NOVARTIS

Clinical Development

Trametinib + DabrafenibProtocol

MEK116540 / NCT02124772

An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the MEK Inhibitor Trametinib in Children and Adolescents Subjects with Cancer or Plexiform Neurofibromas and Trametinib in Combination with Dabrafenib in Children and Adolescents with Cancers Harboring V600 mutation

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List of Abbreviations

ADL	Activities of daily living
AE(s)	Adverse Event(s)
AKT	Serine/threonine kinase AKT (protein kinase B)
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATRX	ATP-dependent transcriptional regulating X-linked helicase
AUC	Area under the concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-last)	Area under the concentration-time curve until the last measurable plasma concentration time point
AUC(0-t)	Area under the concentration-time curve over a period of time (t)
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-HCG	Beta-Human Chorionic Gonadotropin
BAL	Bronchioalveolar lavage
BCR/ABL	Breakpoint cluster region/Abelson murine leukemia virus oncogene homolog 1 gene fusion (Philadelphia chromosome translocation)
BID	Twice daily
BM	Bone marrow
BRAF/*BRAF*	B-Raf serine/threonine-protein kinase/proto-oncogene encoding B-Raf
BRAT	Bananas, rice, apples, toast (diet)
BSA	Body surface area
BUN	Blood urea nitrogen
CAP	College of American Pathologist
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CENP-E	Centromere-associated protein –E
[redacted]	[redacted]
CI	Confidence Interval
CL/F	Apparent clearance following oral dosing
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CR	Complete response/ Complete remission
CSF	Cerebrospinal fluid
CT	Computed tomography
C_τ	(trough) concentration

[redacted]

cuSCC	Cutaneous Squamous Cell Carcinoma
CV	Coefficient of variation
DICOM	Digital Imaging and Communications in Medicine
dL	Deciliter
DLT	Dose Limiting Toxicity
DMPK	Drug Metabolism and Pharmacokinetics
[redacted]	[redacted]
DSS	Disease-specific survival
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
eCRF	Electronic case report form
ERK	Extracellular signal-regulated kinase
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FLT3	Feline McDonough stain (Fms)-like tyrosine kinase 3
FSH	Follicle Stimulating Hormone
FSEIR	Fast spin echo-inversion recovery
FTIH	First time in human
G	CTCAE Grade
G6PD	Glucose 6 Phosphate Dehydrogenase Deficiency
GAP	GTPase activating protein
GCP	Good Clinical Practice
GCPH	Global Clinical Program Head
GDP	Guanosine diphosphate
GFR	Glomerular filtration rate
GGT	Gamma glutamyltransferase
gIC50	Concentration causing 50% growth inhibition
GLP	Good Laboratory Practice
GLS	Geometric least square
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSK	GlaxoSmithKline
GTP	Guanosine-5'-triphosphate
GVHD	Graft versus host disease
HAs	Health Authorities
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
H&E	Hematoxylin and Eosin
HgF	Fetal Hemoglobin
HGF	Hepatocyte Growth Factor
h/hr	Hour(s)
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatograhy
HPMC	Hydroxypropyl Methylcellulose

[redacted]

HR	Hazard Ratio
HVA/VMA	Homovanillic Acid / Vanillylmandelic Acid (ratio)
^{123}I	Iodine-123 (radioisotope)
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IDSL	International Data Standards Library
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IR	Incomplete Response
IRB	Institutional Review Board
IU	International Unit
ka	Absorption rate constant
kg	Kilogram
KRAS/*KRAS*	Kirsten rat sarcoma virus homolog/oncogene encoding KRAS
L	Liter
LCH	Langerhans Cell Histiocytosis
LDH	Lactate Dehydrogenase
LGG	Low Grade Glioma
LLN	Lower limit of normal
LS	Least squares
LSLV	Last subject's last visit
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-activated protein kinase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
mg	Milligram(s)
MIBG	Meta-iodobenzylguanidine
µl/ mcL	Microliter(s)
mm	Millimeter(s)
MPNST	Malignant peripheral nerve sheath tumors
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Millisecond(s)
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin serine/threonine protein kinase
MYNC	Proto-oncogene of the transcription factor MYC
NCI	National Cancer Institute

[redacted]

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NF-1	Neurofibromatosis Type-1
NF-1 with PN	Neurofibromatosis Type-1 associated plexiform neurofibromas
ng	Nanogram(s)
NIH	National Institutes of Health
NRAS/*NRAS*	Neuroblastoma RAS virus homolog/oncogene encoding NRAS
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OIRR	Overall intracranial response rate
OS	Overall Survival
OTC	Over the counter
PD	Pharmacodynamic or Progressive Disease
[redacted]	[redacted]
PET	Positron emission tomography
PFS	Progression-free survival
pg	Picogram(s)
PI	Principal Investigator
PI3K	Phosphatidylinositide 3-kinase(s)
PK	Pharmacokinetic
pmol	Picomolar
PN	Plexiform Neurofibroma
PO	Orally administered
POB	Pediatric Oncology Branch
PP	Polypropylene
PPES	Palmar Plantar Erythrodysaethesia Syndrome
PR	Partial Response or P wave interval
PT	Prothrombin time
PTC	Papillary Thyroid Carcinoma
PTEN	Phosphatase and tensin homolog
PTPN11/ *PTPN11*	Protein-tyrosine phosphatase non-receptor type 11/gene encoding PTPN11
QTc	Corrected QT interval duration
QTcB	QT interval corrected for heart rate by Bazett's formula
RAF	Serine/threonine-specific protein kinase Raf (Rapidly accelerated fibrosarcoma)
RANO	Response Assessment in Neuro-Oncology
RAP	Reporting and Analysis Plan
RAS/*RAS*	Ras (Rat sarcoma) proto-oncogene product/oncogene encoding RAS
RBC	Red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RPED	Retinal pigment epithelium detachment
RR	Response Rate
RVO	Retinal vein occlusion
SAE(s)	Serious adverse event(s)

[redacted]

SCARs	Severe cutaneous adverse reactions
SD	Stable Disease
SEER	Surveillance, Epidemiology and End Results
SPF	Skin protection factor
SPM	Study Procedures Manual
t½	Half-Life
TARGET	Therapeutically Applicable Research to Generate Effective Treatments
Tmax	Time of occurrence of Cmax
U/L	Units/Liter
ULN	Upper limit of normal
UK	United Kingdom
US/USA	United States/United States of America
Vc/F	Central volume of distribution
VEGFR	Vascular endothelial growth factor receptor
V/F	Volume of distribution
XRT	X-Ray Therapy
WBC	White blood cell(s)
WHO	World Health Organization

Amendment 9 (21-Aug-2020)

Amendment Rationale

As of 17-Jul-2020, 139 patients have received study treatment in 5 countries. Parts A, B, C and D have enrolled 50, 41, 18 and 30 patients, respectively. All cohorts have completed enrollment and are now closed. 80 patients in parts A, B, C and D have discontinued study treatment and 13 have enrolled into the CDRB436G2401 Rollover and Follow-up study.

The purpose of this amendment is to add updated RANO criteria specifically for low grade glioma (RANO-LGG; Wen 2017) as the basis for independent review. These more recent RANO-LGG criteria allow for the identification of measurable target lesions in patients with LGG that may not be gadolinium enhancing and are best seen by T2/FLAIR imaging sequences. These updated RANO - LGG criteria will be utilized in supplemental independent RANO response determination for those patients with LGG. Note that the independent response determinations that were originally intended to be applied using the older RANO criteria will be retained for analysis purposes. Also note that the response category of 'minor response' will not be used in this trial.

In addition, the contraception information has been updated following results from a trametinib PK study which showed that no loss of efficacy of combined hormonal contraceptives (norethindrone and ethinyl estradiol) is expected when coadministered with trametinib monotherapy.

Changes in the protocol:

[redacted]

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

- List of Abbreviations table: updated to include LGG and RANO
- Removal of named contact details and integrated signature pages in alignment with current Novartis template and standards.
- Section 10.1.1: Updated highly contraceptive methods for female subjects on trametinib monotherapy.
- Appendix 15.5.1: added updated RANO criteria for LGG patients (RANO-LGG) and removed the minor response category in the "Response assessment of target lesions" table as it is not used in this clinical trial.

IRBs/IECs

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

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

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

[redacted]

Amendment 8 (23-Jan-2020)

Amendment Rationale

As of 21-Nov-2019, 138 patients have received study treatment in 5 countries. Parts A, B, C and D have enrolled 50, 41, 18 and 29 patients, respectively. Currently, the only cohorts open to enrollment are: C (BRAF V600 melanoma), and D2 (LCH). All other cohorts have completed enrollment and are now closed. 71 patients in Parts A, B, C and D have discontinued study treatment.

The main purpose of this amendment is to add dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which have been reported during treatment with dabrafenib in combination with trametinib outside this clinical study. This change was made in order to align with updated information available in dabrafenib and trametinib Investigator's Brochure Edition 11.

The definition of 'Study Completion' has also been amended, reducing the minimum treatment duration from 12 months to 6 months. The primary analysis for safety and efficacy (response rate) will not be impacted, but this change allows for an earlier final analysis of this study. Longer term follow-up of study subjects will be available through the rollover follow-up study [CDRB436G2401].

Dabrafenib powder for oral suspension (150 mg stickpack, 10 mg/mL in oral suspension), and trametinib 0.125 mg tablets have been removed, as the manufacturing of these formulations has been discontinued, and they are no longer in use in CTMT212X2101. Patients have changed to dabrafenib 10 mg dispersible tablets and trametinib 0.5 mg and 2 mg tablets.

The contraception requirement post end of treatment, for patients on dabrafenib monotherapy has been updated to 2 weeks, in line with the latest Investigator Brochure.

Changes in the protocol:

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

- Section 3.13.1: Added dose modification requirements for patients taking solid dosage forms of dabrafenib and trametinib.
- Section 3.13.3.3: Added dose modification requirements for cases of SCARs, which have been reported during treatment with dabrafenib in combination with trametinib. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be permanently discontinued.
- Section 6.5: Reduced the minimum on-study duration from 12 months to 6 months.
- Multiple sections: Removal of references to dabrafenib powder for oral suspension (150 mg stickpack, 10 mg/mL for oral suspension), and trametinib 0.125 mg tablets.
- Section 10.1.1: Reduced contraception requirement for subjects on dabrafenib monotherapy from 4 to 2 weeks.
- Update to contact details and integrated signature pages.

[redacted]

IRBs/IECs

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

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

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

[redacted]

Amendment 7 (04-Apr-2019)

Amendment Rationale

As of 06-Feb-2019, 133 patients have received study treatment in 5 countries. Parts A, B, C and D have enrolled 50, 39, 18 and 26 patients, respectively. Currently, the only cohorts open to enrollment are: B1 (neuroblastoma), C (BRAF V600 melanoma), and D2 (LCH). All other cohorts have completed enrollment and are now closed. 59 patients in Part 1 or 2 have discontinued study treatment. The purpose of this amendment is to add additional interim analyses of data to support health authority requests/publication requests.

Changes in the protocol:

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

- Section 6.3 : Removal of the requirement for patients to discontinue study treatment, where a >28 day delay has been due to administrative/scheduling reasons
- Section 9.2.2 : Table 9-1 updated to remove oxcarbazepine from list of prohibited medications during study treatment. Based on review of the literature, oxcarbazepine is not a strong CYP3A4 inducer, but more as a moderate inducer. Therefore, significant drug-drug interaction risk between oxcarbazepine and the investigated drug is considered relatively low.
- Section 10.1.1 : Minor update to the language for female contraception to remove the term 'hormonal methods' from the sentence to clarify that oral contraceptives are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib.
- Section 12.4: Updated to include additional interim analyses to support health authority requests or publication requests.
- Section 14: Added two references to confirm that oxcarbazepine is not a strong CYP3A4 inducer.

IRBs/IECs

The changes described in this amended protocol are considered to be non-substantial.

[redacted]

Amendment 6 (17-Sep-2018)

Amendment Rationale

Study CTMT212X2101 has enrolled 128 patients and additionally has completed enrollment in Cohort C Extension (total 6 patients) as well as Cohort D1 LGG (total 20 patients) according to the current protocol. Due to the completion of enrollment in Cohort C Extension, RP2D/MTD has been declared for combination therapy of trametinib and dabrafenib in patients under 6 years of age.

The purpose of this amendment is:

1. Addition of a new pediatric formulation dosage form of dabrafenib 10mg as dispersible tablets.
2. Update the withdrawal of consent language to align with the new Global Data Protection Requirements.

Changes in the protocol:

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

- Update Sponsor Information Page to correct current study team
- Protocol Synopsis table updated to reflect language in protocol
- Section 1.2.2: minor update to include current program data
- Section 1.3.1: Addition of PK data of Dabrafenib dispersible tablet formulation
- Section 1.4: Addition of Trametinib in text referring to Investigator Brochure
- Section 3.1, 3.11.2, 3.13, 4.1.2, 4.2.2, 4.3: Addition of Dabrafenib dispersible tablet language
- Section 6.7: Withdrawal of consent wording added to align with new Global Data Protection Requirements
- Section 10.1: Updated program standard language regarding contraceptive methods
- Appendix 2: Dosing nomogram updated for dispersible tablet formulation.

IRBs/IECs

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

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

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

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Amendment 5 (8-Mar-2017)

Amendment rationale

Amendment 5 incorporates two major changes to this ongoing study.

1. Two new specific BRAFV600 mutant disease cohorts (LGG and LCH) are added for study of combination therapy of dabrafenib and trametinib to obtain preliminary efficacy information in these diseases, as well as additional safety, tolerability and PK data for the combination. The added cohorts in Part D are part of an agreement with the US Food and Drug Administration (FDA).
2. Two current dose escalation portions of the protocol (Part A and Part C) are extended to allow additional dose exploration of trametinib in patients under 6 years of age in an effort to obtain target exposure comparable to adults in this age group.

As of 8-Mar-17:

- A total of 86 patients have received study treatment in five countries and twenty one patients have discontinued study treatment.
- In Part A (dose escalation and age expansion with trametinib monotherapy) of the study, a total of 38 patients have been treated with trametinib monotherapy at 0.0125, 0.025 or 0.04mg/kg/day dose in the dose escalation and age expansion cohorts. The trametinib dose of 0.04mg/kg/day was not tolerable and has shown to exceed the maximum tolerable dose (MTD). The 0.025mg/kg/day trametinib is tolerable and has been declared the recommended phase 2 dose (RP2D) for patients aged 1 month to <18 years.

Results from completed and ongoing cohorts (Parts A, B and C) of this trial have shown that the 0.025 mg/kg/day dose level also achieved target exposures that are associated with the recommended efficacious adult dose for melanoma treatment, in most patients older than 6 years of age. However, patients under the age of 6 are less likely to achieve the target exposure when dosed at 0.025 mg/kg/day than are the older patients. The exposure-efficacy relationship for trametinib when combined with dabrafenib in adult melanoma patients demonstrates an apparent threshold effect and provides further rationale to optimize trametinib exposures in pediatric patients. Therefore, Part A extension has been added to test the intermediate trametinib dose level of 0.032 mg/kg/day in patients under 6 years of age for safety, tolerability and pharmacokinetics.

- In Part B (disease expansion with trametinib monotherapy) of the study, a total of 36 patients have been treated with trametinib monotherapy at the RP2D of 0.025mg/kg/day in four disease expansion cohorts. Planned enrollment is ongoing in this part. No specific changes to this part have been made in this amendment.
- In Part C (dose escalation with trametinib and dabrafenib combination therapy) of the study, a total of 12 patients have been treated with a fixed trametinib dose at 0.025mg/kg/day and dose escalated with dabrafenib first at 50% pediatric RP2D dose and then with 100% pediatric RP2D. It has been found that 100% pediatric RP2D of dabrafenib in combination with trametinib is safe and well tolerated for patients 12 months to < 18 years. Based on the trametinib exposure results seen and as explained above, trametinib dose of 0.025mg/kg/day and dabrafenib dose of 100% pediatric RP2D has been

[redacted]

declared combination RP2D for patients aged 6 years to <18 years only. Part C extension has been added to assess the trametinib dose determined from Part A extension with 100% pediatric RP2D of dabrafenib in patients under 6 years of age.

This amendment also adds Part D to test trametinib and dabrafenib combination in two BRAF V600 mutant disease expansion cohorts in pediatric patients with relapsed or refractory low grade glioma (LGG) and relapsed or refractory Langerhans Cell Histiocytosis (LCH). The preliminary efficacy observed in patients with BRAF V600 mutant relapsed or refractory LGG or LCH in the ongoing dabrafenib monotherapy study [CDRB436A2102] is favorable. In adult patients, the combination of dabrafenib with trametinib has demonstrated improved therapeutic benefit in BRAF V600 mutant metastatic melanoma and NSCLC, and a similar improved benefit may also be anticipated in these two pediatric populations. Investigation of combination therapy in these two pediatric populations may contribute to improved treatment options for these molecularly defined subsets of patients.

Additional changes were made to the overall protocol.

- Trametinib and dabrafenib dosing were clarified or updated for intra-subject dose escalations in all study parts, maximum total daily dose and dose reduction schemes.
- Consuming grapefruit, Seville orange and pommello juices concomitantly with study treatment is now allowed. Grapefruit only affects CYP3A substrate drugs with low oral bioavailability. Based on dabrafenib's high oral bioavailability of ~95%, the risk of grapefruit having an effect on dabrafenib exposure is little to none. The safety monitoring and management sections have been revised to clarify the procedures that are recommended or mandatory and to clarify which study drug(s) are to be dose modified in the management of adverse events.
- Dose modification guidance for uveitis and grade 2 diarrhea was added.
- Study completion period was changed from 6 months to 12 months due to slow progression of studied disease.
- Palatability questionnaire requirement was clarified and indicated to be required for both trametinib and dabrafenib.
- Details on the dermatological follow-up requirement for patients in France that was implemented in amendment 3 was added.Imaging scans from the most recent prior chemotherapy will be collected from patients with LGG.
- PK sampling has been simplified for patients on combination therapy in Parts C and D.
- Allowable female contraceptive methods updated to reflect current list of highly effective method of contraception per Clinical Trial Facilitation Group (CTFG) guidelines and due to possible drug-drug interaction of hormone based contraceptives with dabrafenib.
- Male patients are now required to use condom to avoid unnecessary exposure of trametinib and/or dabrafenib to the fetus.
- Data analysis and statistical consideration updated to clarify and reflect current analysis plan.
- Two interim analyses are added and planned for decision making of future development options.

[redacted]

- PK parameters updated to include analysis of dabrafenib metabolites and to exclude parameters that are not calculable based on PK sample collection schedule.
- Additional information was added to provide clarity on assessment procedures and timing.
- Editorial changes and text corrections were made for clarification, where required, and to align with Novartis terminology and procedures.

Details of the specific changes made in each section of the protocol are described below in Changes to the Protocol section.

Changes to the protocol

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

- Revision Chronology for Protocol Amendment 3 was corrected to reflect no change to the HbA1c monitoring schedule
- Protocol synopsis: Section was updated to align with changes made in the protocol body.
- Section 1.4: Added study background at time of Protocol Amendment 5
- Section 2: Updated objectives and endpoints for combination treatment.
- Section 2, Section 12.5.3.1: Certain PK parameters were removed because based on the current PK sample collected, it may not be possible to estimate these parameters.
- Section 3.1, Section 3.2.1, Section 3.2.6, Section 3.4, Section 3.4.1, Section 3.5, Section 3.8, Section 3.9.3.1, Section 3.9.3.2, Section 3.9.4, Section 5.1, Section 5.2.1.1, Section 7.1, Section 15.2: Added or modified language related to adding Part A extension and Part C extension for evaluating an additional trametinib dose level (0.032 mg/kg/day) in monotherapy and in combination treatment with dabrafenib
- Section 3.1, Section 3.5, Section 3.6, Section 3.8, Section 3.9.3.3, Section 3.9.4, Section 3.10.1, Section 5.1, Section 5.2.1, Section 5.2.1.1, Section 5.2.1.5, Section 7.1, Section 7.4.1, Section 7.5, Section 7.5.1.2, Section 9.2, Section 12.1.4, Section 12.2.4, Section 12.4.4: Added or modified language related to adding disease expansion cohorts in combination treatment in Part D
- Section 3.1, Section 12.4.2, Section 12.4.4: Added language on 2 interim analyses
- Section 3.2.3: Text modified to clarify the definition of DLT population
- Section 3.3: Text was added to clarify that safety and tolerability is also evaluated in this part of the study and to clarify the tumor tissue requirement.
- Section 3.7: Updated to provide additional details on intra-subject dose escalations for Parts B and C and to add Part D intra-subject dose escalation details
- Section 3.9.2: Updated to provide rationale for Part C and Part D
- Section 3.9.4: Clarified rationale for endpoints in Part B
- Section 3.10.1: Text updated to provide clarity on randomization number assignment
- Section 3.11.1: Text added to provide maximum total daily dose of trametinib allowed in the study

[redacted]

- Section 3.11.2: Text added to provide maximum total daily dose of dabrafenib allowed in the study
- Section 3.11.3: Language was updated to specify that fasting requirements apply for both trametinib and dabrafenib. Restriction related to grapefruit juice and other citrus products was removed due to minimal/no effect on dabrafenib exposure.
- Section 3.12, Section 3.13, Section 3.15: The tables in these sections were updated to provide clarity on the safety monitoring and management procedures that are recommended or mandatory in the management of adverse events. The adverse event management guidelines remains largely the same as protocol amendment 4.
- Section 3.12.1.2: Text added to indicate blood samples are to be sent to the central lab for testing related to liver events.
- Section 3.13.4: Added dose discontinuation requirement for grade 2 diarrhea lasting >7 days
- Section 3.14: Added dose modification guidance for persistent ≥ grade 2 uveitis
- Section 3.15 and Section 15.2 (Appendix 2): Modified to provide clarity on dose reduction scheme for dabrafenib and updated the dosing nomograms and instructions.
- Section 4.1.2: Text added to indicate that Novartis will provide dabrafenib
- Section 5.2.1.3: Text was clarified on the tissue submission requirement in Part B4
- Section 5.2.2: Clarified exclusion criterion for prior treatments
- Section 6.3: Text deleted to align with current dose modification guidelines. Updated adverse event and safety event follow-up period to 30 days to align with program standard.
- Section 6.5: Definition for study completion period has been changed from 6 months to 12 months.
- Section 6.5 and Section 6.6: The GSK rollover study numbers have been removed due to the change in sponsorship. New Novartis numbers will be assigned at a later time.
- Section 7: Corrected the blood volume collected over the study duration to align with the Time and Events table
- Section 7.1: Tables in this section were updated to provide clarity on the assessments, in particular the efficacy assessment for the various disease types, and to correct typographical errors. Simplified the PK collection schedule for patients on combination treatment.
- Section 7.1 and Section 7.2: Added details on collection of scans from the most recent prior chemotherapy for patients with LGG.
- Section 7.1, Section 7.3.7: Clarified palatability questionnaires are required for both trametinib and dabrafenib for patients on combination treatment
- Section 7.1, Section 15.10: Added details on dermatological follow-up requirement for patients in France, which were implemented in protocol amendment 3
- Section 7.3.1: Clarified the timing of baseline plain radiographs
- Section 7.3.4: Clarified details of baseline vital signs measurement requirement

[redacted]

- Section 7.3.6: Text added to clarify when the collected ECHO scans will be analyzed
- Section 7.3.7: Text added to reduce HbA1c assessment to baseline
- Section 7.4, Section 12.5.3: Text added to indicate dabrafenib metabolite levels will be analyzed.
- Section 7.4.1: Text added to compile all additional PK sample collection for certain adverse events as indicated in other sections.
- Section 7.4.2: Updated language regarding analytical procedure
- Section 7.5: Table in this section has been updated to provide updated plans for translational research
- Section 5.2.1.3, Section 5.2.1.4, Section 7.5.1.2: Updated to allow CLIA equivalent lab for analysis
- Section 7.6: Table added to clearly and concisely provide disease response assessment methodologies and assessment modalities for each of the possible disease types to be enrolled in this study.
- Section 8.3.1: Added symptomatic LVEF decrease as an event to be recorded on the specific cardiovascular eCRF and reinforced SAE reporting requirement, if applicable.
- Section 8.4.2: Table in this section was updated to provide clarity on reporting timeframes and tools on SAEs, DLTs and certain AEs
- Section 10.1.1: Updated allowed female contraceptive methods to reflect current list of highly effective method of contraception per Clinical Trial Facilitation Group (CTFG) guidelines. Double barrier method and hormone based contraception methods are now excluded.
- Section 10.1.2: Added male contraception requirements for trametinib monotherapy and combination therapy with dabrafenib
- Section 12.1.2: Section was modified for providing additional clarity on analysis plan in Part B
- Section 12.2.2: Updated to provide confidence intervals around potential observed objective responses
- Section 12.3.1: Updated to provide clarity on analysis populations
- Section 12.5.1: Clarified how anti-cancer activity analyses, including investigator and independent review data, will be performed.
- Section 12.5.2: Text was modified to indicate that safety analysis will be based on Safety Population
- Section 12.5.2.1 and Section 15.5.2.2: Text modified to indicate that additional details are provided in the SAP
- Section 12.5.2.3: Text modified to reflect planned analyses for laboratory data
- Section 12.5.3.2: Text added to align with objective added in Section 2
- Section 14: Two references were added
- Section 15.3: Title was updated to indicate this assessment methodology is not indicated for glioma patients

[redacted]

- Section 15.4: Text was added to clarify requirement for Overall Best Response Assessment for Neuroblastoma
- Section 15.6: Appendix 6 was updated to clarify MRI submission requirements for PNs

IRBs/IECs

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

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

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

[redacted]

Amendment 4

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GSK1120212 and GSK2118436 by Novartis, the purpose of this protocol Amendment 4 is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of 02-Aug-16:

- 64 patients have received study treatment in 5 countries;
- 10 patients have completed or discontinued study treatment.

