence interval will be calculated [Clopper and Pearson 1934] reference has been added.	9.3.5.1 Primary Efficacy Analyses	New reference is added.
10	Correct the constant K in the Crockcroft-Gault fomula as follows: K=1.04 for female K=1.23 for male	Appendix 2	The constant K in the Crockcroft-Gault fomula was a typo. The correct constant is provided.

Amendment 7 (15-Feb-2019) from the Amendment 06 (22-Mar-2018)

No	Proposed Change	Sections Affected	Rationale for Change
1	Update the Sponsor Signatory	Sponsor Signatory page	[redacted] has taken the role of [redacted] from [redacted].
2	Update the methods of contraception for female participants.	7.3.7.1. Pregnancy Testing and Prevention	Double barrier contraception methods do not fulfill the definition of highly effective contraception as per Clinical Trial Facilitation Group (CTFG) and Novartis internal guidelines. For subjects taking trametinib, contraception using only oral contraceptives is not allowed until

			the results from the ongoing drug drug interaction trial of trametinib in combination with oral contraceptives are available. Based on clinical evidence from GSK studies, the contraception duration was decreased from 4 to 2 weeks after dabrafenib monotherapy discontinuation.

Amendment 8 (27-Nov-2019) from the Amendment 07 (15-Feb-2019)

No	Proposed Change	Sections Affected	Rationale for Change
1	Replace “vials” wording by “bottles”	5.7 Treatment Compliance	Study treatments are supplied in bottles and not in vials.
2	Clarification on dose modification instructions for Severe Cutaneous Adverse Reactions (SCARs)	5.8.4 Guidelines for Skin-related Adverse Events	Dose modification instructions for SCARs, which have been reported during treatment with dabrafenib in combination with trametinib, is now aligned to the most recent dabrafenib and trametinib Investigator’s Brochure edition 11.