The changes described in this amended protocol require Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) approval prior to implementation.

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

Amendments 1 to 3

Amendment rationale and summary of changes for previous amendments 1 to 3 are provided below in Revision Chronology section and also in Appendix 11 as tracked changes.

Revision Chronology

[redacted]

Sponsor Information Page

Clinical Study Identifier: MEK116540 (CTMT212X2101)

Sponsor Contact Information

Novartis Pharmaceuticals Corporation

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

Sponsor Serious Adverse Events (SAE) Contact Information:

For study conduct questions not related to study subject safety, the first line of contact should be with the designated local country company contact. In the event that the designated company contact is not available please contact the Medical Lead. Please refer to the Study Procedures Manual (SPM) for further details.

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

Regulatory Agency Identifying Number(s):

Compound Number	IND Number	EudraCT Number
GSK1120212 (trametinib) GSK2118436 (dabrafenib)	119,309	2013-003596-35

[redacted]

Protocol Synopsis

Title	An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the MEK Inhibitor Trametinib in Children and Adolescents Subjects with Cancer or Plexiform Neurofibromas and Trametinib in Combination with Dabrafenib in Children and Adolescents with Cancers Harboring V600 mutations.
Protocol Number	MEK116540 (CTMT212X2101)
Clinical Phase	I/II
Compound(s)	GSK1120212 (trametinib), GSK2118436 (dabrafenib)
Study rationale	Despite the advances made over the past 30 years in the treatment of pediatric cancer, there remain important subpopulations within this group of patients for whom efficacious therapies have yet to be discovered. Specifically, pediatric patients with recurrent high grade gliomas, and patients with metastatic or recurrent solid tumors, continue to have a poor prognosis. Use of second- and third-line cytotoxic chemotherapies, even in dose-intensive regimens, has yet to yield significant impact on progression-free survival or overall survival. Increased understanding of the molecular mechanisms of pediatric tumors allows for rationale investigation of agents targeting these mechanisms. Development of new therapeutic options for pediatric cancer patients is needed and clinical testing of targeted approaches may provide these options.
Study objectives, endpoints and hypotheses	Primary Objective: ● To determine the safe and tolerable trametinib dose(s) for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (trough concentration [C_τ]) to the recommended adult dose Secondary Objectives: ● To characterize the pharmacokinetics of trametinib ● To characterize the safety and tolerability of trametinib ● To assess any preliminary anti-tumor activity of trametinib ● To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach ● To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination ● To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination ● To determine the safe and tolerable dabrafenib dose(s) when administered in combination with the recommended trametinib dose for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures to the recommended adult dose ● To assess any preliminary anti-tumor activity of trametinib in combination with dabrafenib ● To determine the acceptability and palatability of trametinib and dabrafenib in pediatric subjects [redacted] Primary Endpoint(s): ● Adverse Events (AEs); electrocardiograms (ECGs); echocardiograms (ECHOs); changes in laboratory values and vital signs. Steady state C_τ of trametinib

[redacted]

	Secondary Endpoint(s): ● Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax) and half-life (t½) of trametinib, as appropriate ● AEs; ECG; changes in laboratory values and vital signs ● Tumor response to trametinib monotherapy and trametinib in combination with dabrafenib by investigator assessment as defined in Appendix 3 through Appendix 7. ● CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates ● Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F), Cmax, tmax, and Cavg of trametinib and dabrafenib when administered in combination, if the data permit Hypothesis: ● Infants, children and adolescents will tolerate doses of trametinib alone or in combination with dabrafenib that achieve steady state trough concentrations associated with clinical benefit in adults.
Study design	This is a 4-part (Part A, Part B, Part C and Part D), Phase I/IIa, multi-center, open label, study in pediatric subjects with refractory or recurrent tumors. Part A will be a pharmacokinetically driven limited dose escalation in subjects and will include an expansion for safety, tolerability, and pharmacokinetics (PK) in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase. Part A will be extended to include an age-specific trametinib dose (0.032 mg/kg/day) exploration in up to 12 subjects aged 1 month to < 6 years old. Part B will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of proto-oncogene RAS (Ras)/ mitogen-activated protein kinase (MAPK) activation in childhood solid tumors. At least forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts. ● Refractory or relapsed neuroblastoma ● Recurrent or unresectable low grade gliomas associated with BRAF tandem duplication with fusion, or NF1 subjects with gliomas, not suitable for the NF1 with PN cohort ● Neurofibromatosis Type -1 associated plexiform neurofibromas that are unresectable and medically significant. ● BRAF V600 mutant tumors Part C is a limited dose escalation part of the study evaluating the combination of trametinib with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will enroll approximately 18 subjects (including up to 6 adolescent subjects with BRAF V600 mutant metastatic melanoma)and will not open to accrual until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib is established in Part A and review of the available safety and PK data of trametinib and dabrafenib monotherapy in children is completed. Amendment 3 provides the updated safety data and dabrafenib dosing in children. Parts B and C may be open to accrual simultaneously. Patients who have had prior dabrafenib therapy may enroll in part C if they have had prior benefit to dabrafenib monotherapy, as determined by the investigator. Part C will be extended to include an age-specific dose exploration in up to 6 subjects aged 12 months to < 6 years old. If the trametinib dose of 0.032

[redacted]

	mg/kg/day is tolerated in Part A extension, a combination of trametinib 0.032mg/kg/day and the full dabrafenib RP2D will be tested in this cohort. Part D will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of the combination of trametinib and dabrafenib at the recommended phase 2 combination dose in tumor-specific pediatric populations listed below. ● BRAF V600-mutant, relapsed or refractory low grade glioma (LGG) ● BRAF V600-mutant, relapsed or refractory Langerhans cell histiocytosis (LCH) Approximately 20 subjects with LGG and 10 subjects with LCH will be enrolled. Subjects may not enroll in more than one part of the study. Subjects will receive study treatment until disease progression, death or unacceptable toxicity. All parts of the study will use trametinib tablet strengths (0.5, and 2 mg tablets) for children who are able to reliably swallow tablets. In addition, an oral solution formulation (0.05 mg/mL) is available. Doses will be calculated using body weight and prescribed using a dosing nomogram. Rules for dose modifications in response to toxicity are provided in the protocol. For Parts C and D of the study, dabrafenib capsules (50, 75 mg) or 10mg dispersible tablets will be used.
Number of subjects	Approximately 142 subjects will be enrolled in the study (approximately 48 subjects in Part A, 40 subjects in Part B, 24 subjects in Part C and approximately 30 subjects in Part D).
Inclusion / Exclusion criteria	**General Inclusion Criteria for All Parts** (for complete details and further eligibility criteria for specific parts please see full protocol): 1. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including pharmacokinetics sampling will be obtained according to institutional guidelines; 2. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form 3. Part C and Part D subjects between 12 months and <18 years of age, inclusive; 4. Part A subjects < 2 years of age will not be included in the initial dose escalation 5. Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or must have a current disease for which there is no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life. 6. Prior therapy: The subject's disease (i.e. cancer, NF-1 with Plexiform Neurofibromas, or Langerhans Cell Histiocytosis [LCH]) must have relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. Subjects must have recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment. 7. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale (Yates, 1980). 8. Females of child-bearing potential must be willing to practice acceptable methods of birth control. Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment; 9. Must have adequate multi organ function. 10. In France, subjects will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

[redacted]

	General Exclusion Criteria for All Parts: 1. Lactating or pregnant female. 2. History of another malignancy including resected non-melanomatous skin cancer. 3. Subjects with Neurofibromatosis Type-1 (NF-1) associated optic pathway tumors are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for Plexiform Neurofibroma or malignant solid tumor. 4. Subjects with a history of NF-1 related cerebral vascular anomaly (such as Moyamoya). 5. Subjects with NF-1 actively receiving therapy for the optic pathway tumor 6. Subjects with NF-1 and only Plexiform Neurofibroma (PN) lesions that cannot be evaluated by volumetric analysis. 7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures. 8. Any prohibited medication(s) as described in Section 9.2. 9. Any medications for treatment of left ventricular systolic dysfunction 10. Part B cohorts 1, 2 and 3: Previous treatment with dabrafenib, trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted). Patients who have had prior dabrafenib therapy may enroll into cohort B4. Patients who have had prior dabrafenib therapy and had benefit from that therapy as determined by the investigator, are allowed in Part C or Part D 11. Administration of an investigational study treatment within 30 days preceding the first dose of study treatment(s) in this study. 12. Have a known hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment or excipients that contraindicate their participation. 13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or liver metastases). 14. History of hepatic sinusoid obstructive syndrome (Venoocculsive disease) within the prior 3 months. 15. History of heparin-induced thrombocytopenia. 16. History of interstitial lung disease or pneumonitis. 17. History of or current evidence of retinal vein occlusion (RVO) 18. For subjects with solid tumors that are not primary central nervous system (CNS) tumors or NF-1 associated plexiform neurofibromas, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression are excluded. 19. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. 20. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia. 21. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs. If clarification is needed as to whether a condition will significantly affect absorption of drugs, contact the Medical Lead for guidance to enrol the subject. 22. A history or evidence of cardiovascular risk (as detailed in protocol Section 5.2.2)
Study treatment dose / route / regimen	Trametinib is administered orally once daily under fasting conditions, either 1 hr before or 2 hr after a meal. The starting dose of trametinib (0.0125 mg/kg) is 50% of the recommended fixed dose in adults (2 mg once daily) based on an 80 kg adult. A dosing nomogram based on weight and dose level will be used to prescribe trametinib to minimize inter-subject dosing variability. Dabrafenib is administered orally twice daily either 1 hr before or 2 hr after a meal. Subjects should be encouraged to take their doses at approximate 12 hr intervals and at similar times every day. When taken together, trametinib should be taken consistently with either the morning or evening dose of dabrafenib.

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Safety assessments	Collection of AEs, 12-lead ECGs, ECHOs, physical exam, dermatologic exam, ophthalmologic assessments, vital signs, laboratory assessments including hematology, serum chemistry, urinalysis, pregnancy test. AEs and laboratory values will be graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.
Pharmacokinetic assessments	Pharmacokinetic samples for PK analysis of trametinib and dabrafenib will be collected on protocol specified days in Cycle 1 in the appropriate parts of the study.
Clinical activity assessment	Disease assessments will be performed as appropriate every 8-12 weeks, except for plexiform neurofibroma, for which assessments are at Weeks 33, 49 and every 24 weeks thereafter. Assessments will include magnetic resonance imaging (MRI) or computed tomography (CT) scans or MIBG scans as specified for each disease cohort.
Translational research	A fresh tumor biopsy at screening, Day 15, and upon progression is optional. [redacted]
Statistical methods	The total number of subjects to be enrolled in the study will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. The All Treated Population and Safety Population are defined as all subjects who receive at least one dose of study treatment. This All Treated Population will be used for summaries of demographic / baseline characteristics and evaluation of anti-cancer activity. Safety will be evaluated based on the Safety population. The Response-evaluable Population is defined as those subjects fulfilling the 'All treated' population criteria with a pre-dose and at least one post-dose disease efficacy assessment. In addition, for patients evaluated by RANO criteria, their disease must be 'measurable' at baseline to be included in the Response-evaluable Population. This population will be used for sensitivity analysis on the efficacy endpoints. The Dose Limiting Toxicity (DLT) Evaluable' Population is defined as those subjects participating in dose determining portion of the study (Part A and 3+3 design portions of Part A extension, Part C and Part C extension) fulfilling the 'All Treated' population criteria and having received an adequate treatment (e.g., 75% of doses in the absence of toxicity) for the first 28 days to enable an appropriate evaluation of study treatment related DLTs. The PK Population will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed. Demographic and baseline characteristics will be summarized. Anti-cancer activity will be evaluated by investigator based on clinical evidence and disease specific response criteria. For LGG and NF-1 tumor types, tumor response will also be assessed by independent reviewers. If data warrant, the response data will be summarized by dose level. Adverse events (AEs) will be graded by the investigator according to the NCI-CTCAE v4.03, coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), and summarized. Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4.03. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. For subjects in whom the full blood sampling scheme was used, PK parameters

[redacted]

	for trametinib, dabrafenib and its metabolites will be calculated with standard non-compartmental methods. All trametinib and dabrafenib concentration-time data may be combined and included in a population PK analysis that will examine the influence of demographics (especially age and weight) on the PK of study treatment. Complete details will be provided in the Statistical Analysis Plan (SAP).

[redacted]

1 Introduction

1.1 Background

The Ras/Raf/MEK/ERK or the mitogen-activated protein kinase (MAPK) pathway is a critical signal transduction cascade implicated in normal growth and the uncontrolled proliferation of many human cancers. Under normal physiological conditions, signal transduction through the MAP kinase pathway is tightly regulated through multiple negative feedback mechanisms (Niault 2010). However, in cancer cells, this regulation is frequently disrupted most prominently through somatic mutations of cell-surface receptors, or mutations of Ras- as well as the down-stream serine/threonine kinase B-Raf (BRAF) constitutively activating the downstream kinases MEK1 and MEK2. Activating mutations in *RAS* or *BRAF* occur in approximately 30 % of human cancers. Activation of the MEK/ERK pathway has been implicated in childhood cancer including neuroblastoma (Wu 2009, Castelletti 2010), Wilms tumor (Timofeeva 2006, Hu 2011), soft tissue sarcoma (Tatevossian 2010, Dodd 2013), osteosarcoma (Tatevossian 2010), gliomas (Zebisch 2007), acute leukemia (Sasaki 2011, Steelman 2011) and juvenile myelomonocytic leukemia (Chang 2013). In addition Ras pathway activation is well described in malignant and non-malignant tumors associated with Neurofibromatosis Type-1 (NF-1) (Jessen 2013) because wildtype neurofibromin encodes a GTPase activating protein which hydrolyzes active Ras-GTP to the inactive Ras-GDP.

Complex signal transduction pathway feedback and development of resistance to monotherapy necessitate testing of combination therapies that target multiple points the signal transduction cascade (Montagut 2009, Akinleye 2013). Combinations of BRAF, MEK, and PI3K/mTOR inhibitors may overcome acquired resistance (Greger 2012), however, cross resistance can develop to combined BRAF/MEK inhibition (Gowrishankar 2012).

1.2 Trametinib

Trametinib is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. Trametinib interferes with cellular signal-transduction and inhibits proliferation by inducing cell apoptosis in tumor cell lines in vitro and human tumor xenografts in mice. Analysis of >300 solid cancer cell lines demonstrated that 80% of *B-RAF* mutant and 72% of *RAS* mutant cell lines were sensitive (half maximal inhibitory concentration [IC50] <50 nM) to trametinib, while only 28% of cell lines with wildtype *RAS* and *RAF* were sensitive, suggesting that Ras and Raf mutational status may be predictors of sensitivity. Twenty-two out of 25 melanoma cell lines were sensitive to trametinib. The three melanoma cell lines that did not respond to trametinib had IC50s >1 µM. In vitro and in vivo studies of trametinib in neuroblastoma, malignant peripheral nerve sheath tumor (MPNST), NF-1 associated plexiform neurofibromas (PNs) are ongoing.

Please refer to the most current version of the trametinib Investigator's Brochure (IB) for the updated safety information and additional details.

[redacted]

1.2.1 Pharmacokinetics of Trametinib in Humans

Trametinib pharmacokinetic (PK) parameters were determined after single- and repeat-dose oral administration. Trametinib was absorbed rapidly, requiring 1.5 hr to reach the maximum concentration (Tmax) after single oral administration under fasting conditions. The absolute oral bioavailability of a single trametinib 2 mg tablet is moderate to high (72%) relative to a co-administered intravenous microdose. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in maximum observed concentration (Cmax) and a 10% decrease in area under the concentration-time curve from time zero (pre-dose) extrapolated to infinity [AUC(0-∞)] compared to fasted conditions.

Following repeat-dosing, the mean area under the concentration-time curve over the dosing interval (AUC0-τ) and Cmax increased in a dose proportional manner. Trametinib accumulates with repeat dosing, with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97. Terminal half-life is 5.3 days, determined after single dose administration. Steady state is achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (Cτ), Cmax and area under the concentration-time curve from time zero (pre-dose) to 24 hr [AUC(0-24h)] between Day 15 and Day 21. In adults receiving trametinib 2 mg daily for 15 days (n=13) the geometric mean (Coefficient of variation [CV] %) AUC(0-24h) was 370 (22%) ng•hr/mL, Cmax 22.2 (28%) ng/mL, Tmax 1.75hr (range 1-3hr), and Cτ 12.1 (19%) ng/mL. (Infante, 2012). It is important to note that the 95% confidence interval (CI) associated with the adult mean of Cτ 12.1 ng/mL was 10.86 to 13.4 ng/mL. The lower bound of the 95% CI (approximately 10 ng/mL) of the adult mean Cτ will be utilized to guide the recommended Phase 2 dose in the current study.

The oral liquid formulation (0.05 mg/mL) had similar bioavailability to the trametinib tablet formulation. Single dose administration of trametinib as a 2 mg oral solution compared to the oral tablet resulted in a 12%, 10% and 71% increase in AUC(0-∞), AUC(0-last), and Cmax, respectively.

In the adult population PK model, trametinib CL/F was estimated as 5.07 L/hr and was dependent on gender and weight. The typical CL/F of trametinib in male subjects was 24% higher than that observed in female subjects. The effect of body weight at the minimum and maximum weight observed was within 16% of the typical CL/F value. Although smaller female subjects will tend to have higher exposure than heavier male subjects, no dosage adjustment is warranted in this population.

1.2.2 Clinical Safety and Efficacy of Trametinib

Based on the adverse events (AEs) observed in the dose escalation phase of the early phase trials in adults, the Maximum Tolerated Dose (MTD) of trametinib was 3 mg once daily, and the recommended Phase II dose of trametinib was 2 mg once daily. Across clinical multiple studies in more than 500 subjects, adverse events have been reported by 50% to 100% of subjects, with the most common being rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. In these studies up to 32% of subjects reported serious AEs (SAEs), and up to 13% permanently discontinued study treatment due to AEs.

[redacted]

Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs,hypertension, bleeding events, edema and pneumonitis are considered AEs of special interest for trametinib because they are either known class effects (i.e., were observed with other MEK inhibitors) or potentially life-threatening. Please refer to the trametinib IB for the most current safety information and additional details.

Data from Phase I, II and III studies indicate substantial clinical activity of trametinib in unresectable, *BRAF* mutation positive melanoma (Gilmartin 2011, Infante 2012, Falchook 2012a, Falchook 2012b). The pivotal Phase III study, MEK114267 (METRIC), showed significant improvement in 6 month overall survival (OS, 81% vs 67%, P=0.01) and progression-free survival (PFS, 4.8 months versus 1.5 months, P<0.001) in favor of trametinib over standard dacarbazine or paclitaxel chemotherapy in the treatment of patients with advanced or metastatic BRAF V600E/K mutation positive melanoma (Flaherty 2012, Sausville 2012).

Trametinib (MEKINIST®) was approved by the Food and Drug Administration (FDA) on 29 May 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with the BRAF V600E or V600K mutation.

1.2.3 Trametinib Preclinical Juvenile Toxicity

In juvenile rat toxicity studies, there were dose-dependent effects on growth (body weight and long bone length), bone (physeal thickening), increased serum phosphorus, eye (corneal mineralization/dystrophy), skin, liver, heart (increased heart weight) and female reproductive system effects, consisting of a delay in a physical landmark of sexual maturity and mammary gland development, lower corpora lutea and lower ovarian weights. All of the female reproductive effects were reversible. With the exception of the heart and eye findings, similar effects have been observed in adult animals given trametinib.

In bone, physeal thickening was reversible following a recovery period and may be associated with inhibition of MEK-dependent fibroblast growth factor (FGF) signaling, as similar effects have been observed in rats given a small molecule inhibitor of FGF receptor (FGFR) tyrosine kinase (Brown 2005) or in FGFR-3-deficient mice (Deng 1996). Unlike in adults, where bone growth has completed and the physeal plates have closed, children (2 to 11 years of age) and adolescents (12 to <18 years of age) may represent sensitive populations to chronic MEK inhibitor treatment and may demonstrate growth velocity impairment.

Gonadal maturation and development is a potentially sensitive process in children who have yet to reach sexual maturity. In female rats given trametinib at subclinical exposures, ovarian function perturbations were observed, including increases in cystic follicles and decreases in cystic corpora lutea. Pharmacologic inhibition of MEK activity in ovarian granulosa cell cultures blocked ovulatory gene expression, follistatin signaling and granulosa cell survival (Shiota 2003, Kihara 2006 and Sriraman 2008), indicating a potential role of MEK in folliculogenesis. In juvenile rats, similar ovarian findings occurred, as well as delays in onset of physical hallmarks of sexual maturity and mammary gland development. Therefore, onset of female reproductive maturation is a concern in pediatric populations receiving trametinib.

[redacted]

1.2.4 Trametinib Pediatric Experience

Prior to the initiation of this trial, no subject under the age of 18 has received trametinib monotherapy in a GSK or Novartis sponsored clinical trial.

1.2.5 Trametinib Pharmacokinetic/Pharmacodynamics Relationships

Repeat administration of trametinib doses of 0.5 mg, 1 mg, and 2 mg once daily in adults resulted in dose-dependent modulations in tumor biomarkers. Higher doses resulted in greater inhibition of phosphorylated ERK (pERK), Ki67 and increases in p27, confirming inhibition of the MAPK/ERK pathway. In adults with solid tumors, paired tumor biopsies were obtained at baseline and on day 15 of trametinib administration. Pathway modulation was dose dependent in subjects with *BRAF*, *NRAS* mutant melanoma. For all subjects receiving trametinib 2 mg daily the median change was 30% inhibition of pERK, 54% inhibition of Ki67, and 83% increase in p27. In the melanoma subgroup at this dose, median change was 62% inhibition of pERK, 83% inhibition of Ki67, and 171% increase in p27. Day 15 trametinib $C\tau$ was 9.51-18.2 ng/mL (Infante 2012).

An exposure-response analysis was conducted using data from the first time in human (FTIH) study (Study MEK111054) to determine the relationship between the independently manually-read corrected QT interval duration (QTc) and plasma concentrations of trametinib using a non-linear mixed effects model. The electrocardiogram (ECG) data obtained in Part 1 of the study were matched to trametinib concentration and used in these analyses. Data were available in 50 subjects with a total of 498 matched QTc values. Trametinib showed no apparent potential to alter the QTc interval. At the mean Cmax value observed at the recommended dose of 2 mg once daily, median (90% confidence interval [CI]) increase in QTc is 2.2 msec (0.2, 4.0).

1.3 Dabrafenib

Dabrafenib (GSK2118436) is a potent and selective inhibitor of BRAF kinase activity with a mechanism of action consistent with adenosine triphosphate (ATP)-competitive inhibition. Dabrafenib has demonstrated suppression of a downstream pharmacodynamic (PD) biomarker pERK in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutation-positive tumor cell lines, achieved biomarker suppression and tumor regression in BRAF mutant xenograft models, and has demonstrated significant anti-tumor efficacy in BRAF V600-mutation positive melanoma.

Please refer to the most current version of the dabrafenib Investigator Brochure for the most current safety information and additional details.

1.3.1 Pharmacokinetics of Dabrafenib in Humans

Following single-dose oral administration of dabrafenib in hydroxypropyl methylcellulose (HPMC) capsules, plasma concentrations peaked approximately 2.0 hr post-dose and decreased thereafter following a bi-exponential decline. Median terminal half-life in adults is approximately 8 hr after a single dose. Increases in maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) were generally dose-proportional following single doses up to 300 mg (gelatin capsules), but less than proportional to dose following repeat

dosing. There was no accumulation with repeat daily dosing, with a steady state/single-dose AUC ratio of 0.65 following administration of dabrafenib 150 mg twice daily (BID) HPMC capsules. The decrease in exposure noted with repeat dosing of dabrafenib was likely due to induction of its own metabolism.

Oral absorption of dabrafenib HPMC capsule is nearly complete, with a geometric least square (GLS) mean (90% confidence interval [CI]) absolute bioavailability of 94.5% (81.3, 109.7). Administration of dabrafenib HPMC capsules with a high-fat, high-calorie meal resulted in a decrease in the rate and extent of absorption with fed:fasted ratios (90% CI) for Cmax and area under the concentration-time curve from time zero (AUC(0-∞)) of 0.49 (0.35, 0.69) and 0.69 (0.57, 0.85), respectively.

Treatment with dabrafenib dispersible tablets resulted in a decrease of AUC and Cmax by 20% and 49%, respectively relative to administration of HPMC dabrafenib capsules. Tmax was comparable between the two formulations.. This difference in AUC is not considered clinically relevant based on the exposure-response relationship in adult melanoma and therefore no dose adjustment will be made for the dispersible tablets in this study. Cmax is not associated with response.

In the adult population PK model for dabrafenib, body weight also impacted oral volume of distribution (Vc/F) and distributional clearance (Q/F). The difference between female and male subjects (9%) and between subjects with low (50 kg) or high (140 kg) body weight relative to a typical body weight of 80 kg (<20%) was not considered clinically relevant.

1.3.2 Clinical Safety and Efficacy of Dabrafenib

As of 22 June 2015, approximately 2,000 patients with various cancers have received dabrafenib for up to 6 years and approximately 3,200 subjects have received trametinib in combination with dabrafenib for up to 5 years in Novartis-sponsored ongoing or completed studies and compassionate care programs. Cumulative postmarketing exposure to dabrafenib through 31 March 2015 is estimated to be 3,546.16 patient-years.

Integrated safety data from subjects (N=586) receiving 150 mg BID showed that 97% had experienced AEs, the most common (≥20%) being hyperkeratosis (32%), headache (30%), pyrexia (30%), arthralgia (29%), fatigue (26%), nausea (25%), alopecia (23%), skin papilloma (21%), and rash (20%). A total of 174 (30%) subjects experienced any serious adverse event (SAE), and 114 (19%) subjects had treatment-related SAEs. The proportion of subjects who experienced AEs leading to discontinuation of study treatment was low (3%).

In the pivotal Phase III study BRF113683 (BREAK-3), dabrafenib was associated with a 70% reduction in the risk of progression or death compared with dacarbazine with a hazard ratio (HR) of 0.30 (95% CI: 0.18, 0.51; p<0.0001) in subjects with BRAF V600E mutation positive melanoma and no brain metastases (Hauschild 2012). Dabrafenib provided a clear and meaningful benefit in subjects with BRAF V600E mutation-positive melanoma with brain metastases as demonstrated by overall intracranial response rate (OIRR) over 30% and median OS exceeding 7 months in study BRF113929 (BREAK-MB). Subjects with BRAF V600E mutation positive melanoma also benefit from dabrafenib treatment, with a confirmed response rate of 13% and the median duration of response of 5.3 months (BRF113710, BREAK-2).

[redacted]

Dabrafenib (TAFINLAR®) was first approved by the FDA on 29 May 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with the BRAF V600E mutation.

1.3.3 Dabrafenib Preclinical Juvenile Toxicity

In juvenile rat toxicity studies, there were dose-dependent decreases in body weight and/or gain, food consumption and long bone growth. In testes, there were similar effects (testicular degeneration/atrophy and tubular dilation) in juvenile animals as seen in adults.

In juvenile rat studies, dose-dependent effects on kidney (tubular deposits with secondary changes, increased incidence of cortical cysts and tubular basophilia, tubular dilation and reversible increases in serum urea and/or creatinine concentrations) were observed. Renal toxicity has not been observed in adult rats, dogs or mice given dabrafenib for up to 3 months. The spectrum of renal changes noted in juvenile rats suggests obstructive injury. In general, renal toxicity was observed with greater incidence and severity in juvenile rats where dosing was initiated pre-weaning compared to post-weaning. When dosing of dabrafenib was initiated post-weaning (postnatal day 22), there was no progression in the severity of renal findings nor were there any secondary changes. The observation of greater renal toxicity in rats < 22 days old suggests a higher risk for tubular injury for human infants <1 years of age based on comparison of renal maturation rates, and a correspondingly lower risk for patients between 1 and 4 years of age.

1.3.4 Dabrafenib Pediatric Experience

A Phase 1 clinical trial of dabrafenib is ongoing in children with solid tumors (BRF116013).

1.3.4.1 Background data from part 1 of study BRF116013

Twenty seven subjects were enrolled, with a median age of 9.0 years, ranging from 11 months -17 years old; 56% were male. Most subjects (89%) were caucasian. Most subjects (21 subjects, 78%) had measurable disease at baseline per the investigator, and all were previously treated for this tumor. Dose escalation was pharmacokinetically driven, to achieve exposures (measured as AUC 0-12) in pediatric patients that is similar to that seen in adults treated at recommended doses. Note that an MTD has not been determined in adults.

Similar to the experience in adults, a maximally tolerated dose was not identified in this study. Based on the doses in part 1 that achieved target exposures (AUCs 0-12 hours > 4000 ng*hr/mL, parent molecule) there are currently separate phase II dose recommendations for those under 12 years of age (5.25mg/kg/day), and those 12 and older (4.5mg/kg/day). The doses will be further defined based on modelling and simulation of all available data at the time of finalizing the protocol.

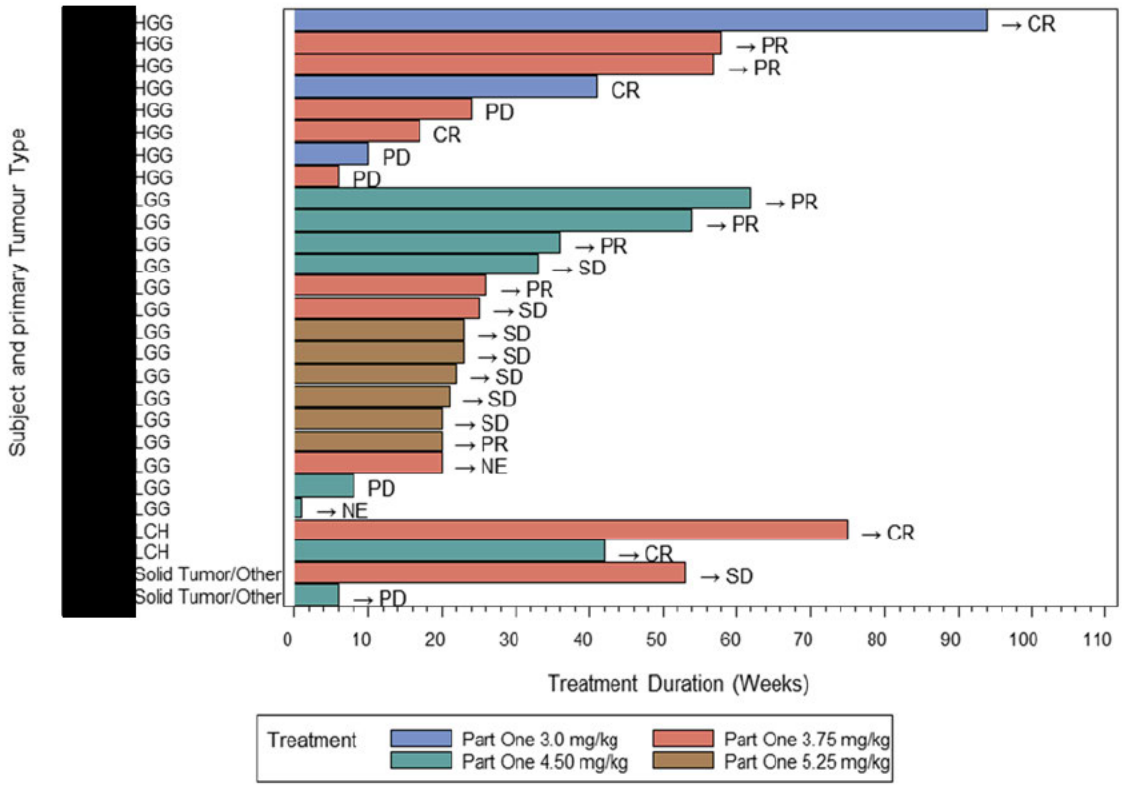
An interim data cut from this ongoing study was made 7 March 2015, and resultant tables and listing prepared for the 27 patients enrolled into part 1. Twenty-one of these 27 patients were continuing to receive dabrafenib at the time of the data cut off.

[redacted]

Table 1-1 Patient Numbers Enrolled at Each Dose: Extent of exposure

Dose	Numbers enrolled
3 mg/kg	3
3.75 mg/kg	10
4.5 mg/kg	8
5.25 mg/kg	6
Total	27

Figure 1-1 Duration of Study Treatment (as of 7th March 2015)



Mark indicates ongoing subjects.
Treatment duration counts time difference between first dosing date and dosing end date without accounting for dose interruptions.
Solid Tumor/Other : [redacted] - Thyroid; [redacted] - Neuroblastoma:
Confirmed Best Response: CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Not Evaluable, NA = Not Applicable.
HGG = High Grade Glioma , LGG = Low Grade Glioma ,LCH = Langerhans cell histiocytosis.
gullapv :/projects/gsk207418/stats/primary/prog/figures/f_study_drug.SAS 30APR2014 16:44:11.

Efficacy Results

HGG

Eight pediatric patients with relapsed, refractory or progressive HGG with BRAFV600 mutations were enrolled into the dose finding portion of BRF116013. Of these eight patients, 3

[redacted]

had CRs, 2 had PRs and 4 of the eight patients were on study treatment for 9 months or more. This is shown graphically in Figure 1-1 above.

These results compare very favorably to the historical data where paediatric patients with relapsed, refractory or progressive HGG are expected to have a less than 10% RR and a median survival of 5 months, using conventional therapy.

LGG

Fifteen pediatric patients with relapsed, refractory or progressive LGG with BRAFV600 mutations were enrolled into the dose finding portion of BRF116013. Of these 15 patients, 5 had partial responses (33%), 7 had stable disease (47%), one had progressive disease and two were not yet evaluable for response.

LCH

Two pediatric patients with previously treated severe LCH and BRAFV600 mutations were enrolled into BRF116013. Both achieved complete responses as assessed by the investigator.

Other

Two patients with other solid tumors and BRAFV600 mutations were enrolled; neither had a response to dabrafenib therapy.

Safety Results

Adverse events

All subjects reported at least one AE. The most common (>30%) AEs were pyrexia, fatigue, vomiting, headache, and nausea. There were nine subjects (33%) with AEs of maximal grade 3, and 2 subjects with maximal grade 4 (intracranial hemorrhage, hypotension). No grade 3 event occurred in >2 subjects. The most common body system impacted by AEs was skin (93% all grades, including 7% G2 and 7% G3 with multiple terms for rash most common), general disorders (81% all grades, including 33% G2, with pyrexia and fatigue most common), and metabolic (74% all grades, including 15% G2 and 11% G3, various electrolyte abnormalities).

Serious Adverse Events

Nine subjects (33%) reported 22 SAEs during this time period, all resolved. Three subjects had related SAEs, one with rash, one with arthralgia, and one with pyrexia followed by DIC, hypotension, and increased INR. All three remain on study as of July, 2015.

Dose limiting toxicity

There was one subject with low grade glioma [redacted] years old at 4.5 mg/kg/d dose) who experienced a DLT of Grade 3 maculopapular rash with onset on day 1 of dosing. After protocol specified dose interruption, the subject was able to resume treatment at 3.75 mg/kg/day and continues on treatment beyond one year, with tolerable skin toxicity of grade <=2.

[redacted]

Dose modifications

Eleven of the 27 subjects had at least one dose interruption while on study, mostly for rash and/or pyrexia, and followed protocol guidelines. Two subjects required dose reductions for toxicity, per protocol.

Discontinuations for toxicity

There were no subjects prematurely withdrawn from study for toxicity in part 1. However, through 7 March 2015, one subject in part 2 of the study was withdrawn for painful rash related to study drug, noted in the first week of study start, with recurrence upon re-challenge. The patient was aged [redacted] years, with a primary diagnosis of grade I Pilocytic Astrocytoma. An AE of grade 2 Erythema Nodosum resulted in study withdrawal.

Deaths

There were no deaths on study treatment.

Laboratory data

Review of laboratory data reveals no apparent safety signals. In most cases, it was possible to grade the laboratory data in this interim data analysis using local normal ranges. There were two events of G3 elevated hemoglobin and one event of G3 hypokalemia during viral upper respiratory tract infection. There was one patient with G2 hypokalemia and all other graded laboratory values were G1 or less.

Safety Conclusions

Based on preliminary data, the toxicity profile observed in these initial 27 paediatric subjects is generally similar to that observed in the adult subject experience. Both populations experienced frequent rash, pyrexia, fatigue, arthralgia and headache (m2.7.4 Section 2.1.1, common adverse events). The frequency of rash and similar adverse events may be higher in this paediatric population than in adults. There were two subjects (7%) with grade 3 Rash in the paediatric population while there is less than 1% rate in adults. Rash management guidelines suggested in the protocol were followed for subjects with rash as they remained on therapy. In contrast, there were no cases of cutaneous SCC observed in these paediatric subjects and fewer paediatric subjects have discontinued treatment due to toxicity (0 of 27 in part 1) than adult subjects. The most common AEs were in the Skin body system. There was one dose limiting toxicity, a G3 Rash, although higher doses were later shown to be tolerable in this age group. There were no discontinuations due to toxicity. Adequate exposures were obtained without reaching a maximally tolerated dose.

Overall Conclusion

Overall, these results suggest that dabrafenib monotherapy represents a potentially favorable benefit risk to pediatric patients < 18 years old with BRAFV600 mutant relapsed refractory or progressive gliomas including HGG.

[redacted]

1.4 Combination of Trametinib and Dabrafenib

Please refer to the most current version of the dabrafenib and trametinib Investigator Brochure for the most current safety information and additional details. Data summarizing the clinical safety profile for dabrafenib 150 mg BID in combination with trametinib 2 mg QD in adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma were pooled from two large randomized Phase III studies (N=559). The Phase III data are supported by data from the Phase II Study BRF113220 Part C (150/2 combination therapy group, n=55) , providing a total of over 600 subjects on randomized combination treatment. The safety profile of the combination of dabrafenib and trametinib generally reflect AEs of the individual agents. The AE profile for combination therapy in both Phase III studies, including SAEs and AEs leading to dose modifications, were similar, indicating that the pooled data is a reliable representation of the combination therapy safety profile. The incidence of discontinuations and temporary dose modifications to manage AEs was higher for subjects on the combination therapy (discontinuations, 12%; dose reductions, 31%; dose interruptions, 55%) compared to dabrafenib monotherapy (discontinuations, 7%; dose reductions, 14%; dose interruptions, 37%) but similar to vemurafenib (discontinuations, 12%; dose reductions, 39%; dose interruptions, 56%). The intended dosing in subjects receiving combination therapy was not compromised.

The most common SAE reported for combination therapy was pyrexia, followed by ejection fraction decreased and chills. Discontinuations due to pyrexia and ejection fraction decreased each occurred in 3% of subjects in the combination therapy group.

There were 8 fatal AEs reported for combination therapy; 6 of the 8 fatal SAEs were intracranial hemorrhages. The presence of various confounding factors in 5 of the 6 subjects with intracranial hemorrhage makes the evaluation of causality difficult; contribution of the combination therapy cannot be ruled out.

The rate of permanent discontinuation due to AEs for combination therapy was 12%. Dose reductions due to AEs were required in approximately one-third of subjects receiving combination therapy (31%). Dose interruptions due to AEs were required in more than one-half of subjects receiving combination therapy (55%). The most frequently occurring AEs requiring dose modifications were those where management guidance was provided in the protocols. AEs of special interest were identified based on the clinical significance, frequency and the potential association with the mode of action of BRAF and MEK inhibitors.

Pyrexia occurred at increased frequency and severity for combination therapy subjects as compared to either monotherapy arm. Approximately 60% of the dose interruptions and 50% of the dose reductions in the combination therapy group were due to AEs of pyrexia. With appropriate management and dose modifications, most patients were able to continue on treatment.

Bleeding events occurred at a similar frequency on combination therapy compared to dabrafenib monotherapy, and at a higher frequency compared to vemurafenib monotherapy. The majority of bleeding events for all treatments were Grade 1, and resolved without dose modification. There were 6 fatal intracranial hemorrhages for combination treatment. Bleeding in other critical sites (e.g., gastrointestinal, pulmonary, genitourinary) have also occurred, none of which were fatal.

[redacted]

Ejection fraction decreased occurred in 7% of subjects for combination therapy and the majority of the LVEF decreases that met interruption criteria were asymptomatic and resolved. Most subjects who were re-challenged were able to continue on treatment without further dose modification. These findings suggest that by regular, longitudinal monitoring with appropriate dose modification, more severe sequelae may be prevented.

Hyperproliferative skin lesions, including keratoacanthoma and cuSCC, occurred at a reduced frequency and with a prolonged latency in subjects receiving this combination regimen as compared to BRAF inhibitors as monotherapy; substantiating the non-clinical hypothesis that addition of trametinib abrogates an important safety concern resulting from the paradoxical activation of the MAP kinase pathway exerted by BRAF-inhibitors.

Other treatment-emergent malignancies (for example pancreatic and colorectal) were reported at rates of 1% for combination treatment, which is not higher than what would be expected in the population, and comparable to that observed with monotherapy.

Other adverse events of special interest such as renal insufficiency and pancreatitis for dabrafenib, and skin-related toxicities, ocular events, pneumonitis, and diarrhea for trametinib, appeared at a frequency and/or severity consistent with the known AE profiles of either dabrafenib or trametinib monotherapy.

The safety profile for dabrafenib + trametinib combination therapy in adult subjects with unresectable/metastatic melanoma has been established and is well-characterized with consistent results across two randomized Phase III studies, with 33% of subjects receiving >12 months of combination treatment. There were no new or unexpected safety concerns compared to those observed in the Study BRF113220 Part C combination group. In addition, no new or unexpected safety concerns have been identified for subjects on combination treatment in studies with prolonged additional follow-up (an additional 17 months for MEK115306; an additional 20 months for BRF113220 Part C. The safety profile of the combination generally reflects the safety profiles of the individual agents.

The combination regimen of dabrafenib at the recommended dose of 150 mg BID and trametinib at the recommended dose of 2 mg QD has an acceptable safety profile in adult patients with unresectable or metastatic BRAF V600 mutation positive melanoma, with toxicities that are manageable with appropriate intervention. Administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib relative to administration of either compound alone.

In adults, data from phase I/II and phase III studies of the combination of these two agents demonstrate that both agents can be delivered together at their full recommended monotherapy doses, and that generally the observed AE profile represents the profiles of each individual agent. Some events were higher in the combination arms than in dabrafenib alone arms, including pyrexia, diarrhea, chills, vomiting and hypertension. Some events were lower in the combination arms than in the dabrafenib arms, including cuSCC alopecia, hyperkeratosis, PPES and skin papilloma. Bleeding events overall were similar in dabrafenib monotherapy and combination arms, although there were 6 fatal intracranial hemorrhage events out of 559 adult subjects treated in the combination therapy arms versus none in the 211 adult subjects on dabrafenib monotherapy. These events of intracranial hemorrhage were generally confounded

[redacted]

and were considered not related to treatment by the treating physicians but were more frequent in the combination therapy arms.

The combination therapy in the pediatric population may result in a higher frequency and severity of pyrexia as compared to dabrafenib monotherapy, including pyrexia requiring dose interruption and the use of antipyretics, as well as increased rates of chills, diarrhea, vomiting, and edema peripheral. The combination may result in a lower rate of hyperkeratosis, skin papilloma, alopecia, palmar plantar erythrodysesthesia syndrome (PPES), and palmoplantar keratoderma as compared to dabrafenib monotherapy.

The efficacy of the combination of dabrafenib plus trametinib in the treatment of adults with BRAFV600 mutant advanced melanoma has been shown to be superior to that of dabrafenib alone. Similarly, the combination of dabrafenib and trametinib appears superior to that of dabrafenib alone in the treatment of adult subjects with BRAFV600 mutant NSCLC. Current clinical trial data on dabrafenib monotherapy in the treatment of pediatric subjects with BRAFV600 mutant solid tumors suggests clinically relevant efficacy that compares favorably with the current standard of care available for the various diseases that have been studied. Nonetheless, there may be an opportunity for further improvement in efficacy with combination therapy, perhaps manifest as higher response rates, and/or responses of longer duration.

This is the first clinical study of trametinib and dabrafenib combination in pediatric patients. At the time of Amendment 5 release, preliminary data supports RP2D of 100% dabrafenib and 100% trametinib for combination therapy in patients 6 years of age and older. In patients less than 6 years of age, an additional dose level of trametinib will be evaluated as monotherapy and if tolerated, as combination therapy. Based on the results of these evaluations, combination therapy RP2D will be established in this age cohort

1.5 Rationale for BRAF and MEK inhibitors in Pediatric Cancers

Given the central role of MAPK signaling in cell proliferation, growth, and adhesion, and available evidence of enhanced MAPK activity in many human cancers, it is hypothesized that the MEK inhibitor trametinib may confer beneficial effects against the pediatric cancers including:

- Relapsed or refractory neuroblastoma
- Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion
- Neurofibromatosis (NF)-related PNs.
- BRAF V600 mutant tumors
- Langerhans cell histiocytosis with MAP2K1 mutation

The safety and activity of the combination of dabrafenib with trametinib in adults with BRAF V600 mutation positive melanoma has been demonstrated. Once the doses of dabrafenib and trametinib monotherapy are determined in children and adolescents, a treatment arm to evaluate the safety of dabrafenib in combination with trametinib in children and adolescents will be opened.

[redacted]

1.6 Malignant Solid Tumors in Infants, Children, and Adolescents

Survival rates for childhood cancer, primarily leukemia and lymphoma, continue to improve. However, the 5 year survival for children and adolescents with solid tumors except neuroblastoma has not changed in the past 20 years and improvement in survival for children with brain tumors has not improved significantly in the past 15 years (Smith 2010). The Ras/MEK/ERK pathway has been evaluated in a number of pediatric solid tumors.

Neuroblastoma is a neoplasm of the sympathetic nervous system. It is the most common extra-cranial malignant tumor of childhood, and the most common solid tumor of infancy. Ten to 20% of children and adolescents with high risk neuroblastoma have disease that is refractory to primary therapy, an additional 50% will relapse after intensive multimodality therapy (Park 2010, Cheung 2013, Maris 2010). The National Cancer Institute (NCI) Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative has demonstrated that somatic mutations in neuroblastoma including anaplastic lymphoma kinase (*ALK*) (9.2%), Protein-tyrosine phosphatase non-receptor type 11 (*PTPN11*) (2.9%), adenosine triphosphate (ATP)-dependent transcriptional regulating X-linked helicase (*ATRX*) (2.5%, 7.1% with focal deletion), proto-oncogene for transcription factor MYC (MYNC) (1.7%) and *NRAS* (0.83%) are rare. However, multiple lines of evidence indicate that MEK/ERK activation and signaling are critical to neuroblastoma cell survival (Hsu 2013, Martinez 2012). In pre-clinical neuroblastoma models and other cell lines, MEK 1/2 inhibition was synergistic with inhibition of centromere-associated protein –E (CENP-E) (Mayes 2013).

1.6.1 Low-grade glioma

In children with low grade gliomas, gross total resection is curative. For patients who do not achieve a gross total resection, observation or adjuvant chemotherapy is considered. Radiation therapy is typically reserved for salvage treatment. In young children, chemotherapy (typically vincristine combined with carboplatin) can be used to delay radiotherapy to decrease risk of neurocognitive damage. With this current treatment paradigm, progression-free survival in children with low grade glioma is 80-90% at 10 years. For patients who have recurrent tumor, radiation therapy is considered. For children who have received radiation and chemotherapy, younger children for whom the risk of radiation therapy remains high, and children with relapsed/recurrent low-grade gliomas, new therapeutic approaches are needed.

MAPK pathway deregulation occurs in low grade gliomas (Tatevossian 2010). Constitutively active Braf signaling has been identified in >50% of pilocytic astrocytoma, as a result of the tandem duplication of chromosome 7q34. This caused an oncogenic gene fusion of *BRAF* and *KIAA1549* (Pfister 2008, Forshew 2009, Jacob 2009, Jones 2009, Korshunov 2009, Horbinski 2010, Schiffman 2010). Due to the loss of the N-terminal autoregulatory domain, the *BRAF-KIAA1549* gene fusion product has increased Braf kinase activity resulting in a wild-type Braf sequence with catalytic activity similar to *BRAF* V600 sequence mutations. This fusion product has also been identified in >80% of cerebellar pilocytic astrocytoma specifically (Jacob 2009, Jones 2009, Horbinski 2010). Cells expressing the *KIAA1549-BRAF* fusion kinase have a paradoxical activation of MAPK signaling that may decrease the effectiveness of specific V600 BRAF inhibitors in these tumors (Sievert 2013).

[redacted]

1.6.2 Neurofibromatosis Type-1 Related Plexiform Neurofibromas

Neurofibromatosis Type-1 is an autosomal dominant, multisystem, tumor predisposition syndrome (Evans 2006, Boyd 2009, Williams 2009). Patients with NF-1 have an increased susceptibility to the development of a number of tumors including: PNs, astrocytomas (particularly optic pathway), and MPNST (Benesch 2010). The incidence of NF-1 is approximately 1 in 3,000 (Poyhonen 2000, Lammert 2005, Boyd 2009). At least 30% of patients with NF-1 suffer from PNs, which are benign tumors that originate from peripheral nerves and can arise in various parts of the body (Friedrich 2005). These tumors are often present at birth and can progress rapidly during the first years of life. PNs can cause facial disfigurement, functional deficits, and severe clinical complications following resection (Friedrich 2005).

The NF-1 gene, located on chromosome 17q11.2, encodes the tumor suppressor neurofibromin (Boyd 2009, Wetmore 2010). Neurofibromin functions as a GTPase activating protein (GAP) for Ras by accelerating the conversion of active Ras-GTP to inactive Ras-Guanosine diphosphate (GDP), thereby converting Ras from its active to inactive conformation. Loss of NF-1 function leads to loss of neurofibromin activity, leading to Ras being locked in its active confirmation, which stimulates MEK, and then ERK activity (Boyd 2009).

1.6.3 Langerhans Cell Histiocytosis (LCH)

LCH is a rare proliferative disorder of unknown etiology that primarily affects children. It is distinguished by the clonal proliferation of pathologic histiocytes with the morphologic characteristics of Langerhans cells. Langerhans cells are bone-marrow derived dendritic cells, characterized by the expression of CD1a, S100 and the production of Birbeck granules. The pathogenesis of LCH is poorly understood. Clinical manifestations are related to the pattern of infiltration or organ involvement (Stockschlaeder 2006, Arico 1998). The clinical presentation is heterogeneous, can involve single or multiple organs, and can be associated with varying, often unpredictable outcomes ranging from spontaneous regression to multiple episodes of reactivation, long term debilitating sequelae, rapid progression, and death.

Patients with localized (single system) disease in ‘low risk’ organs typically have good prognosis and may require minimal treatment (for example, isolated bone lesion). On the other hand, multisystem disease, especially disease involving key ‘high risk’ organs (hematopoietic, spleen, liver, lung), carries higher risk of poor outcomes and recurrent events (reactivation disease) after initial therapy.

LCH occurs at an estimated rate of 2 to 10 per million children/adolescents under the age of 15 years (NCI 2012, Stalemark 2008), as compared to approximately 1 to 2 cases per million in adults. Approximately 76% of cases occur in children less than 10 years old. Risk of morbidity and mortality increases substantially when multifocal or multi-organ disease is present (Satter 2008).

In a recent report, which is also the first to show activation of any oncogenic signalling pathway in LCH, BRAF V600E mutations were identified in nearly 60% of a cohort of archival lesion samples obtained from children and adults with LCH (Badalian-Very 2010). The identification of BRAF V600E mutations in LCH has been confirmed in a recently published second report (Satoh 2012).

[redacted]

Mutational analysis of BRAF V600 wild type LCH tumors has very recently revealed a second pathway activating alteration, MAP2K1 (Brown 2014). Of the roughly half of LCH specimens lacking the BRAF V600E mutation, half (about 25% overall) were found to have activation mutations of MAP2K1. This finding reinforces the important role of this pathway in the genesis of LCH and related diseases, and provides a rationale for additional investigation of inhibition of this pathway at more downstream positions, including that provided by inhibitors of MEK1/2.

1.6.4 V600 Mutations in Childhood Cancer

1.6.4.1 High Grade Gliomas

BRAF V600E point mutants have been reported to occur in up to 30% of high-grade astrocytomas (Schiffman 2010, Basto 2005). The frequency of BRAF activating mutations may be more common in pediatric astrocytomas than in adult tumors (Knobbe 2004). Similar to adults, high-grade gliomas in children have poor outcomes overall. However, in children the extent of surgical resection is of prognostic significance with a benefit being derived from near total (>90%) resection. Focal radiation and adjuvant temozolomide demonstrate an overall one-year survival of approximately 68% and a one-year event-free survival of 31% and 36% for anaplastic astrocytoma (World Health Organization [WHO] Grade III) and glioblastoma (WHO Grade IV), respectively (Cohen 2011).

BRAF V600E point mutants have been reported to occur in approximately 50-60% of gangliogliomas (MacConaill 2009, Dougherty 2010), approximately 2-12% of pilocytic astrocytomas (Forshew 2009, Pfister 2008, MacConaill 2009, Qaddoumi 2009, Jacob 2009, Dias-Santagata 2011), and in as many as 30% of high-grade astrocytomas (Schiffman 2010, Basto 2005).

1.6.4.2 Melanoma

Melanoma in children is rare (Lange 2007). Histopathologically, adult and pediatric melanoma appears to be similar. In 2013, it was estimated that approximately 337 new cases are expected to be diagnosed among those aged 0-18 years in the United States (SEER 2013, US Census 2008). Of all patients with melanoma diagnosed before 19 years of age, 6.8% of male patients and 4.6% of female patients had an initial diagnosis of stage IIIC and IV melanoma. The frequency of *BRAF* mutations in melanoma has been reported to be approximately 50% (range: 27% to 70%) (Garnett 2004, Chapman 2011).

1.6.4.3 Papillary Thyroid Carcinoma (PTC)

Thyroid nodules are rare in childhood and adolescence; however, they are more frequently malignant than in adults (approximately 20% of cases) (Corrias 2010). Pediatric Papillary Thyroid Carcinoma (PTC) usually presents at an advanced stage, but has a 5-year survival rate of >99% (SEER 2013, Hay 2010). At presentation, 70% of patients typically have regional nodal involvement, and 10 to 20% may have distant metastasis, with the most common site of metastases being the lungs (Alessandri 2000).

[redacted]

BRAF V600E activating mutations are common in adult PTC, reported at a rate of approximately 50% (Nikiforova 2009, Melck 2010). *BRAF* V600E mutations were identified in approximately 20% of cases in patients aged <20 years (Rosenbaum 2005, Kumagai 2004).

1.7 Summary of Risk Management

1.7.1 Predicted Toxicities for Trametinib

The data and guidance presented in this section are derived from all of the available safety information at the time of compilation; this includes pre-clinical safety data and data available from the clinical study program. Updated safety information may be found in the most recent IB for trametinib and local prescribing information for trametinib.

Ocular effects: Visual impairments, including chorioretinopathy, retinal pigment epithelium detachment (RPED), and retinal vein occlusion (RVO), were reported with trametinib. Cases of ocular toxicities were reported with other MEK inhibitors in clinical development. Subjects with a history of RVO should not receive trametinib.

Comprehensive stopping criteria, dose modifications, and ocular effects management guidelines are incorporated in this protocol.

Cardiovascular effects: Left ventricular dysfunction was reported with trametinib as well as with other MEK inhibitors in clinical development. Adult subjects with a history or evidence of cardiovascular risk including current ≥ Class II congestive heart failure as defined by New York Heart Association are not being enrolled in current studies. Subjects must also have a normal left ventricular ejection fraction (LVEF) on screening assessment. Comprehensive stopping criteria, dose modifications, and left ventricular dysfunction management guidelines are provided in in Section 3.12.3.

Rash: In clinical studies with trametinib, rash has been observed in about 60% of subjects. The majority of these AEs was Grade 1 or 2 and did not require any dose interruptions or dose reductions. Rash management guidelines are provided in Section 3.13.3.

Renal impairment: No dosage adjustment is required in subjects with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the PK of trametinib. There are no data with trametinib in subjects with severe renal impairment. Eligibility criteria for this study will include normal age adjusted creatinine or creatinine clearance greater than 60 ml/min per 1.73 m^2 for all infants, children and adolescents.

Hepatic impairment: No dosage adjustment is required in subjects with mild hepatic impairment. In a population PK analysis, trametinib oral clearance and thus exposure was not significantly different in subjects with mild hepatic impairment compared to subjects with normal hepatic function. There are no clinical data in subjects with moderate or severe hepatic impairment. Trametinib should be used with caution in subjects with moderate or severe hepatic impairment.

Reproductive Effects: Trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC. However, in animal repeat dose

[redacted]

toxicity studies, there were no treatment effects observed in male reproductive tissues. Developmental toxicity was observed in animals at sub-clinical exposures and consisted of decreased fetal weights, increased post-implantation loss, increased abortions and increased incidence of incomplete ossification and skeletal malformations.

There are no adequate and well-controlled studies of trametinib in pregnant women. Therefore, the compound must not be administered to pregnant women or nursing mothers. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation. Pregnant women are excluded from this study, and periodic pregnancy tests will be performed on women of childbearing potential to confirm continued eligibility. Women who are breast-feeding are also excluded; although it is not known whether trametinib is excreted in human milk a risk to the nursing infant has not been discharged.

1.7.2 Predicted Toxicities for Combination of Trametinib and Dabrafenib

The assessment of the risk for the combination of trametinib and dabrafenib, and suggestions for management of risk, are based on clinical data from the concluded and ongoing combination studies in adults. Additional information may be found in the IB for trametinib and dabrafenib.

Pyrexia: Pyrexia was reported in clinical trials with dabrafenib monotherapy and in combination with trametinib. In dabrafenib monotherapy clinical studies, pyrexia was one of the most frequently occurring AEs in up to 27% of subjects across all dabrafenib studies. Most of the pyrexia events (64%) were considered to be related to study treatment. The incidence and severity of pyrexia are increased when dabrafenib is used in combination with trametinib. In patients who received the combination dose of dabrafenib 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had 3 or more events. Pyrexia may be accompanied by severe rigors, dehydration and hypotension which in some cases can lead to acute renal insufficiency.

Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials. Subjects should be evaluated for signs and symptoms of infection and work up considered as clinically indicated. Dabrafenib must be held for fever of 38.5C or higher, and blood samples for an absolute neutrophil count (ANC) and serum creatinine must be drawn in the setting of fever. Trametinib can be continued in subjects receiving combination therapy.

Dermatological Effects

Cutaneous Squamous cell carcinoma (cuSCC): In vitro experiments have demonstrated a paradoxical activation of MAP-kinase signaling in keratinocytes and potentially other cells harboring a wild-type BRAF kinase but a mutated RAS kinase upon exposure to a BRAF inhibitor. This paradoxical MAP-kinase pathway activation is potentially associated with a higher risk for the development of squamous cell carcinoma induction.

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with dabrafenib in combination with trametinib.

[redacted]

In patients who received the combination dose of dabrafenib in combination with trametinib, cutaneous SCC (including keratoacanthoma [KA]) occurred in a lower percentage of subjects and events occurred later than with dabrafenib monotherapy, with the median time to onset of the first occurrence of 20 to 32 weeks as compared to approximately 8 weeks with dabrafenib monotherapy. Most patients on combination therapy who developed cuSCC continued on dabrafenib treatment without dose modification. Skin examination should be performed prior to initiation of dabrafenib and during treatment with dabrafenib, every 2 months throughout therapy. An additional examination should be considered 2 to 3 months after discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy. Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new skin lesions develop.

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

Rash: Skin-related toxicities, primarily rash (maculopapular type rash with dabrafenib and acneiform-type rash with trametinib) have been reported with both trametinib and dabrafenib monotherapies. The incidence of skin-related events reported with the combination regimen appears to be lower than what has been observed following trametinib monotherapy. Rash management guidelines are provided in Section 3.13.3.

Hemorrhage: Major hemorrhagic events including fatal events can occur in patients receiving dabrafenib in combination with trametinib. Monitor for signs and symptoms of bleeding.

Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving dabrafenib in combination with trametinib.

Interstitial lung disease (ILD)/Pneumonitis:

Pneumonitis has been observed in subjects receiving trametinib and trametinib in combination with dabrafenib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests if clinically indicated. No modification of dabrafenib is required when taken in combination with trametinib.

Pancreatitis – Pancreatitis has been observed in subjects receiving dabrafenib and dabrafenib in combination with trametinib. Subjects will be monitored for abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis.

Hyperglycemia: Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Serum glucose levels will be monitored as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia.

Hepatic Events:

[redacted]

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib.

Ocular effects: Both trametinib and dabrafenib have been associated with ocular toxicities which appear to be class effects, including papilledema, RPED, and RVO associated with trametinib, uveitis and iritis associated with dabrafenib. Please refer to Section 1.7.1 and Section 3.13.5.

Decreased LVEF: Left ventricular dysfunction was reported with trametinib as well as with other MEK inhibitors in clinical development. Please refer to Section 1.7.1 and Section 3.12.3.1.

Non-cutaneous secondary/recurrent malignancy: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling in BRAF wild type cells with RAS mutations which are exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have been seen with BRAF inhibitors including dabrafenib, and with dabrafenib/trametinib combination therapy. Patients should be monitored as clinically appropriate.

Reproductive Effects: Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals given dabrafenib. In repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Male subjects should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. In combined female fertility, early embryonic and embryofetal development studies in rats, numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects were seen at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC). There are no adequate and well-controlled studies of dabrafenib in pregnant women.

2 Objective(s), Endpoint(s) and Hypothesis(es)

Table 2-1 Objective(s), Endpoint(s) and Hypothesis(es)

Objective	Endpoint	Hypothesis(es)
Primary		
To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures ($C\tau$) to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state $C\tau$ of trametinib	Infants, children and adolescents will tolerate doses of trametinib that achieve steady state trough concentrations associated with clinical benefit in adults
Secondary		
To characterize the pharmacokinetics of trametinib	$C\tau$ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral	

Objective	Endpoint	Hypothesis(es)
	dosing (CL/F) Cmax, tmax and Cavg, as appropriate	
To characterize the safety and tolerability of trametinib	AEs; ECG; changes in laboratory values and vital signs	
To assess any preliminary anti-tumor activity of trametinib	Tumor response to trametinib as defined in Appendix 3 through Appendix 7 will be assessed by investigator assessment.	
To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach	CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates	
To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination	$C\tau$ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg of trametinib and dabrafenib when administered in combination, if the data permit	
To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs.	
To determine the safe and tolerable dabrafenib dose(s) when administered in combination with the recommended trametinib dose for chronic continuous daily dosing in pediatric subjects (infants, children and adolescents) that achieves similar exposures to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state $C\tau$ of trametinib; steady state AUC(0-12) of dabrafenib	
To assess any preliminary anti-tumor activity of trametinib and dabrafenib when administered in combination	Tumor response to dabrafenib and trametinib combination as defined in Appendix 3 through Appendix 7 by investigator assessment.	
To determine the acceptability and palatability of trametinib and dabrafenib in pediatric subjects	Palatability questionnaire data	

[redacted]

[redacted]

3 Investigational Plan

3.1 Discussion of Study Design

This is a 4-part (Part A, Part B, Part C, and Part D), Phase I/IIa, multi-center, open label study in pediatric subjects with refractory or recurrent tumors likely to have pathway activation and thus more likely to benefit from therapy. The overall goal of this trial is to efficiently establish safe, pharmacologically relevant dose of trametinib in infants, children and adolescents and determine preliminary activity of trametinib monotherapy in selected recurrent, refractory or unresectable childhood tumors. In addition, Part C and Part D of the study are designed to establish the safety, tolerability and activity of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAFV600E mutated tumors.

- **Part A** will be a pharmacokinetically driven limited dose escalation in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase (subjects less than 2 years of age will not be included in the initial dose escalation until the age specific cohorts are opened).
- **Part A extension** will be an age-specific dose exploration in up to 12 subjects aged 1 month to < 6 years old. Preliminary PK analysis of pediatric patients in this current study suggests that for patients < 6 years old, an intermediate dose (i.e., 0.032 mg/kg/day) may increase the proportion of these patients who achieves exposures similar to adults. The goal of this additional dose exploration is to establish the safety, tolerability, PK and further refine the RP2D of trametinib in this younger age cohort. **Part B** will be an expansion study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of Ras/MAPK activation in childhood solid tumors. Forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts. Part B will use the dose determined in Part A.
  - B1: Refractory or relapsed neuroblastoma
  - B2: Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion
  - B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant.
  - B4: BRAF V600 mutant tumors.
- **Part C** will be a limited dose escalation of the combination of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will establish the RP2D of dabrafenib and trametinib when given in combination in children and adolescents. This part of the study, with a planned enrollment of up to 18 subjects with up to 6 adolescent subjects with BRAF V600 mutant metastatic melanoma, will not open until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib monotherapy is

[redacted]

established in Part A and all available PK and safety data is reviewed. Amendment 3 provides the updated safety data and dabrafenib dosing in children to allow enrollment into Part C. Parts B and C may be open to accrual simultaneously.

  - **Part C extension** will be an age-specific dose exploration in 6 subjects aged 12 months to < 6 years old. If the trametinib dose of 0.032 mg/kg/day is tolerated in Part A extension, a combination of trametinib 0.032mg/kg/day and the full dabrafenib pediatric RP2D will be tested in this cohort. The goal of this additional dose exploration is to establish the safety, tolerability, PK and RP2D of the trametinib and dabrafenib combination in this younger age cohort

- **Part D** will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of the combination of trametinib and dabrafenib in tumor-specific pediatric populations listed below.
  - D1: BRAF V600-mutant, relapsed or refractory LGG
  - D2: BRAF V600-mutant, relapsed or refractory LCH

Disease cohorts are selected based on current data of childhood solid tumors with BRAF V600 driver mutations (Héritier 2016). Pediatric subjects 12 months to less than 18 years of age are to be enrolled. Approximately 20 subjects with LGG and 10 subjects with LCH will be enrolled.

Every attempt will be made to enroll at least 4 children under the age of 12 in Part C or Part D. Part D will use the dose determined in Part C, Part C (extension) and Part A (extension).

Subjects may not enroll in more than one part of the study.

All parts of the study will use currently available trametinib tablet strengths (0.5, and 2 mg tablets) for children who are able to reliably swallow tablets. In addition, an oral solution formulation (0.05 mg/mL) is available. Doses will be calculated using body weight in kilograms and prescribed using a dosing nomogram (See Appendix 2).

For Part C and Part D of the study dabrafenib capsules (50, 75 mg) or 10mg dispersible tablet will be used.

General outline of study conduct:

- The screening visit will be completed within 14 days prior to enrollment.
- Safety and PK assessments will be performed at regular intervals as outlined in the Time and Events Tables (Section 7.1).
- [redacted]
- Overall response will be assessed at regular intervals as outlined in the Time and Events Tables according to the appropriate guidelines as determined by the disease(s) under study (see Appendix 3 through Appendix 7).
- Additional details for the conduct of each part of the study are provided in Section 3.2 (Part A) Section 3.3 (Part B), Section 3.4 (Part C) and Section 3.5 (Part D).

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential.

[redacted]

Two interim analyses (IAs) are planned for decision making of future development options and the data may be used for publication. No decision regarding the conduct of this study will be made at IAs. The first IA will be performed after all subjects in Cohort B3 (NF-1 with PN) have been enrolled and have completed at least three post baseline tumor assessments or have discontinued treatment earlier. The second IA will be performed after all subjects have been enrolled in cohort D1 (LGG) and have completed at least 12 months of treatment or have discontinued treatment earlier. At the time of each IA, the data from other disease cohorts and study parts will also be analyzed. Safety and tolerability will be monitored closely on a continuing basis.

Final analysis will be performed at the time of study completion (see Section 6.5).

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

3.2 Part A: Trametinib Dose-Determination

Part A is a repeat dose, dose escalation monotherapy study that will identify the RP2D on the continuous dosing schedule using a 3 + 3 dose-escalation procedure. The goal of the study is to find a RP2D based on PK criteria (PK target dose), defined as achieving in children a steady state (Day 15) mean trough concentration (Cτ) of trametinib that is equivalent to a mean steady state (Day 15) trough concentration of 10 ng/mL trametinib observed in adults at the recommended dose of 2 mg once daily.

During dose escalation, children will be closely monitored for drug-related toxicity. If MTD is determined, the RP2D will be defined by the MTD rather than by PK criteria.

3.2.1 Trametinib Dose Levels

The starting dose of trametinib (0.0125 mg/kg/day) is 50% of the recommended fixed dose in adults (2 mg once daily) based on an 80 kg adult (Table 3-1). In adults (n=2) after 15 days of continuous trametinib dosing (1 mg administered orally [PO] daily), the individual steady state Cτ was 8.44 and 19.1 ng/mL. The lowest trough concentration associated with an objective response in adults with melanoma was approximately 7 ng/mL; one complete response (1 mg dose) and one partial response (0.5 mg dose) were observed out of 12 subjects with Cτ of 7 ng/mL.

The second dose level (0.025 mg/kg/day) is equivalent to the recommended dose in adults (2 mg PO daily). In adults (n=13) receiving this dose, the Day 15 mean steady state Cτ was 12.1 ng/mL (range 8.26-16.9; 95% CI=10.86-13.4). In adults trametinib 2 mg PO daily on a continuous schedule is not associated with dose limiting toxicity and PK-PD modelling in adults with melanoma predict that 79% of subjects would exceed the mean target trough concentration over the entire dosing interval.

The third dose level (0.040 mg/kg/day) is equivalent to the MTD in adults (3 mg PO daily).

[redacted]

In the absence of establishing a pediatric MTD, if the PK target (Day 15 Cτ ≥10 ng/ml) is not achieved at the maximum dose level of 0.04 mg/kg/day, safety and PK data will be examined to consider amending the protocol for inclusion of additional higher dose levels.

Table 3-1 Trametinib Dose Levels for Part A

	Trametinib Oral Dosing
Dose Level 1 – Starting Dose	0.0125 mg/kg/day
Dose Level 2	0.025 mg/kg/day
Dose Level 3	0.04 mg/kg/day
Additional Dose Levels	Protocol amendment to explore additional dose according to observed PK values relative to target concentrations

3.2.2 Trametinib Dose Escalation

Subjects enrolled at each dose cohort will be observed for DLT during the first 28 days.

Dose escalation will occur according to Table 3-2 and will be determined by both toxicity and observed PK values.

DLT Criteria for Escalation:

- Escalation may occur once the initial 3 subjects on Dose Level 1 or Dose Level 2 meet all of the following criteria:
  - have completed the first 28 days, and
  - have completed PK sampling on Day 15, and
  - are evaluable for toxicity (received at least 75% of prescribed (21/28) doses), and
  - have not experienced DLT attributable to trametinib in the first 28 days
- If one of the initial 3 subjects in the dose cohort experiences a DLT in the determinative period, the cohort will be expanded to 6 subjects. Dose escalation may occur once all 6 subjects at the current dose level meet all of the following criteria:
  - have completed the first 28 days, and
  - have completed PK sampling on Day 15, and
  - are evaluable for toxicity (received at least 75% of prescribed (21/28) doses), and
  - no more than one subject (≤1/6) experienced a DLT attributable to trametinib during the first 28 days
- If 2 or more of the initial 3-6 subjects enrolled at a dose level experience DLT, accrual will be suspended and the MTD will have been exceeded.

Table 3-2 Dose Escalation Procedure

Number of Subjects with DLT	Action
0 out of 3 subjects	Escalate to next dose level
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to the next dose level
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Expand prior dose level to at least 6 subjects

[redacted]

PK Criteria for Escalation:

Detailed PK sampling will be required on Day 15 for trametinib (see Section 7.4.1). Subjects who have a day 15 trametinib Cτ <10 ng/mL will be considered to have failed to reach the PK target. If more than 1 out of 3 to 6 patients at a dose level have failed to reach the PK target, and MTD criteria have not been met, dose escalation will continue. The Day 15 trametinib Cτ of all subjects in a dose level cohort will be compared to the target Cτ (10 ng/mL) in adults who were treated with the recommended dose in adults. In the absence of an MTD, the RP2D will be the PK target dose defined as the dose that meets the PK criteria for adequate exposure (Day 15 trametinib Cτ ≥10 ng/mL in at least 80% of subjects in a cohort of at least 6 subjects (i.e.; 5/6 subjects) treated at that dose level (Appendix 9).

3.2.3 Dose Limiting Toxicity Definitions

The DLT evaluable population is defined as those subjects participating in dose determining portion of the study (Part A and 3+3 design portions of Part A extension, Part C and Part C extension) fulfilling the 'All Treated' population criteria and having received at least 21 doses in the first 28 days to enable an appropriate evaluation of study treatment related DLTs. Subjects who are either withdrawn or dose reduced due to toxicity during the first 28 days will be included in the DLT evaluable population. Patients enrolled for only PK characterization (Part A extension, Part C, or Part C extension) or for the melanoma cohort in Part C will not be observed for DLTs.

If a subject is withdrawn before completing at least 75% of doses (at least 21 doses during the first 28 days of study treatment), for any reason other than toxicity, the subject will be replaced with the next available subject if escalation or de-escalation rules have not been fulfilled.

An AE will be considered a DLT if it is considered by the investigator to be at least possibly related to study treatment, meets any of the criteria listed in Section 3.2.3.1 or Section 3.2.3.2 and occurred during the first 28 days of treatment in the dose determining portion of the study (Part A and 3+3 design portions of Part A extension, Part C and Part C extension). DLTs will be reported to Novartis using the procedures outlined for reporting of SAEs and other events (Section 8.4.2).

3.2.3.1 Non-Hematological Dose Limiting Toxicity

- Any Grade 4 non-hematological toxicity with the exception of
  - Grade 4 fever/pyrexia that resolves to grade <2 within 72 hr with supportive care (anti-pyretics)
- Any Grade 3 non-hematological toxicity with the specific exclusion of:
  - Grade 3 nausea and vomiting of less than 3 days duration,
  - Grade 3 fever or infection of less than 7 days duration,
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplements within 7 days,
- Dose limiting hypertension will be considered as the following:
  - Grade 4 hypertension

[redacted]

- Any Grade 2 non-hematological toxicity that persists for greater than or equal to 7 days and is considered medically significant or sufficiently intolerable by subjects that it requires treatment interruption.
  - Grade 2 allergic reactions that necessitate discontinuation of study treatment will not be considered a dose-limiting toxicity
- Grade 2 left ventricular ejection fraction decrease (see Section 3.12.3.1)
- Grade 2 cardiac valvular toxicity (mitral/aortic/tricuspid) (see Section 3.12.3.2)
- Grade 2 diarrhea (see Section 3.13.4)
- Grade 2 pneumonitis (see Section 3.13.7)
- Treatment interruption longer than 14 days due to delayed recovery from toxicity will be dose limiting. Treatment delays for non-hematological toxicity (Section 3.6) that exceed 28 days meet the criteria for permanent discontinuation of study treatment (Section 6.3).

3.2.3.2 Hematological Dose Limiting Toxicity

- Any hematologic toxicity requiring treatment interruption for greater than 14 days or requires a dose reduction. Treatment delays for hematological toxicity (Section 3.6) that exceed 28 days meet the criteria for permanent discontinuation of study treatment (Section 6.3).
- Grade 4 neutropenia on 2 consecutive measurements at least 72 hr apart (continue study treatment for first measurement of Grade 4 neutropenia, recheck within 72 hr, if Grade 4 neutropenia confirmed then hold study treatment and declare as DLT)
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring platelet transfusion (exception: prophylactic platelet transfusions for platelet count ≥25,000 administered prior to procedures will not be considered dose limiting)
- Grade 4 anemia
- Grade 3 or 4 hemolysis
- Grade ≥3 leukopenia is not a dose-limiting toxicity in the absence of dose-limiting neutropenia (see above).
- Grade ≥3 lymphopenia will not be considered dose limiting.
- Grade ≥3 decrease in hemoglobin that can be corrected to at least 8.0 g/dL (Grade 2) by transfusion of red blood cells is not a dose-limiting toxicity

Maximum Tolerated Dose

The MTD is the highest dose at which no more than 1 out of 6 subjects (or < 33%) experience DLT during the first 28 days of therapy. If 2 or more subjects in a dosing cohort of 3-6 subjects (or ≥ 33%) experience DLT, the MTD has been exceeded.

3.2.4 Part A: Age Group Expansion

Following the initial 3+3 dose escalation (Section 3.2.2), the dose will be confirmed and evaluated in the following specific age groups (age on day of consent):

- Infants and toddlers (age 1 month to <2 years).

[redacted]

- Children (age 2 to ≤12 years).
- Adolescents (age >12 years to <18 years).

Note: For the purposes of this study, age 12 is considered to be the day of a subject's 12th birthday. The day after the 12th birthday, a subject is considered to be greater than 12 years.

Approximately 4 to 6 subjects may be enrolled in each age group and treated at the dose determined in the 3+3 escalation. Subjects in the age expansion cohorts will continue to be monitored for DLTs and PK as described for the initial dose escalation in Part A. The goal of the age expansion cohorts is to confirm the RP2D for each age group.

If the criteria for MTD are not met, and less than 80% of subjects in any age group (out of all subjects treated at that dose in that age group) achieve trametinib Cτ ≥10 ng/mL, subjects in that age cohort may not be enrolled on Parts B or C until the study sponsor and study team review all available safety and PK data.

Effect of sample size and PK sampling scheme on characterization of trametinib PK

A modeling and simulation exercise was undertaken to assess the effect of sample size (N=4 versus N=5 versus N=6 patients) and PK sampling scheme (5 versus 8 PK samples per patient) needed to estimate with adequate precision trametinib clearance (CL/F) and central volume of distribution (Vc/F) in pediatric patients. Two hundred studies each were simulated in 4 different age groups (i.e. 1 month-12 months, >12 months to < 2years, 2-12 years and >12 to <18 years) with varying body weight ranges and PK sampling schemes. As trametinib is metabolized predominantly via deacetylation (non-CYP450 mediated) alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways, a maturation factor (applied to lowest age group) in addition to allometric scaling was utilized to predict trametinib exposures in pediatric patients. The 60 and 140% CIs around the adult mean CL/F and Vc/F parameters from the final population PK model developed in BRAF-mutation melanoma were calculated and considered the pre-specified "goal posts" for comparison to the pediatric data. Results of this analysis suggest that for all three sample sizes evaluated (i.e. N=4 versus N=5 versus N=6 patients) with either 5 or 8 PK samples per patient, 80% of the pediatric data for CL/F fell within the adult pre-specified "goal-posts". These results suggest that the study would have 80% power to meet the 60 to 140% criterion for CL/F in all age groups to be studied with either PK sampling scheme. However, for Vc/F, regardless of sample size or PK sampling scheme, the study would not be adequately powered in each age group to be studied. Given the long elimination half-life of trametinib (~ 5 days), this is likely due to the limited PK sampling schemes utilized as input into the model. In spite of these results for pediatric Vc/F, possible dose adjustments in the pediatric population would most likely be based on CL/F. Therefore, PK sampling schemes of 8 PK samples per patient (i.e. ≥10 kg and above) and 5 PK samples per patient (<10 kg) for sample sizes between N=4-6 patients were incorporated into Part A of the pediatric protocol for trametinib.

DLT and MTD monitoring during expanded age cohorts

In any age cohort of 4 to 6 subjects, if the MTD is exceeded (≥2 subjects experience DLT in the first 28 days in that age cohort), accrual in all age cohorts will be suspended until all subjects

are fully evaluable for toxicity during the first 28 days and the sponsor and study team review safety data for all age cohorts.

- If ≥33% of all enrolled subjects, regardless of age, have had a DLT during the first 28 days, all additional subjects, regardless of age, will be enrolled at a lower dose level. If this review occurs at Dose Level 1, accrual will be suspended to all subjects until review of safety and PK data are complete.
- If <33% of all enrolled subjects, regardless of age, experience a DLT during the first 28 days, then dose reduction will occur only in the age group where a DLT was reported. Up to 6 additional subjects in that age group will be accrued and treated at a lower dose level. If this review occurs at Dose Level 1, accrual will be suspended to subjects in that age group until review of safety and PK data are complete.

Determination of the RP2D for each age group is independent of the other age groups. After the RP2D for any age group has been determined, enrollment into Parts B and C for that age range may begin even if dose determination is still ongoing in a different age group.

3.2.5 Definition of Recommended Phase 2 Dose (RP2D) of Trametinib

The RP2D is established by age groups (1 mo-<2 years, 2 years to ≤12 years, >12 years of age) as the dose level at which <33% of subjects in the age group experience DLT and >80% of subjects in the age group have trametinib Cτ ≥10 ng/mL.

3.2.6 Part A Extension: Intermediate Trametinib Dose Exploration

Preliminary trametinib PK analysis of 52 patients at the 0.025 mg/kg/day dose level from Parts A, B and C of this study (data cut-off 31-Oct-2016) indicated that the median trametinib Cτ was 8.2 ng/mL (< 10 ng/mL) in patients < 6 years old, whereas the median trametinib Cτ was 11.7 ng/mL in patients 6 years of age and older. A dose of 0.04 mg/kg/day exceeded the MTD and was not well tolerated across age categories. An intermediate dose of 0.032 mg/kg/day will be explored in patients under 6 years of age in an effort to achieve a Cτ similar to that achieved in adults (> 10 ng/mL) without exceeding the MTD in this age group. This is the only additional dose level intended for this age group. Using the DLT definition provided in Section 3.2.3 RP2D will be declared based on safety and tolerability. The 0.032 mg/kg/day dose may replace the previously determined RP2D of 0.025 mg/kg/day for trametinib monotherapy for patients under 6 years of age.

- Initially, three patients will be enrolled at the intermediate dose level (0.032 mg/kg/day) and observed for DLT (dose determining cohort).
- If 0 DLTs are noted, then 0.032 mg/kg/day will be declared the new trametinib monotherapy RP2D for patients under 6 years of age, and 9 more patients enrolled to further characterize the PK of this dose in this age group.
- If 1 DLT is observed in the initial 3 patients, then three additional patients will be enrolled into the dose determining cohort. If no additional DLTs are observed (i.e., a total of 1 DLT in first 6 patients), then 0.032mg/kg/day will be declared the RP2D for trametinib monotherapy for patients under 6 years of age, and 6 more patients will be enrolled to further characterize the PK of this dose in this age group.

[redacted]

- If 2 or more DLTs are observed in the first 3 (or 6) patients in the dose determining cohort, no further patients will be enrolled at that dose and 0.032 mg/kg/day will have exceeded the MTD, and 0.025 mg/kg/day will be confirmed as the RP2D for trametinib monotherapy in this age group.

PK samples will be collected on Day 15 and Day 22.

3.3 Part B: Tumor-Specific Expansion

Part B will evaluate the safety, tolerability, and preliminary activity of trametinib monotherapy in 4 disease-specific cohorts of subjects. Each cohort will enroll at least 10 response-evaluable subjects (evaluable for response is defined as a subject with a pre-dose and at least 1 post–dose disease assessment or clinical assessment of progression of disease).

PK samples will be collected on Day 15 only.

Archived or fresh tumor tissue to confirm BRAF V600 (cohort B4) [redacted] is required from all subjects at screening, unless the patient is specifically exempt from the requirement for histologic confirmation (e.g. NF-1, some brainstem gliomas (refer to inclusion criteria)). If tissue is unavailable, from non-exempt patients, then enrollment is not permitted.

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Trametinib will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

3.4 Part C: Trametinib in Combination with Dabrafenib

Part C will be a 3+3 study design to determine the safety, tolerability and preliminary activity of the RP2D of trametinib in combination with a limited dose escalation of dabrafenib (50% of pediatric RP2D and 100% RP2D). Part C will enroll up to 24 subjects aged 1 to <18 years with recurrent or refractory malignant solid tumors harboring a V600 mutation.

Amendment 3 provides information from the pediatric Phase 1 study of dabrafenib (BRF116013), which has established the recommended dabrafenib dose in children and provides relevant safety information for dabrafenib monotherapy in children and dabrafenib/trametinib combination therapy in adults. Once Part A of this study has been completed for at least one of the three age specific cohorts, enrollment into Part C will commence. Enrollment for Part C will close upon enrollment of 18 non melanoma pediatric patients and up to 6 BRAF V600 mutant melanoma patients or 36 months from the time Part C was opened for enrollment, whichever should come first.

PK samples will be collected on Day1, Day 15, and Day 22.

[redacted]

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Study treatment will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

3.4.1 Part C Extension: Intermediate Trametinib Dose Exploration with Dabrafenib

A total of 6 patients under 6 years of age will be enrolled in this extension part.

If the trametinib dose of 0.032 mg/kg/day is tolerated in Part A extension, a combination of trametinib 0.032mg/kg/day and full dabrafenib RP2D will be tested in this extension part in a 3+3 study design to determine the RP2D of trametinib in combination with dabrafenib for patients < 6 years of age.

- Initially three patients will be enrolled at trametinib 0.032 mg/kg/day and full dabrafenib RP2D and observed for DLT (dose determining cohort).
- If 0 DLTs are noted, then 0.032/mg/kg/day will be declared the new trametinib RP2D in combination with dabrafenib (full RP2D) for patients under 6 years of age, and 3 more patients will be enrolled to further characterize the PK of this dose in this age group.
- If 1 DLT is observed in the initial 3 patients, then 3 additional patients will be enrolled into the dose determining cohort.
    - If no additional DLTs are observed (i.e., a total of 1 DLT in 6 patients), then 0.032/mg/kg/day will be declared the trametinib RP2D in combination with dabrafenib (full RP2D) for patients under 6 years of age.
    - If 2 or more DLTs are observed in these 6 patients, 0.032 mg/kg/day will have exceeded the MTD, and 0.025 mg/kg/day will be confirmed as the trametinib RP2D in combination with dabrafenib (full RP2D) for this age group.
- If 2 or more DLTs are observed in the initial 3 patients, 0.032 mg/kg/day will have exceeded the MTD, and 0.025 mg/kg/day will be confirmed as the trametinib RP2D in combination with dabrafenib for this age group. The remaining three patients allocated for this part will be enrolled at trametinib 0.025 mg/kg/day and full dabrafenib RP2D to further characterize the PK.

If the trametinib dose of 0.032 mg/kg/day is not tolerated in Part A extension, 0.025 mg/kg/day will be confirmed as RP2D for trametinib monotherapy and for use in combination with dabrafenib in this age group. The 6 patients allocated for this extension part will be enrolled at trametinib RP2D (0.025 mg/kg/day) and full dabrafenib RP2D to further characterize the PK in this age group.

PK samples will be collected on Day 1, Day 15, and Day 22.

[redacted]

3.5 Part D: Tumor-Specific Expansion of Trametinib in Combination with Dabrafenib

Part D will evaluate the safety, tolerability, and preliminary activity of the combination of trametinib and dabrafenib in 2 disease-specific cohorts in patients from 12 months to less than 18 years of age. BRAF V600-mutant LGG cohort will enroll approximately 20 subjects and BRAF V600-mutant LCH cohort will enroll approximately 10 subjects.

At the time of Amendment 5 release, RP2D of trametinib and dabrafenib combination has been established in Part C in children and adolescents ages 6 years to <18 years. Patients who are 6 to < 18 years old will start enrolling in Part D in parallel with the testing of the additional dose level of trametinib in Part A extension, (patients aged 1 month to < 6 years) and then in Part C extension, (patients aged 12 months to <6 years). Once the RP2D of trametinib and dabrafenib combination is determined for patients <6 years in Part C extension (or in Part A extension), Part D will start enrolling patients aged 12 months to <6 years.

Archived or fresh tumor tissue to confirm BRAF V600 is required from all subjects at screening. If tissue is unavailable, then enrollment is not permitted.

PK samples will be collected on Day 1, Day 15, and Day 22.

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Study treatment will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

3.6 Criteria for Continuing in the Study

For subjects enrolled on Part A, Part B, Part C, and Part D, the following criteria must be met to advance beyond the first 28 days:

- Subjects have not met discontinuation of treatment criteria (Section 6.3)
- No evidence of progressive disease (See Section 7.6) defined as no clinical evidence of progression for assessments that do not require imaging/disease assessment or no evidence of radiographic or histologic/morphologic progression if disease assessment included imaging (solid tumor)
  Patients will be permitted to continue study treatment beyond initial Investigator-assessed disease progression, as long as they meet the following criteria:
  - Investigator assessed clear evidence of clinical benefit
  - Tolerance of study drug
  - Continuation of study treatment is in the best interest of the patient as determined by the Investigator. For this determination, the investigator should consider all relevant data, such as:

[redacted]

- Absence of symptoms and signs of progressive disease
- No decline in performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomic sites (e.g., cord compression) that would require urgent medical intervention.
- Patient/guardian is willing to continue on the study

If the Investigator determines that all above criteria are met, the patient may continue study treatment and follow all study related procedures, including tumor assessments, as scheduled in the appropriate Time and Events Tables (Section 7.1 table.

- After each tumor assessment, the investigator must confirm if the patient is still benefitting from study treatment, and document this in patient medical records. Toxicity resolved to baseline or grade ≤ 2 with specific exception of:
  - Specific criteria for Ejection Fraction Results (Section 3.12.3).
  - For subjects in Part B who are not evaluable for hematological toxicity due to marginal bone marrow function from disease infiltration or prior therapy, the following hematologic criteria must be met:
    - Absolute neutrophil count > 500 cell/μL,
    - Platelet count > 25,000/μL (without transfusion in ≥ 7 days),
    - No life threatening consequences of anemia (no grade 4 anemia per NCI-CTCAE v4.03) (NCI 2009).

3.7 Intra-subject Dose-Escalation

3.7.1 Part A: Intra-subject Dose Escalation

For subjects enrolled on Part A, an individual subject's dose level may be increased up to the RP2D in the appropriate age cohort if the subject has (all of the following must be true):

- completed at least 56 days of treatment,
- $C\tau$ is less than 10 ng/mL,
- not experienced a drug related toxicity greater than Grade 2,
- met criteria for continuation of study treatment (Section 3.6),
- approval was obtained from a Medical Lead.

Subjects who meet criteria for intrasubject dose escalation will repeat evaluations for the first 28 days (See Section 3.2.2), including Day 15 PK.

No subject may dose escalate beyond the RP2D or currently evaluated dose for their age group. No subject may have the dose of trametinib escalated above 0.04 mg/kg/day.

For individual subjects who meet criteria for intrasubject dose escalation, data from the escalated dose will not contribute to the definition of MTD or to establishing the recommended dose but will be summarized in the study toxicity data reporting. Data from subjects who are able to increase their dose may be incorporated into PK-PD modelling.

[redacted]

3.7.2 Part B Intra-subject Dose Escalation

For subjects ages below 6 years enrolled in Part B at 0.025 mg/kg/day dose level, an individual subject's trametinib dose level may be increased up to 0.032 mg/kg/day if this dose is found to be tolerated in Part A extension and if the subject has (all of the following must be true):

- completed at least 56 days of treatment,
- not experienced a drug related toxicity greater than Grade 2,
- met criteria for continuation of study treatment (Section 3.6),

Subjects who meet criteria for intra-subject dose escalation and receive the higher dose may continue to follow the time and event table using the originally assigned study day 1

Subjects may be allowed to re-escalate following dose reduction for AE upon resolution of AE. Please follow guidelines in Section 3.13.

3.7.3 Part C Intra-subject Dose Escalation

For subjects ages below 6 years enrolled in Part C at 0.025mg/kg/day trametinib dose, an individual subject's trametinib dose level may be increased up to 0.032 mg/kg/day if this dose is found to be tolerated in Part C extension and if the subject has (all of the following must be true):

- completed at least 56 days of treatment,
- not experienced a drug related toxicity greater than Grade 2,
- met criteria for continuation of study treatment (Section 3.6),

For subjects enrolled in Part C at Dose Level 1, an individual subject's dabrafenib dose may be increased to Dose Level 2 (full dabrafenib RP2D) if the subject has (all of the following must be true):

- completed at least 56 days of treatment,
- not experienced a drug related toxicity greater than Grade 2,
- met criteria for continuation of study treatment (Section 3.6),

Subjects who meet criteria for intra-subject dose escalation and receive the higher dose may continue to follow the time and event table using the originally assigned study day 1

Subjects may be allowed to re-escalate following dose reduction for AE upon resolution of AE. Please follow guidelines in Section 3.13, Section 3.14 and Section 3.15.

3.7.4 Part D Intra-subject Dose Escalation

Subjects may be allowed to re-escalate following dose reduction for AE upon resolution of AE. Please follow guidelines in Section 3.13, Section 3.14 and Section 3.15.

[redacted]

3.8 Study Schematics

Figure 3-1 Trametinib Dose Escalation (Part A)

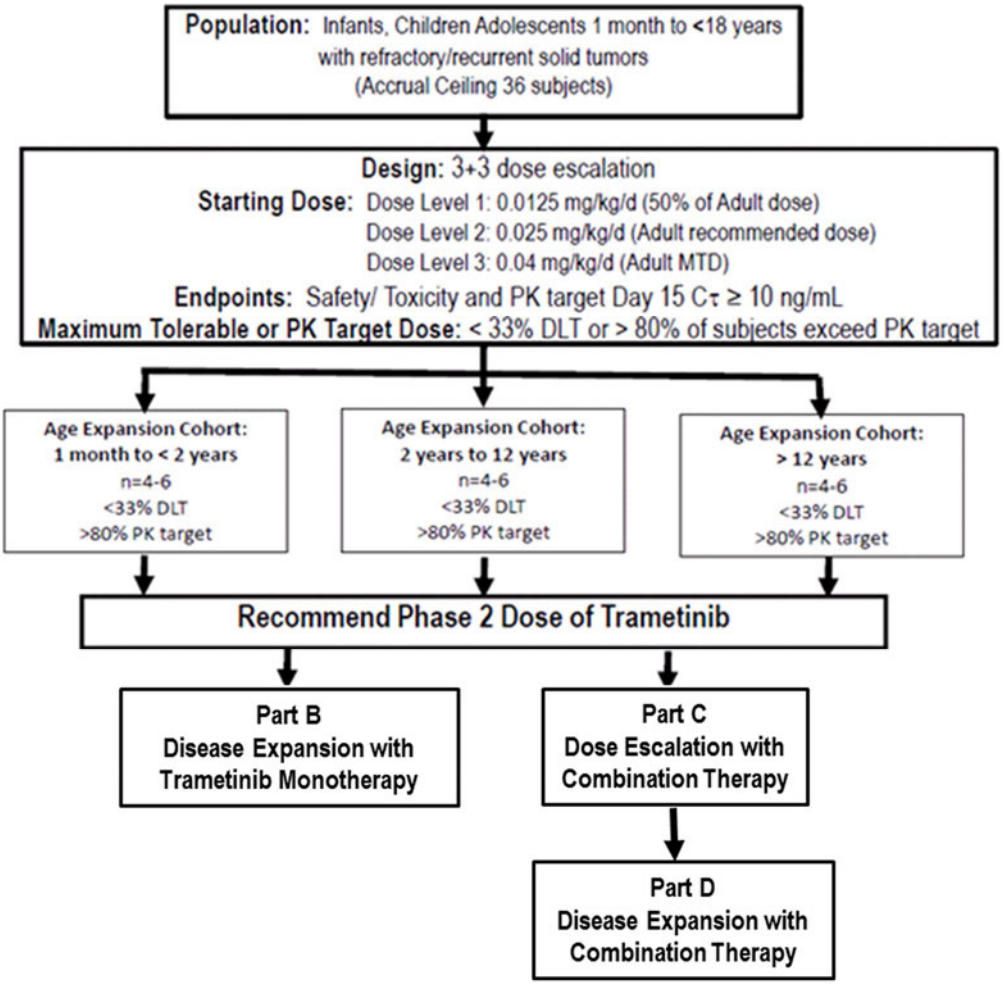
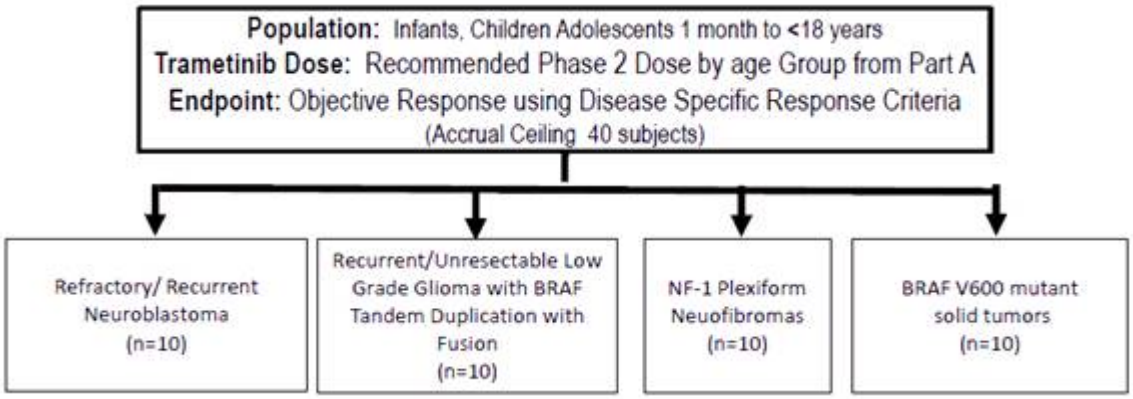


Figure 3-2 Trametinib Disease Specific Expansion (Part B)



Note: A minimum of four subjects age younger than 6 years old is required in each of the four groups.

[redacted]

Figure 3-3 Trametinib in Combination with Dabrafenib (Part C)

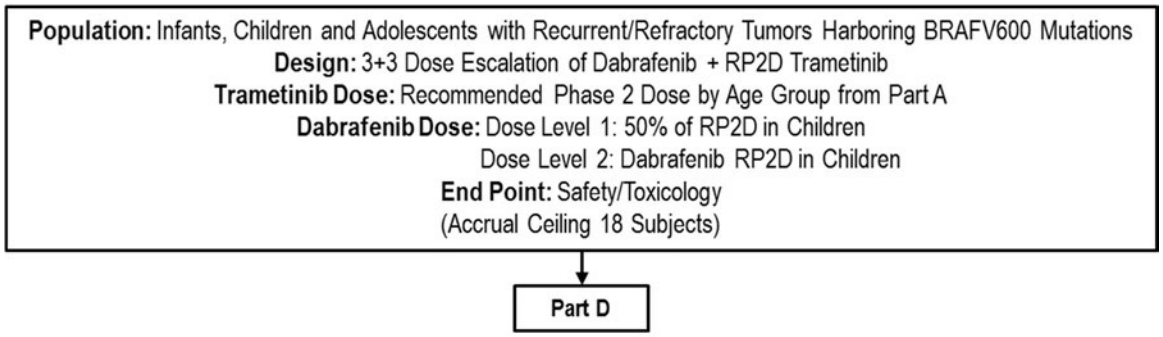


Figure 3-4 Tumor-Specific Expansion of Trametinib in Combination with Dabrafenib (Part D)

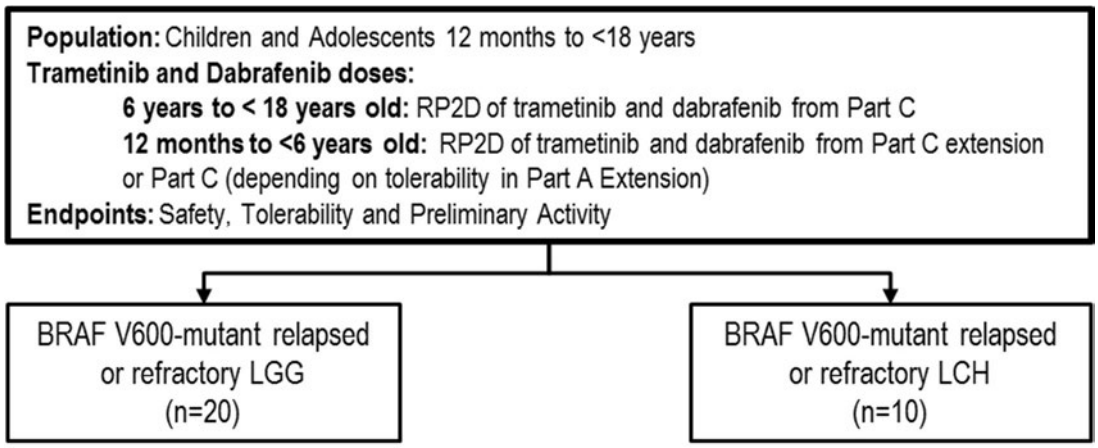
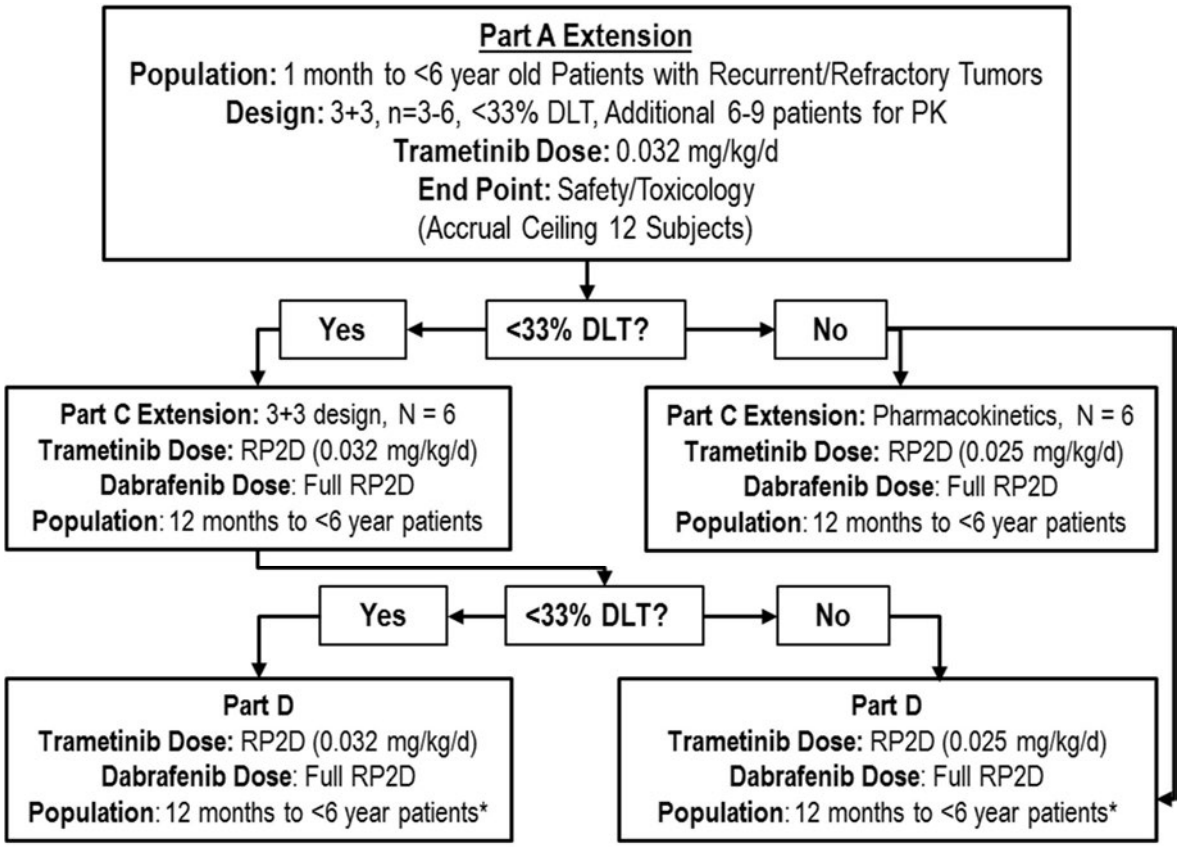


Figure 3-5 Additional Dose Exploration (Part A Extension and Part C Extension)



*Note: Part D design for 6 years to <18 years old patients is provided in Figure 3-4

3.9 Rationale

3.9.1 Rationale for Study

Despite the advances made over the past 30 years in the treatment of pediatric cancer, there remain important subpopulations within this group of patients for whom efficacious therapies have yet to be discovered. Specifically, pediatric patients with recurrent high grade gliomas, and patients with metastatic or recurrent solid tumors, continue to have a poor prognosis and lower rates of long-term survival than patients with localized or non-recurrent disease. Use of second- and third-line cytotoxic chemotherapies, even in dose-intensive regimens, has yet to yield significant impact on progression-free survival or overall survival. Therefore development of new therapeutic options for pediatric cancer patients is needed.

3.9.2 Rationale for Populations

Trametinib is FDA approved for the treatment of adults with BRAF V600 mutant-positive malignant melanoma that is unresponsive to standard therapies or for which there was no approved or curative therapy. Preliminary data from ongoing studies of trametinib in adult subjects with other advanced solid tumors (e.g., pancreatic cancer) as well as results from other MEK inhibitor clinical programs, suggest that trametinib may have beneficial effects in tumour

types beyond melanoma. Trametinib is being proposed for study in pediatric subjects with advanced solid tumors, with a focus on those that have been reported in the medical literature to potentially involve activation of the RAS/RAF signalling pathway. These include tumors positive for BRAF V600 mutation, BRAF gene duplication (e.g., juvenile pilocytic astrocytoma, low grade gliomas); NF-1 related PN; and neuroblastoma.

Part A and B of this study will focus on development of trametinib monotherapy in infants, children and adolescents with advanced or relapsed/recurrent solid tumour types that may involve activation of the RAS/RAF/MEK signalling pathway.

A concurrent study of dabrafenib in pediatric subjects with BRAF V600 mutation positive tumors is ongoing. Recent data from adult studies indicate that the combination of trametinib with dabrafenib is well tolerated and may provide more benefit to subjects with BRAF V600 mutation in tumors. Therefore, subjects with BRAF V600 mutation in tumors may be enrolled .

Part C and D of this study will focus on development of trametinib and dabrafenib combination therapy in children and adolescents with BRAF V600 mutation positive tumors.

3.9.3 Rationale for Dose

3.9.3.1 Trametinib

The targeted dose and schedule of trametinib is based on the adult clinical dose and schedule required to achieve therapeutic benefit in BRAF mutant melanoma. In adults, the mean (range) AUC(0-τ) following repeat dosing of 1 and 2 mg once daily was 175 ng•hr/mL (107-243 ng•hr/mL) and 360 ng•hr/mL (204-536ng•hr/mL), respectively. The mean (range) Cτ following repeat dosing of both the 1 and 2 mg once daily doses were 13.8 (n=2, 8.44 and 19.1 ng/mL) and 12.1 ng/mL (n=13, 8.3-16.9 ng/mL, CV=19%, 95%CI=10.86-13.4), respectively. The lowest Cτ concentration associated with an objective response was approximately 7 ng/mL, where 1 complete response (CR) (1 mg dose) and 1 partial response (PR) (0.5 mg dose) were observed of 12 subjects with Cτ of 7 ng/mL.

Given the safety and tolerability observed at the adult dose of 2 mg once daily and the variability associated with the mean adult trough concentration (95%CI=10.86-13.4), therapeutic benefit in pediatric subjects may be achieved by attaining trough concentration at steady state (day 15 C$\tau \geq$ 10 ng/mL) that is similar to those achieved in adults at the recommended dose. In the absence of DLT, if the PK exposure (Cτ) is significantly lower than those achieved in adults, higher doses for subsequent cohorts may be modified in a protocol amendment in order to achieve PK target during dose escalation.

The starting dose in the pediatric population will be based on 1 mg as given to average 80 kg adult subject (0.0125 mg/kg) which is 50% of the recommended and FDA approved dose in adults. Steady state trough concentration (Cycle 1 Day 15 Cτ (trough) data for trametinib from adults will be compared to PK data in the pediatric subjects and will guide pediatric dose recommendations. Exposure and Day 15 Cτ will be assessed in-stream during the study. PK sampling at day 15, modelling and simulation will allow prediction of trametinib dosage regimens for children that will deliver target trametinib steady-state concentrations and exposure similar to adults.

[redacted]

Three dose levels are planned in pediatric subjects. In the absence of DLT, if the PK exposure is significantly lower than those achieved in adults,, higher doses for subsequent cohorts may be modified in a protocol amendment in order to achieve PK target during dose escalation.

Since the approval and implementation of Amendment 3, the dose of 0.04 mg/kg/day was found to result in DLTs and 0.025 mg/kg/day was established as the RP2D of trametinib in Parts B and C based on safety and tolerability. Based on preliminary trametinib PK analysis in patients at the selected dose of 0.025 mg/kg in Parts A, B and C (data cut-off 31-Oct-2016), the median trametinib $C\tau$ was 8.2 ng/mL in patients < 6 years (Table 3-3). Due to this trend of lower trametinib exposure in patients < 6 years, an intermediate dose of 0.032 mg/kg/day may achieve exposures that are similar to those in adults. This dose will be explored as single agent first. If safety and tolerability permit, this dose will be tested in combination with dabrafenib.

Table 3-3 Median trametinib PK (Day 15) by age groups

Age Range	Dose (mg/kg)	N	Ctrough (ng/mL)
< 6 years	0.025	22	8.2
6-17 years	0.025	30	11.7

Age-related anatomical and physiological changes occur in the first 6 months to 24 months that may affect drug absorption and disposition. This study will evaluate appropriateness of weight based dosing across three age groups; those less than 2 years of age, those 2 years of age to 12 years of age (inclusive), and those over 12 years of age up to <18 years of age.

3.9.3.2 Starting dose for Part C, Trametinib in Combination with Dabrafenib

In adults the recommended dose of trametinib in combination with dabrafenib is the full adult monotherapy dose of each: trametinib 2 mg PO daily and dabrafenib 150 mg PO twice daily. In the context of this clinical trial, the trametinib dose administered in Part C will be the trametinib monotherapy RP2D from Part A. The monotherapy RP2D of dabrafenib in children was established on a separate trial (BRF116013). The following RP2D doses were determined for dabrafenib:

- < 12 years old subjects: 5.25 mg/kg/day dabrafenib administered orally, divided into two equal doses
- ≥ 12 years old subjects: 4.5 mg/kg/day dabrafenib administered orally, divided into two equal doses

For the evaluation of combination therapy on this trial, the starting dose of dabrafenib (Dose Level 1) will be 50% of the RP2D, divided into two equal doses. If tolerated a single dose escalation to the full dabrafenib RP2D (Dose Level 2) will be evaluated. If dose levels proposed are not well tolerated, intermediate dose levels of dabrafenib and/or trametinib may be evaluated if warranted.

Table 3-4 Recommended dabrafenib dose levels

	Dabrafenib		Trametinib
Dose Level	**< 12 years**	**≥ 12 years**	**All ages**
1 (Starting dose)	2.63 mg/kg/d	2.25 mg/kg/d	RP2D
2	5.25 mg/kg/d	4.5 mg/kg/d	RP2D

The RP2D for trametinib monotherapy determined in Part A extension for patients aged 1 month to < 6 years (either 0.025 mg/kg/day or 0.032mg/kg/day) along with full dabrafenib RP2D will be the starting dose for Part C extension patients (aged 12 months to <6 years).

3.9.3.3 Starting dose for Part D, Trametinib in Combination with Dabrafenib

Based on safety, tolerability and PK, the dose of trametinib and dabrafenib in patients 6 years to <18 years will be the RP2D (0.025mg/kg/day trametinib and full RP2D of dabrafenib) already determined from Part C. For patients <6 years old, the trametinib dose will be determined from Part C extension (or Part A extension) and will be either 0.025 mg/kg/day or 0.032 mg/kg/day. The selected dose of trametinib will then be combined with the full RP2D of dabrafenib (100% of monotherapy dose) in patients under 6 years of age, just as in other age groups. Patients who are 6 to < 18 years old will start enrolling in Part D in parallel with the testing of the additional dose level of trametinib in Part A extension, (patients aged 1 month to < 6 years) and then in Part C extension, (patients aged 12 months to <6 years).

The safety of the combination of trametinib and full dose dabrafenib has been confirmed in adults and pediatrics. Similar to other age groups, the dose of 0.025 mg/kg/day trametinib was tolerated with full dose dabrafenib (5.25 mg/kg/day) in patients under 6 years of age in Part C. The dose of 0.032 mg/kg/day trametinib will be brought forward into Part D for patients under 6 years of age only if it is shown to be safe when given as monotherapy in Part A extension and as combination therapy in Part C extension.

3.9.4 Rationale for Endpoints

This study will be the first administration of trametinib to pediatric subjects. Safety parameters will be carefully and systematically monitored.

Part A: The expectation is that a PK endpoint will help define a dose that will provide an efficacious exposure in pediatric subjects without the need to reach maximum toxicity levels. In the absence of DLT in this pediatric study, a PK target endpoint will be used as the primary endpoint for dose determination. In adults, there is minimal intersubject variability in the steady state $C\tau$ (CV 19%, 95%CI=10.86-13.4), and responses were observed at exposures as low as $C\tau$ = 7 ng/mL in subjects with melanoma, while efficacy has been clearly identified at known plasma levels of study drug (≥10 ng/mL trough) which were well tolerated. However, safety will be carefully reviewed and DLT definitions are incorporated in the protocol should safety in pediatric subjects differ from those in adult subjects following treatment with trametinib.

Part A extension: Based on preliminary PK data from Parts A, B and C, there was a trend for lower trametinib exposure in patients < 6 years old. An intermediate dose that is between the RP2D established in Part A and the higher dose that exceeded MTD will be explored. Safety, tolerability and PK are the primary endpoints of this part of the study.

[redacted]

Part B: The RP2D established in Part A and verified by age cohorts (1 month to <2 years, 2 years to ≤12 years and >12 years) will be administered in Part B. Safety, tolerability and preliminary activity assessed by investigator are the primary endpoints of this part of the study..

Part C: Subjects will be monitored for DLT and toxicity using the same DLT criteria as in Part A. Safety, tolerability and preliminary activity are the primary endpoints of this part of the study. In the absence of DLT, dose escalation will not exceed the trametinib monotherapy RP2D in combination with the dabrafenib monotherapy RP2D.

Part C extension: If Part A extension indicates trametinib 0.032mg/kg/day is tolerated in patients < 6 years old, the same trametinib dose will be explored in Part C extension with full dabrafenib RP2D. Safety, tolerability and PK are the primary endpoints of this part of the study.

Part D: Safety and tolerability are the primary endpoints of this part of the study.

3.10 Study Treatment

3.10.1 Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Each site will be given a subject number range. These ranges and details regarding assignment of subject numbers can be found in the SPM.

Treatment will not be randomized; nonetheless, each subject will be assigned a randomization number as described in SPM.

At the time of enrollment, subjects will be assigned to one part of the study designated Part A or Part B or Part C or Part D. Individual subjects will participate in the specified part of the study, however, data analysis may combine parts of the study. For example, all subjects treated at the trametinib RP2D dose in Part A will contribute to age expansion in Part A of the study. Response evaluations in subjects in Part A of the study at the RP2D will be considered in analysis of Part B for specific disease cohorts.

3.11 Dosage and Administration of Study Treatments

3.11.1 Trametinib

Please note that study drug dispensed to subjects in the original container should not be repackaged without explicit permission from the Sponsor. Trametinib is administered orally once daily under fasting conditions, either 1 hr before or 2 hr after a meal. Subjects should be encouraged to take trametinib approximately 24 hours apart at the same time each day. Dose levels are provided in Section 3.2.1.

Ideally, patients will take the trametinib study drug in the morning up through the PK day. After the PK day, the patient may change to evening dosing, if they prefer. If the patient is on an evening dosing regimen as they enter the PK testing period, the evening dose prior to the PK day SHOULD BE taken by the patient. In all cases, the timing of the dose prior to the PK sampling must be maintained and recorded accurately.

[redacted]

For trametinib tablets, it is recommended that subjects drink approximately 4 to 6 mL of water/kg body weight with each dose.

Trametinib pediatric oral solution formulation will be administered with a graduated syringe. It is recommended that subjects drink 4 to 6 mL of water/kg body weight following dosing.

A dosing nomogram (see Appendix 2) based on weight and dose level will be used to prescribe trametinib to minimize inter-subject dosing variability. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose. If a subject misses a dose, subject should not double the next regularly scheduled dose. However, subject can take the missed dose immediately if the next scheduled dose is at least 12 hr later. Subject should take the next dose at its usual time.

The total daily trametinib dose should not exceed the adult dose (2mg) in any subject.

Refer to Section 3.13, Section 3.14 and Section 3.15 for dose modifications for toxicity.

3.11.2 Dabrafenib

Please note that study drug dispensed to subjects in the original container and should not be repackaged without explicit permission from the Sponsor.

Capsules: Dabrafenib capsules will be supplied by Novartis (for subjects able to reliably and consistently swallow capsules). For capsule administration, only 50 mg and 75 mg dose strengths are available. Therefore, the dose recommendations by weight range are within 20% of the ideal dose. The same dosing recommendation was applied to the suspension nomograms, at the same weight ranges that overlap with the capsule nomograms.

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Dispersible tablets: Dabrafenib will be supplied by Novartis as dispersible tablets. The tablets will be dispersed with a specified volume of water at the time of use to form a suspension. Administration will be performed using a dosing cup / PP oral liquid dispenser.

Detailed instructions for the dispersion of the tablets and dosing will be provided in the SPM.

Dabrafenib (applicable for all formulations) will be administered orally, twice daily based on weight at the appropriate study dose level. A dosing nomogram (Appendix 2, also in the SPM) based on weight and dose level will be used to prescribe dabrafenib to minimize inter-subject dosing variability.

The total daily dabrafenib dose should not exceed the adult dose (300mg) in any subject.

Dabrafenib capsules will be taken with approximately 1 ounce (30 mLs) of water for every 10 pounds of body weight, twice a day. Subjects should be encouraged to take their doses at approximate 12 hour intervals and at similar times every day.

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

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

[redacted]

Children younger than 6 years and subjects, regardless of age, with a risk of choking when swallowing capsules will be required to use the dispersible tablet formulation.

3.11.3 Meals and Dietary Restrictions

All subjects will fast except for water ad libitum for 2 hr prior and 1 hr following administration of trametinib and/or dabrafenib in either formulations. Data from the adult trametinib food effect study (MEK113709) demonstrated that administration of trametinib with a high-fat, high-calorie meal resulted in an approximate 70% decrease in Cmax and 10-24% decrease in AUC compared to administration under fasting conditions. Data from the adult dabrafenib food effect study (BRF113468) demonstrated that administration of dabrafenib following a high-fat, high-calorie meal resulted in an approximate 30% decrease in exposure and 50% decrease in Cmax compared to administration under fasting conditions.

- If it is not possible for a subject to tolerate the fasting conditions noted above, trametinib and/or dabrafenib can be administered with a small non-fat meal (e.g., small amount of apple juice/sauce, a piece of dry toast). Children that are breastfeeding may continue to breast feed on demand. If child is breast fed during collection of PK samples the time of breastfeeding should be recorded.
- Avoid administration with high-fat or high calorie food or beverages, examples milk, beverages containing dairy products or high protein beverages or supplements for 2 hr prior and 1 hr following administration of trametinib and/or dabrafenib in either formulation.

3.11.4 Blinding

This is an open-label study.

3.12 Safety Management Guidelines

3.12.1 Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Upper limit of normal (ULN) for ALT in this study will be 45 U/L. **Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met**:

1. ALT ≥3 times upper limit of normal (ULN) and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and international normalization ratio [INR] >1.5)
   - NOTE: Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
2. ALT ≥5 times ULN.
3. ALT ≥3 times ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥3 times ULN persists for ≥4 weeks.

[redacted]

5. ALT ≥3 times ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3 times ULN **and** <5 times ULN **and** bilirubin <2 times ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. See following section for details on weekly follow-up procedures for these subjects.

3.12.1.1 Liver Chemistry Follow-up Procedures

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria 1 through 5 defined in Section 3.12.1:

- Immediately discontinue study treatment(s).
- Notify the Medical Lead within 24 hr of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event electronic case report forms (eCRFs). If the event also meets the criteria of a SAE (see Section 8.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s).

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:

- Monitor subjects **weekly** until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects meeting stopping criterion 1 (ALT ≥3 times ULN and bilirubin ≥2 times ULN [or ALT ≥3 times ULN and INR >1.5]):

- **This event is considered an SAE** (see Section 8.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hr for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, ALP, bilirubin) resolve, stabilize or return to within baseline values.
- In addition, every attempt should be made to carry out the liver event follow-up assessments described in Section 3.12.1.2.

3.12.1.2 Liver Chemistry Testing Procedures

For subjects meeting any of the liver chemistry stopping criteria in Section 3.12.1, make every attempt to carry out the liver event follow-up assessments described below. Laboratory tests for

[redacted]

liver events will be performed at the central laboratory. Additional information can be found in the lab manual and SPM.

- 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, then obtain heterophile antibody or monospot testing)
- Blood sample for pharmacokinetic (PK) analysis, obtained within 20 days of the last dose of study treatment(s). Record the date and time of the PK blood sample draw and the date and time of the last dose of study treatment(s) prior the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date or time of the last dose cannot be approximated, or if a PK sample cannot be collected within the 20-day period following the last dose, do not obtain a PK sample. Instructions for sample handling and shipping are found in the Study Procedures Manual (SPM).
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2 X upper limit of normal (ULN).
- Obtain a complete blood count (CBC) with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE eCRF.
- Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication eCRF.
- Record alcohol use on the liver event alcohol intake eCRF.

Every attempt should be made to obtain the following assessments for subjects with ALT ≥3 X ULN and bilirubin ≥2X ULN (>35% direct). These assessments are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, MRI or CT) to evaluate liver disease.
- Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.
- Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week (James 2009).

[redacted]

3.12.2 QTc Stopping Criteria

QTc-Prolongation[a]	Required adverse event management guidelines	Mandatory dose modification requirements
● QTc ≥501 msec	● 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. ● Consider evaluation with cardiologist (recommended).	● Interrupt all study treatments (trametinib and dabrafenib) until QTc prolongation resolves to grade 1 or baseline ● If event resolves to grade 1 or baseline, restart study treatment at current dose level ● If event does not resolve, permanently discontinue study treatments. ● If event recurs, permanently discontinue study treatments.

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.

Every attempt should be made to obtain a blood sample to test serum potassium, calcium, phosphorus and magnesium levels. If any of these are below the lower limits of normal, correct with supplements to within normal limits.

A review of concomitant medication usage for any medications that may prolong QTc should also be performed.

3.12.3 Left Ventricular Ejection Fraction (LVEF) and Valvular Toxicity Stopping Criteria

3.12.3.1 LVEF Stopping Criteria

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 (Section 7.1). Dose modification guidance and stopping criteria for LVEF decrease are provided inTable 3-5.

ECHO should be performed at baseline and at follow up visit(s). Electronic copies of all ECHO scans will be collected by Novartis for review. Instructions for submission of ECHO scans are provided in the Study Procedures Manual (SPM).

Table 3-5 Mandatory dose modification and required clinical management for LVEF

LVEF-drop (%) & clinical symptoms	Required adverse event management guidelines	Mandatory dose modification requirements
Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	● Report as SAE. ● Closely monitoring LVEF via ECHO, repeat ECHO within 2 weeks. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later ● If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) ● Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter.	Interrupt trametinib (on combination therapy dabrafenib may continue) If the LVEF recovers within 4 weeks, ● restart treatment with trametinib dose reduced to levels indicated in Appendix 2, dose reduction column and continue dabrafenib at the same dose level. ● If the event recurs at the reduced dose level, permanently discontinue trametinib. On combination therapy dabrafenib may continue

[redacted]

LVEF-drop (%) & clinical symptoms	Required adverse event management guidelines	Mandatory dose modification requirements
	● If repeat LVEF does not recover within 4 weeks. ● Consult with cardiologist (recommended) ● Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution	● If the event recurs after the subject re-escalated to previous dose level, Interrupt trametinib (on combination therapy dabrafenib may continue) and manage as first event. Note: To restart trametinib, LVEF must return to ≤10% decrease compared to original baseline ● If more than two occurrence, permanently discontinue trametinib. On combination therapy dabrafenib may continue If LVEF does not recover within 4 weeks ● Permanently discontinue trametinib, (on combination therapy dabrafenib may continue)
Symptomatic: Resting LVEF ≤39% or >20% absolute reduction from baseline	● Report as SAE. ● Consult with cardiologist (recommended) ● Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution	● Permanently discontinue trametinib. ● Interrupt dabrafenib ● Restart dabrafenib if LVEF recovers including resolution of symptoms.

3.12.3.2 Cardiac Valvular Toxicity Stopping Criteria

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (ECHO) (Grade 2 mitral/tricuspid/aortic valvular toxicity per National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.03) should temporarily discontinue study treatment (both trametinib and dabrafenib if on combination therapy) and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks, the subject may be restarted on study treatment at a reduced dose(s) (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue study treatment (both trametinib and dabrafenib if on combination therapy). The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue study treatment (both trametinib and dabrafenib if on combination therapy). Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart study treatment at a reduced dose (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib).

ECHO must be performed at baseline and at the final study visit. Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity will be

required by Novartis for review. Instructions for submitting qualifying ECHOs are provided in the Study Procedures Manual (SPM).

3.13 Dose Delay and Modification for Events Considered Related to Trametinib

A maximum of one trametinib dose reduction is allowed. If a second dose level reduction is required, treatment will be permanently discontinued.

Trametinib dose modification guidelines are outlined in Table 3-6 for clinically significant toxicities with exception for following events of special interest:

- rash (Section 3.13.3)
- diarrhea (Section 3.13.4)
- ejection fraction changes (Section 3.12.3.1)
- hypertension (Section 3.13.5)
- prolonged QTc (Section 3.12.1)
- pneumonitis (Section 3.13.5)
- visual changes (Section 3.13.5)
- liver chemistry elevation (Section 3.12.1)

For these refer to the relevant sections for dose modification guidelines for adverse events of special interest as stated above.

If treatment related toxicities occur when dabrafenib is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions described below.

3.13.1 Dose Delay and Modification for Events Considered Related to Trametinib and/or Dabrafenib

Table 3-6 Dose Delay and Modification for General Events Considered Related to Trametinib and/or Dabrafenib

CTCAE Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1 and tolerable Grade 2	● Monitor closely ● Provide supporting care according to institutional standards	● Continue study drug(s) at current dose level
Intolerable Grade 2 and Grade 3	● Monitor closely. ● Provide supportive care according to institutional standards.	● Interrupt study drug(s) (except for cuSCC, keratoacanthoma, new primary melanoma, and basal cell carcinoma) ● When toxicity resolves to Grade 1 or baseline, restart study drug(s) at reduced levels (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib) ● If the Grade 2 (intolerable) or Grade 3 toxicity recurs while at reduced dose, discontinue study treatment(s) ● If the Grade 2 (intolerable) or Grade 3 toxicity recurs while after re-escalating to previous dose,

CTCAE Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
		● Interrupt dabrafenib and trametinib. ● When toxicity resolves to Grade 1 or baseline, restart study drug(s) reduced levels (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib)
Grade 4	● Monitor closely. ● Provide supportive care according to institutional standards.	● Interrupt study drug (s) ● Once toxicity resolves to ≤ Grade 1 or baseline , restart study drug(s) at reduced levels (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib) ● or permanently discontinue study drug (s) at the discretion of investigator

Table 3-6a Dose Modification for dabrafenib (DRB436) dispersible tablet for patients less than 12 years of age

Weight (kg)	Dose (b.i.d)	Dose Reduction Level 1 (b.i.d)	Dose Reduction Level 2 (b.i.d)
7-9.5	20 mg	10 mg	0 mg
9.6-13.5	30 mg	20 mg	10 mg
13.6-17.5	40 mg	30 mg	20 mg
17.6-20.5	50 mg	40 mg	30 mg
20.6-24.5	60 mg	50 mg	40 mg
24.6-28.5	70 mg	60 mg	50 mg
28.6-32.5	80 mg	70 mg	60 mg
32.6-36.5	90 mg	80 mg	70 mg
36.6-40.5	100 mg	90 mg	80 mg
40.6-43.5	110 mg	100 mg	90 mg
43.6-47.5	120 mg	110 mg	100 mg
47.6-51.5	130 mg	120 mg	110 mg
51.6-55.5	140 mg	130 mg	120 mg
≥55.6 kg	150 mg	140 mg	130 mg
Dose: 5.25 mg/kg/day Dose level 1: 4.5 mg/kg/day Dose level 2: 3.75 mg/kg/day			

Table 3-6b Dose Modification for dabrafenib (DRB436) dispersible tablet for patients greater or equal 12 years of age

Weight	Dose (b.i.d)	Dose Reduction Level 1 (b.i.d)	Dose Reduction Level 2 (b.i.d)
10-11.5	20 mg	10 mg	0 mg
11.6-17.5	30 mg	20 mg	10 mg
17.6-20.5	40 mg	30 mg	20 mg
20.6-24.5	50 mg	40 mg	30 mg
24.6-28.5	60 mg	50 mg	40 mg
28.6-32.5	70 mg	60 mg	50 mg
32.6-36.5	80 mg	70 mg	50 mg

[redacted]

36.6-40.5	90 mg	80 mg	60 mg
40.6-43.5	100 mg	90 mg	60 mg
43.6-47.5	110 mg	100 mg	70 mg
47.6-51.5	120 mg	110 mg	80 mg
51.6-55.5	130 mg	120 mg	80 mg
55.6-64.5	140 mg	130 mg	100 mg
≥64.6	150 mg	140 mg	110 mg
Dose: 4.5 mg/kg/day Dose level 1: 3.75 mg/kg/day Dose level 2: 3.00 mg/kg/day			

For subjects treated with solid dosage forms, dose reductions will occur in increments of 50 mg from the total daily dose for dabrafenib capsules and in increments of 0.5 mg from the total daily dose for trametinib tablets. See also Appendix 2.

3.13.2 Guidelines and Dose Modifications for Trametinib Events of Special Interest

The severity of adverse events (AEs) will be graded utilizing the NCI-CTCAE v4.03 (NCI 2009). Guidelines for dose modifications and interruptions for management of common toxicities associated with trametinib are provided in this section.

3.13.3 Management of Rash

Rash is a frequent AE observed in subjects receiving trametinib and dabrafenib (see the Investigator's Brochure for more information). A proactive approach is recommended. Encourage subjects to avoid unnecessary exposure to sunlight and encourage use of sunscreens and sunblock (see Section 3.13.3.1). If subjects develop rash, verify treatment intervention and consider recommended steps outlined under Section 3.13.3.2 and Table 3-7.

3.13.3.1 Prophylactic Treatment

The following management should be considered (see Table 3-7). The prophylactic regimen should be based on the investigator's experience.

1. Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily.
2. Thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
3. Mild strength topical steroid (e.g., hydrocortisone 1% cream) and topical antibiotics (e.g clindamycin) applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest and upper back with escalation to higher strength and/or oral steroid as detailed below.
4. Offer doxycycline or minocycline for 2 to 3 weeks of study treatment administration. May dose per institutional guidelines or substitute similar antibiotic. Consider topical antibiotics if oral doxycycline or minocycline is not feasible or tolerable.

[redacted]

- Doxycycline:
  - No dosing recommendations for children < 8 years of age
  - Children < 45 kg: 2.2 mg/kg/dose PO twice daily
  - Children ≥ 45 kg: 100 mg PO twice daily
- Minocycline:
  - No dosing recommendations for children < 8 years of age
  - Children < 45 kg: 2 mg/kg/dose PO twice daily
  - Children ≥ 45 kg: 100 mg PO twice daily

3.13.3.2 Reactive Management

It is strongly recommended that subjects who develop rash/skin toxicities receive evaluations for management of the specific side effect.

- For **pruritic lesions**, the use of cool compresses and oral antihistamine agents may be helpful.
- For **fissuring**, the use of Monsel's solution, silver nitrate or zinc oxide cream is advised.
- For **desquamation**, thick emollients and mild soap are recommended.
- For **paronychia**, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended, and if no improvement is seen, a dermatology or surgery consultation is recommended.
- For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

Table 3-7 Mandatory dose modifications and recommended clinical management guidelines for rash

CTCAE v4.03 Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1 (Rash covering < 10% body surface area)	● Initiate prophylactic and symptomatic treatment measures ● Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) ● Reassess after 2 weeks	● Continue study drug(s) ● If rash does not recover to baseline within 2 weeks despite best supportive care, reduce study drug (s) dose (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib)
Grade 2 (10-30% of body surface area)	If tolerable, as per Grade 1: ● Initiate prophylactic and symptomatic treatment measures for first 6 weeks of study treatment ● Use moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream) ● Reassess after 2 weeks.	● Reduce study drug (s) dose (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib) ● 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 drug(s) until recovery to ≤grade 1, restart study drug (s) at reduced dose (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib)
Grade ≥3 (More than	Use moderate strength topical steroids (PLUS consider a brief period of oral high	● Interrupt study drug(s) until rash recovers to Grade ≤1 ● Restart with study drug(s) at reduced dose level (see

CTCAE v4.03 Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
30% of body surface area or Life-threatening)	dose steroid such as methylprednisolone) Consult dermatologist	Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib) ● Escalation of study drug (s) to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment ● If no recovery to grade ≤2 within 4 weeks, permanently discontinue study drug(s). NOTE: suspected cases of SCAR require permanent discontinuation of study treatment, see section 3.13.3.3

3.13.3.3 Severe Cutaneous Adverse Reaction(s)

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. 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.

3.13.4 Diarrhea

Etiology and attribution. Consider evaluation for an alternative etiology for diarrhea as clinically indicated. These include medications (e.g., stool softeners, laxatives, antacids, etc.), infection by C. difficile or Candida species, partial bowel obstruction, malabsorption/lactose intolerance, fecal impaction, or diets high in fiber or lactose.

For **Grade ≤ 2 diarrhea**:

- Dietary modifications may include: stop all lactose-containing products and eat small meals. A bananas, rice, apples, toast (BRAT) diet can be helpful.
- Encourage oral hydration according to institutional weight oral hydration guidelines as clinically appropriate.
  - For subjects ≥ 2 years of age, consider administration loperamide (Table 3-8) with dosing per institutional guidelines or as suggested below. Loperamide is not recommended for children < 2 years of age. Continuation of loperamide is suggested until the subject is diarrhea-free for at least 12 hr.
- If diarrhea resolves to grade≤ 1 within 72 hr of anti-diarrheal measures or supportive care measures, continue study treatment without interruption or dose reduction.
- If grade 2 diarrhea persists after 72 hr total treatment with loperamide or supportive measures in children <2 years, hold study treatment and consider start of second-line agents (octreotide) as clinically indicated. If diarrhea resolves to grade ≤1 or baseline within 7 days resume study treatment(s) with dose reduction (Appendix 2). If grade 2 diarrhea does not resolve in ≤ 7 days without study treatment, discontinue protocol therapy.

[redacted]

Table 3-8 Loperamide Dosing for Study Treatment Related Diarrhea

Age	Weight	Initial Dose (start after first loose bowel movement)	Subsequent Doses	Maximum daily dose
>2 to ≤ 12 years	<13 kg	0.5 mg	0.5 mg every 3 hr while awake, every 4 hr during sleep	4 mg/day
	13 to < 20 kg	1 mg	1 mg every 4 hr	6 mg/day
	20 to < 30 kg	2 mg	1 mg every 3 hr while awake, every 4 hr during sleep	8 mg/day
	30 to < 43 kg	2 mg	1 mg every 2 hr while awake, every 4 hr during sleep	12 mg/day
≥ 13 years	≥ 43 kg	4 mg	2 mg every 2 hr	16 mg/day

For Grade 3 to 4 diarrhea:

- Hold study treatment until symptoms resolve to ≤Grade 1 or baseline then may resume study treatment(s) with a dose reduction (Appendix 2).
- If loperamide has not been initiated, initiate loperamide immediately if age > 2years, using institutional or protocol guidelines for dosing
- For dehydration, use intravenous fluids as appropriate; if severe dehydration, consider administration of octreotide.
- If grade > 2 diarrhea does not resolve in ≤ 7 days without study treatment, discontinue protocol therapy.

3.13.5 Hypertension

The algorithm in Figure 3-6 will be used to grade and manage trametinib and dabrafenib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine,) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 3.12.3.2.

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section 3.13.5.1.

See requirements for Baseline blood pressure measurements in Section 7.3.4.

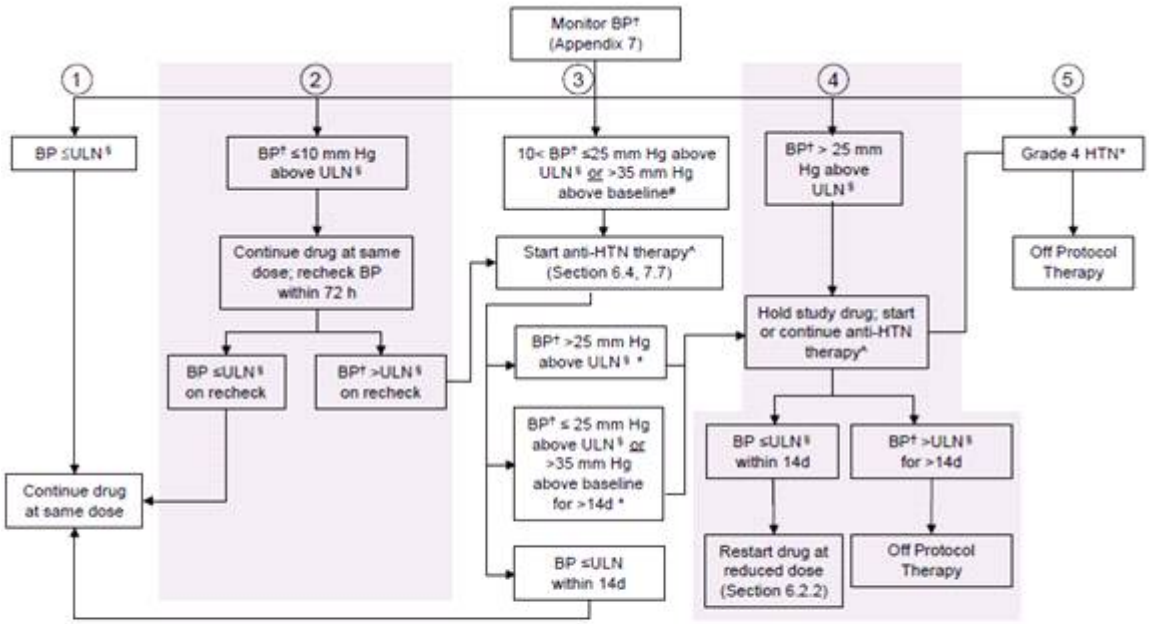
3.13.5.1 Management of Hypertension

- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender (Appendix 7).
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with an elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.

[redacted]

- The algorithm below will be used to manage study drug(s) related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

Figure 3-6 Algorithm For Management of Study Drug(s)-Related Hypertension



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix 7)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 3.13.3.1.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95%ile for age, height, and gender: continue study drug(s) at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue study drug(s) at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue study drug(s) at the same dose.
  - If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

[redacted]

- If BP is 11 to 25 mm Hg above the ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start/adjust anti-hypertensive therapy and continue study drug(s) at the same dose. Monitor BP at least twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue study drug(s) at the same dose and continue anti-hypertensive therapy.
  - If the BP remains elevated ≥ 25 mm Hg above the ULN or > 35 mm Hg above baseline for more than 14 days after the institution/adjustment of anti-hypertensive therapy, **hold study drug(s)**, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that trametinib is held. The anti-hypertensive therapy should be continued until the BP is less than the ULN.
- If the BP returns to ≤ ULN within 14 days, restart sudy drug (s) at a reduced dose.
- If the BP remains > ULN for more than 14 days, patient must be removed from protocol therapy.
  - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, hold study drug(s), but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that study drug(s) is held.
- If the BP is ≤ULN within 14 days, study drug (s) may be restarted at a reduced dose
- If the BP is > ULN for > 14 days, the patient must be removed from protocol therapy (Section 6.3)

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN hold study drug (s), monitor BP, and administer/adjust anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, study drug(s) may be restarted at a reduced dose.
  - If the BP is > ULN for >14 days, the patient must be removed from protocol therapy (Section 6.3).

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension, discontinue study drug(s), monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 6.3).

3.13.6 Visual Changes

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. 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. 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

[redacted]

an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event (Section 7.1 for PK sample volume).

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided in Table 3-9.

Table 3-9 Mandatory dose modification and required clinical management for visual changes and/or ophthalmic examination findings

CTCAE v4.03 Grade*	Required adverse event management guidelines	Mandatory dose modification requirements
Grade 1	● Consult ophthalmologist within 7 days of onset ● If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required. ● Report as SAE if RPED or RVO diagnosed	● 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. On combination therapy dabrafenib may continue. ● If RPED and RVO excluded, continue (or restart) trametinib at same dose level ● If RPED suspected or diagnosed: see RPED dose modification Table 3-10 below ● If RVO diagnosed: Permanently discontinue trametinib (on combination therapy dabrafenib may continue)
Grade 2 and Grade 3	● Consult ophthalmologist immediately ● Report as SAE if RPED or RVO diagnosed	● Interrupt trametinib. On combination therapy, dabrafenib may be continued at the same dose. ● If RPED and RVO excluded, restart trametinib at same dose level ● If RPED diagnosed, see RPED dose modification Table 3-10 below ● If RVO diagnosed: Permanently discontinue trametinib (on combination therapy dabrafenib may continue) ● Permanently discontinue dabrafenib for ≥ Grade 2 uveitis (including iritis and iridocyclitis) of > 6 weeks duration.
Grade 4	● Consult ophthalmologist immediately ● Report as SAE if RPED or RVO diagnosed	● Interrupt trametinib. On combination therapy, dabrafenib may be continued at the same dose. ● If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose ● If RPED or RVO diagnosed, permanently discontinue trametinib (on combination therapy dabrafenib may continue).

* Refers to NCI-CTCAE v4.03 'Eye disorders – Other, specify

Table 3-10 Mandatory dose modification and required clinical management for retinal pigment epithelial detachments (RPED)

CTCAE v4.03 Grade*	Required adverse event management guidelines	Mandatory dose modification requirements
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	● If RPED worsens follow instructions below.	Continue treatment with retinal evaluation monthly until resolution.

[redacted]

Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	● Retinal evaluation monthly.	● Interrupt trametinib (on combination therapy dabrafenib may continue) If improved to ≤ Grade 1, restart trametinib at lower dose (Appendix 2, dose reduction column)

* Refers to CTCAE Version 4.0 'Retinopathy'

3.13.7 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 if clinically indicated. Dose modification and supportive care guidelines for pneumonitis are described in Table 3-11.

Table 3-11 Mandatory dose modifications and recommended clinical management guidelines for pneumonitis

CTCAE v4.03 Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1	● CT scan (high-resolution with lung windows) ● Clinical evaluation and laboratory work-up for infection ● Monitoring of oxygenation via pulse-oximetry ● Consultation with pulmonologist	● Continue study treatment (s) at current dose
Grade 2	● CT scan (high-resolution with lung windows) ● Clinical evaluation and laboratory work-up for infection ● Consult pulmonologist ● If feasible, pulmonary function tests -if <normal, repeat every 8 weeks until ≥normal ● Bronchoscopy with biopsy and/or BAL ● Symptomatic therapy including corticosteroids if clinically indicated	● Interrupt trametinib until recovery to grade ≤1 (on combination therapy, dabrafenib may continue) ● Restart treatment with reduced trametinib dose level (Appendix 2, dose reduction column) ● Escalation to previous dose level after 4 weeks if a period of 4 weeks of treatment have passed since restarting dosing at the lower dose level and there is no recurrence of the AE ● If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib (on combination therapy, dabrafenib may continue)
Grade 3	● CT scan (high-resolution with lung windows) ● Clinical evaluation and laboratory work-up for infection ● Consult pulmonologist ● If feasible, 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 (on combination therapy, dabrafenib may continue) ● When recovered to grade ≤1, treatment with trametinib may be restarted at reduced dose (Appendix 2, dose reduction column) ● If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib (on combination therapy, dabrafenib may continue)
Grade 4	● Same as grade 3	● Permanently discontinue trametinib (on combination therapy, dabrafenib may continue)
Abbreviations: BAL= bronchioalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events		

3.14 Dose Delay and Modification for Events Considered Related to Dabrafenib

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and for which specific guidelines do not apply are provided in Table 3-6. These guidelines are intended primarily for toxicities not easily managed with routine supportive care. For example, alopecia is not an indication for dose modification, nor is grade 2 nausea and vomiting that can be easily managed with anti-emetics.

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

- Palmar Plantar Erythrodysaethesia Syndrome (PPES) – Measures for PPES should include:
  - Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles
  - Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40 % cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.

Dose modification may also be required (See Section 3.15).

- **Pancreatitis** – In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.
- **Uveitis -** Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. Permanently discontinue dabrafenib for persistent ≥ grade 2 uveitis (including iritis and iridocyclitis) of > 6 week duration. No dose modification of trametinib is required when taken in combination with dabrafenib. See Section 3.13.5.
- **Hyperglycemia -** Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

Investigators should always err on the side of caution in these settings if treatment-related toxicity is a possibility.

Please refer to Table 3-6 for general dose modification guidelines for trametinib and dabrafenib.

[redacted]

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

3.15 Guidelines for Dose Modifications and Toxicity Management for Combination Therapy

If treatment related toxicities occur when dabrafenib is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exception shown below:

- Dose modification is necessary for only dabrafenib
  - Mild to moderate pyrexia (Section 3.15.1)
  - Uveitis (Section 3.13.5 and Section 3.14)
- Dose modifications are necessary for only trametinib:
  - Retinal vein occlusions (RVO) and retinal pigment epithelial detachment (RPED) (Section 3.13.5)
  - Left ventricular ejection fraction (LVEF) reduction (asymptomatic, Section 3.12.3.1)
  - Pneumonitis and interstitial lung disease (ILD) (grade 4, Section 3.13.7)

The severity of adverse events (AEs) will be graded utilizing the NCI-CTCAE v4.03 (NCI 2009). Guidelines for dose modifications and interruptions for management of common toxicities associated with dabrafenib are provided in this section.

Trametinib dose reduction for patients enrolled in all parts of the study should follow dose reduction column in the trametinib dosing nomogram in Appendix 2.

Dabrafenib dose reduction should follow the dose reduction column in the dabrafenib dosing nomogram in Appendix 2 provided for patients enrolled in Part C and Part D, as described below

- Dabrafenib dose modification levels in Part C
  - If a subject is dosed at Dose Level 1, and requires dose reduction, treatment must be discontinued
  - If a subject is dosed at Dose Level 2, and requires dose reduction, follow the dose reduction column in dosing nomogram
- Dabrafenib dose modification levels in Part D.
  - Follow dose reduction column in dosing nomogram

Nomograms for each dosing level are provided in Appendix 2.

If a second dose reduction is required, the treatment should be discontinued.

3.15.1 Pyrexia

Pyrexia has been observed in adult subjects receiving dabrafenib. In a minority of cases pyrexia was accompanied by symptoms such as severe chills/rigors, dehydration, and hypotension, which in some cases can lead to acute renal insufficiency. Serious non-infectious febrile events have been observed and typically occurred within the first month of therapy.

[redacted]

Subjects should be instructed on the importance of immediately reporting febrile episodes. Therapy with dabrafenib should be interrupted if the patient's temperature is ≥38.5ºC or 101.3° Fahrenheit. In the event of a fever, the subject should be instructed to take anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol as appropriate to control fever). The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

Guidelines regarding management and dose reduction for pyrexia considered to be related to dabrafenib are provided in Table 3-12.

Table 3-12 Mandatory dose modification and recommended clinical management for pyrexia [a, b]

Occurrence	Recommended adverse event management guidelines	Mandatory dose modification requirements
Any	● Clinical evaluation for infection and hypersensitivity[c] ● Laboratory work-up[c] ● Hydration as required[d]	● See relevant row below
1st Event[b]:	● Administer anti-pyretic treatment[e] as clinically indicated[f]	● Interrupt dabrafenib ● Trametinib may continue (Interrupt trametinib for fever higher than 40°C (104°F)) ● Once pyrexia resolves to baseline (<38.5°C (101.3°F)) , restart dabrafenib at the same dose level (for pyrexia of 38.5°C (101.3°F) to 40°C (104°F)) or at the lower dose level (Appendix 2, dose reduction column) (for pyrexia > 40°C (104°F)) and restart trametinib (if applicable) ● If fever was associated with dehydration, hypotension, rigors or chills, or renal failure, interrupt dabrafenib and trametinib[g]
2nd Event [f]	● Same as for 1st event, and ● Consider oral corticosteroids (i.e. prednisone 10mg) for at least 5 days or as clinically indicated[g]	● Same as first event
Subsequent Events:	Within 3 days of onset of pyrexia: ● Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f] ● If corticosteroids have been tapered and pyrexia recurs, restart steroids	● Interrupt dabrafenib ● Trametinib may continue (Interrupt trametinib for fever higher than 40°C (104°F)) ● Once pyrexia resolves to baseline, restart dabrafenib at lower dose (appendix 2, dose reduction column) and restart trametinib (if applicable). ● Re-escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

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

a. Pyrexia is defined as a body temperature equal to or above 38.5° Celsius or 101.3° Fahrenheit.
b. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended.
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work up should include full blood count, electrolytes, creatinine, BUN, CRP, and liver function tests, blood culture and urine culture.

[redacted]

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 (paracetamol), 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 subjects 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 (Appendix 2, dose reduction column) at discretion of the investigator if pyrexia is accompanied by severe rigors which cannot be managed by best supportive care, including increasing doses of oral steroids.

3.15.2 Renal insufficiency

Cases of renal insufficiency have occurred in adult subjects receiving dabrafenib. 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 3-13.

For the purposes of this guideline, increases from baseline should have *at least* the following *absolute* increase to qualify for the noted *percent* increase in this guideline. The normal serum creatinine values anticipated for young patients on this protocol are near the reporting limits of the laboratory analysis, and are thus subject to variability in reported results and high calculated percent changes. The absolute increase values are intended to alleviate dosing changes due to spuriously high calculations for percentage change.

For a 25% increase – that must also be at least a 0.10mg/dL absolute increase

For a 50% increase – that must also be at least a 0.20 mg/dL absolute increase

For a 100% increase – that must also be at least a 0.40 mg/dL absolute increase

Table 3-13 Mandatory dose modifications and required clinical management guidelines for renal function alterations

For subjects with creatinine rise ≥50% from baseline :	Required adverse event management guidelines	Mandatory dose modification requirements
1 st occurrence	● If patient has fever: treat pyrexia as per Table 3-12 (please note NSAIDs can induce renal insufficiency, especially in patients with dehydration); consider IV hydration ● Pediatric nephrology consult is recommended ● Re-check within 24 hours ● If creatinine rise is < 25% from baseline: ● Monitor creatinine weekly for 4 weeks to ensure levels remain within 25% of baseline ● If creatinine rise is ≥ 25% but < 50% from baseline: ● Monitor creatinine at least twice	● If creatinine rise is < 25% from baseline: ● Continue dabrafenib and trametinib at current dose ● If creatinine rise is ≥ 25% but < 50% from baseline: ● Continue dabrafenib and trametinib at current dose

For subjects with creatinine rise ≥50% from baseline :	Required adverse event management guidelines	Mandatory dose modification requirements
	weekly, can decrease frequency if creatinine rise < 25% from baseline ● Avoid nephrotoxic agents ● If creatinine rise is ≥ 50% but < 100% from baseline: ● Monitor creatinine at least twice weekly ● Avoid nephrotoxic agents	● If creatinine rise is ≥ 50% but < 100% from baseline: ● Interrupt dabrafenib and trametinib ● May restart dabrafenib at reduced dose and trametinib at reduced dose if creatinine rise returns to < 25% from baseline (see Appendix 2 dosing nomogram "Dose Reduction" columns for trametinib and dabrafenib) ● If creatinine rise is ≥ 100% from baseline: ● Permanently discontinue dabrafenib and trametinib
2nd occurrence	See guidance for first occurrence	● Permanently discontinue dabrafenib and continue trametinib

3.15.3 Malignancies

Cutaneous Squamous Cell Carcinomas (CuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been observed in subjects treated with dabrafenib. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however cuSCC should be reported as an SAE. In addition, a biopsy of the lesion should be taken, where possible, and a summary of the results submitted to the Sponsor.

Patients should be instructed to immediately inform their physician if new lesions develop. Skin examination should be performed prior to initiation of dabrafenib and during treatment with dabrafenib, every 2 months throughout therapy. Monitoring of the skin should continue every 2 to 3 months for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

New Primary Melanoma

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

Non-Cutaneous Malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of

RAS-driven malignancies have been seen with BRAF inhibitors. Patients should be monitored as clinically appropriate.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

New non-cutaneous malignancies should be reported as a SAE. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses with the results provided to Novartis. Testing of these biopsies may include analysis of genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens, and would analyze the biological pathways known to be associated with, and relevant to, BRAF-mutant tumor activation. For any new non-cutaneous maligancy every effort should be made to identify the RAS mutation status and submit the results to Novartis.

Refer to Appendix 10 for French country specific dermatological follow up.

3.15.4 Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in Section 3.12.1.

4 Investigational Product(s)

The term 'study treatment' is used throughout the protocol to describe any combination of investigational product(s) (IP) received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatment or the combination of those study treatments.

4.1 Description of Investigational Products

4.1.1 Trametinib

Table 4-1 Investigational Product - Trametinib

Product name:	**Trametinib tablet**	**Trametinib powder for oral solution**
Formulation description:	The drug substance is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with a pink opaque film (Opadry pink, a titanium dioxide-based formulation with iron oxide as colorant).	The drug substance is blended with inert ingredients (β-cyclodextrin sulfobutylether, citric acid monohydrate, sodium phosphate dibasic anhydrous, sucralose, methylparaben, potassium sorbate, strawberry flavor) filled into amber glass bottle with child resistant cap. The powder in bottle is reconstituted with 90 mL of Purified or Sterilized Water to obtain the dosing solution and a syringe adapter is inserted into the bottle to facilitate the withdrawal of the solution.
Dosage form:	Tablets	Powder for Oral Solution

[redacted]

Product name:	**Trametinib tablet**	**Trametinib powder for oral solution**
Unit dose strength(s)/Dosage level(s):	0.5mg, 2mg	0.05mg/mL
Physical description:	0.5mg: yellow, modified oval 4.85x8.86 mm tablet 2mg:pink, round 7.5mm tablet	Powder: White to slight white powder Solution : Clear, colorless solution with strawberry flavor
Route/ Administration:	Oral	Oral
Dosing instructions:	Trametinib should be taken orally, with approximately 4-6 mL/kg of water, 1 hr before or 2 hr after a meal.	A graduated syringe is used to withdraw the volume and administered orally 1 hr before or 2 hr after a meal. Subjects will drink approximately 4-6 mL/kg of water following administration of oral dosing.
Manufacturer/ source of procurement:	Novartis	Novartis

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

4.1.2 Dabrafenib

Table 4-2 Investigational Product - Dabrafenib

Formulation description:	**Dabrafenib capsules**		**Dabrafenib Dispersible Tablets for oral suspension**
Dosage form:	Capsule		Dispersible Tablet
Unit dose strengths:	50 mg and 75 mg		10mg
Route/ Frequency:	Oral / BID		Oral / BID
Physical description:	50 mg: opaque capsules composed of a dark red body and cap, each printed with one thick black line and one thin black line 75 mg: opaque capsules composed of pink body and cap, each printed with one thick black line and one thin black line		White to slightly-yellow round biconvex, beveled edge tablet with debossment “8” on one side and no debossment on the other
Manufacturer/ source of procurement:	Novartis		Novartis
Method for individualizing dosage:	Unit dose capsules		Administered using dosing cup / PP oral iquid dispenser

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

4.2 Preparation/Handling/Storage of Investigational Products

4.2.1 Trametinib

Preparation

A description of the methods and materials required for reconstitution of trametinib Powder for Oral Solution is provided in the SPM.

No special preparation of trametinib tablets is required.

Handling

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

Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the study monitor, the Medical Lead and/or the study manager. Refer to the SPM for detailed procedures for the disposal and/or return of unused study treatment(s).

Storage

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

Trametinib tablets should be refrigerated at 2 to 8^{o}C (36 to 46^{o}F), protected from light and moisture. Trametinib powder for oral solution should be refrigerated at 2 to 8^{o}C (36 to 46^{o}F), protected from light and moisture. Store the solution at room temperature up to 25°C (77°F) and protect from light. The solution can be used for up to 35 days after reconstitution. Maintenance of a temperature log (manual or automated) is required.

4.2.2 Dabrafenib

Preparation

No special preparation of study treatment is required for dabrafenib HPMC capsules.

Dabrafenib dispersible tablets will be dispersed with a specified volume of water at the time of use to form a suspension. Detailed instructions for the dispersion of the tablets and dosing will be provided in the SPM.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may prepare and supply [administration will be performed by caretakers] study treatment.

Patients less than 12 years of age, who weigh less than 16 kg must use dabrafenib dispersible tablets for oral suspension. Patients greater than or equal to 12 years of age, who weigh less than 19 kg must use dabrafenib dispersible tablets for oral suspension

[redacted]

Handling

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from Novartis.

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Lead and/or study manager.

Storage

All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff.

Dabrafenib capsules are to be stored at room temperature up to 30°C. Maintenance of a temperature log (manual or automated) is required.

Dabrafenib dispersible tablets are to be stored at up to 25°C. Maintenance of a temperature log (manual or automated) is required.

4.3 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 IP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable.

The required accountability units for this study will be bottle for trametinib powder for oral solution and tablet for trametinib tablets. For dabrafenib the required accountability units will be tablet for dabrafenib dispersible tablets, and capsule for dabrafenib capsules. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the SPM.

Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

4.4 Treatment Compliance

If subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment(s).

When subjects self-administer study treatment(s) at home, compliance with trametinib and dabrafenib dosing will be assessed through querying the subject during the site visits and

documented in the source documents and eCRF. A record of the number of tablets, capsules, or powder 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 for treatment delays and/or dose reductions will also be recorded in the eCRF.

4.5 Treatment of Investigational Product Overdose

In the event of an overdose (defined as administration of more than the protocol-specified dose) of study treatment, the investigator should:

- contact institutional Principal Investigator (PI) and treating physician immediately to discuss plan for holding study treatment, monitoring for toxicity, or resuming protocol therapy;
- contact the Medical Lead immediately to discuss dosing and monitoring plan;
- closely monitor the subject for adverse events (AEs)/ SAEs and laboratory abnormalities until resolved to baseline or at least 30 days;
- if possible, obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Lead (determined on a case-by-case basis);
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

5 Study Population

5.1 Number of Subjects

Approximately 142 subjects will be enrolled in the study (approximately 48 subjects in Part A, at least 40 subjects in Part B, 24 subjects in Part C and approximately 30 subjects in Part D) In Part A during the age expansion cohort, every attempt will be made to enroll 4-6 subjects in each age group. In Part A extension, up to 12 subjects under 6 years of age may be enrolled. In Part B a minimum of 10 subjects will be enrolled in each group with at least 4 in each cohort under the age of 6. In Part C, no specific age expansion is planned and will be extended with 6 subjects under 6 years of age to further test the selected trametinib dose in combination with dabrafenib. In Part D, approximately 30 subjects will be enrolled. Every attempt will be made to enroll at least 4 children under the age of 12 in Part C or Part D.

5.2 Subject Selection Criteria

5.2.1 Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the study treatment that may impact subject eligibility is provided in the most recent version of the trametinib Investigator Brochure and dabrafenib Investigator Brochure.

[redacted]

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 enrollment in any part (Part A, Part B, Part C or Part D) of the study must meet all of the following criteria in Section 5.2.1.1; in addition, Part (A, B, C or D) Specific Criteria (Section 5.2.1.2 to Section 5.2.1.5) must be met.

5.2.1.1 General Eligibility Criteria (All Parts)

1. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including pharmacokinetics sampling will be obtained according to institutional guidelines.
2. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form (Part C and Part D between 12 months and < 18 years of age, inclusive; Part A extension between 1 month and <6 years of age, inclusive; Part C extension between 12 months and <6 years of age, inclusive.
3. Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or must have a current disease for which there is no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life
4. Prior therapy: The subject's disease (i.e. cancer, NF-1 with PN, or LCH) must have relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. All subjects must have recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.
    - *Myelosuppressive chemotherapy*: The last dose of all myelosuppressive anticancer drugs must be at least 21 days prior to enrollment.
    - *Differentiating Agents/ Biologic response modifiers (small molecules, antibodies, viral therapies) (anti-cancer agent)*: The last dose *of all biologic agents for the treatment of the subject's cancer (such as retinoids) must be at least 7 days prior t*o study entry. The last dose of monoclonal antibodies, immunotherapy, or viral therapy must be at least 30 days prior to enrollment.
    - *Non-myelosuppressive anticancer agents*: (antiangiogenic agents, tyrosine kinase inhibitors): The last dose of non-investigational agent that is not cytotoxic must be at least 2 weeks prior to enrollment.
    - *Investigational agent*: The last dose of all investigational agents must be at least 30 days prior to study entry.
    - *Radiation therapy*: The last dose of radiation (including therapeutic Iodine-131-meta-iodobenzylguanidine [MIBG]) to more than 25% of marrow containing bones (pelvis, spine, skull) must be at least 28 days prior to enrollment. The last dose of all other local palliative (limited port) radiation must be at least 14 days prior to enrollment.
    - *Stem Cell Transplantation or Infusion*. Subjects must be at least 2 months post-autologous transplant or stem cell infusion and must have recovered from toxicities.

[redacted]

Subjects must be at least 6 months post- allogeneic transplant, must have recovered from toxicities, and must have no evidence of active graft-versus-host disease. Subjects must also have been off of immunosuppressive treatment at least 30 days.

- *Number of prior treatment regimens*: No limitation on the number of prior systemic or local treatment modalities that the subject may have received prior to study entry.
- *Colony stimulating factors*: The last dose of colony stimulating factors, such as filgrastim, sargramostim, and epoetin, must be at least 48 hr prior to study entry, and the last dose of long-acting colony stimulating factors, such as pegfilgrastim, must be at least 10 days prior to study entry.
- *Corticosteroids* in subjects with solid tumors are permitted if the dose of corticosteroids is stable or decreasing for at least 7 days prior to enrollment. .

5. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale (Yates 1980, Appendix 1).
6. Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 10.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to start of study drugs, throughout treatment period and for 4 months after last dose of study drugs.
7. Must have adequate organ function as defined by the following values:
   - Renal function: 24 hr creatinine clearance (revised Schwartz formula), or radioisotope glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2; or a serum creatinine ≤ ULN for age and gender as defined in the following table:

Age (Years)	Upper Limit of Normal Serum Creatinine (mg/dl)	
	Male	Female
Less than 6 months	0.4	0.4
6 months to less than 1 year	0.5	0.5
1 year to less than 2 years	0.6	0.6
2 to less than 6 years	0.8	0.8
6 to less than 10 years	1	1
10 to less than 13 years	1.2	1.2
13 years to less than 16 years	1.5	1.4
Greater than 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz 1985) utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

   - Liver function defined as:
     - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age
     - ALT ≤2.5 x ULN; for the purposes of enrollment and toxicity monitoring the ULN for ALT will be 45 U/L.
   - Cardiac function defined as:
     - Corrected QT (QTcB) interval <480 msec
     - LVEF ≥LLN by ECHO

[redacted]

8. Able to swallow and retain enterally (PO or nasogastric or gastric tube) administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
9. Adequate Blood Pressure Control defined as:
10. Blood pressure ≤ the 95th percentile for age, height, and gender) measured as described in Section 7.3.4.
11. **French subjects**: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2.1.2 Specific Eligibility Criteria, Part A

Subjects must meet General Eligibility Criteria. The specific eligibility criteria listed here will apply to subjects enrolling to Part A.

1. For the initial dose escalation to identify the maximum tolerable or PK target dose, age between 2 years and < 18 years (inclusive) at the time of signing the informed consent form. Children < 2 years of age will be enrolled once the age specific expansion cohorts are open.
2. Histologically confirmed solid tumors, which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, primary brain tumors, NF-1 associated plexiform neurofibromas, and Langerhans Cell histocytosis (LCH). In subjects with brain stem gliomas the requirement for histological confirmation can be waived if a biopsy was not performed. For plexiform neurofibromas, histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiological findings, but should be considered if malignant degeneration of a PN is clinically suspected.
3. Measurable or evaluable tumors. Subjects with neuroblastoma that is only detectable by MIBG scan are eligible. Subjects with neuroblastoma that is only detected by bone marrow aspirate/biopsy or elevated homovanillic acid / vanillylmandelic acid (HVA/VMA) are not eligible.
4. Adequate bone marrow function defined as:
   - Absolute neutrophil count (ANC) ≥1000/µL;
   - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)Platelets ≥75,000/µL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

5.2.1.3 Specific Eligibility Criteria, Part B

Subjects must meet General Eligibility Criteria. The specific eligibility criteria listed here will apply to subjects enrolling to different cohorts of Part B.

1. Tumor tissue (archived or fresh) is required and must be available to be shipped to Novartis or site specific laboratory except in subjects where tumor biopsy is not possible.
2. **Solid Tumor Cohort (B1) Specific Criteria**:

[redacted]

- Histologically confirmed neuroblastoma which have been associated with MAPK/RAS/MEK activation. Histological confirmation may be at diagnosis or recurrence. Laboratory documentation of pathway activation is not required; however, archival tissue is requested at the time of enrollment.
- Measurable or evaluable tumors. Subjects with neuroblastoma that is only detectable by MIBG scan are eligible if they have at least one lesion that can be assessed using the Curie scale. Subjects with neuroblastoma that is only detected by bone marrow aspirate/biopsy or elevated HVA/VMA are not eligible.
- If neuroblastoma subjects have only one MIBG positive lesion and that lesion was radiated (external beam or systemic radiolabeled 131I-MIBG), a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma
- *Hematological Toxicity Evaluable Subjects* (at least 6 of cohort of 10) must have adequate bone marrow function defined as:
  - Absolute neutrophil count (ANC) ≥1000/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
  - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
- *Hematological Toxicity Inevaluable Subjects* (up to 4 in a cohort of 10) must have adequate bone marrow function defined as:
  - Absolute neutrophil count (ANC) >500/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
  - Platelets >25,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

3. BRAF Fusion Cohort (B2) Specific Criteria:

- Relapsed or refractory gliomas or other primary brain tumors with BRAF fusion/duplication (documented in Clinical Laboratory Improvement Amendments (CLIA) certified or equivalent laboratory) or NF1 subjects with gliomas who are not suitable for the NF1 with PN cohort.
- Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) ≥1000/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
  - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

4. NF-1 Plexiform Neurofibroma Cohort (B3) Specific Criteria

- Subjects with NF-1 must have a PN(s) that are progressive OR are cause of significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Subjects with paraspinal PN will be eligible for this trial. Histologic confirmation of

[redacted]

tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected.

- A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with connection between the levels or extending laterally along the nerve.
- For subjects enrolled for tumor progression, progression is defined as:
  - Presence of new PN on MRI documented by comparison with prior MRI), OR
  - A measurable increase in PN size (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) documented by comparison of two scans (MRI) in the time period of approximately one year or less prior to evaluation for this study.
- For subjects enrolled for a "major deformity" or "significantly disfiguring" tumor, eligible tumors will be limited to tumors of the head & neck or those on other areas of the body that are unable to be concealed by standard garments.
- All subjects must have either the clinical diagnosis of NF-1 using the National Institutes of Health (NIH) Consensus Conference criteria or have a constitutional NF-1 mutation documented in a CLIA/College of American Pathologist (CAP) certified lab.
- Subjects must have measurable PN(s) amenable to volumetric MRI analysis. For the purpose of this study, the target lesion must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest. Tumors must be at least 3 mL in volume (most PNs 3 cm in longest diameter will meet this criteria). If the tumor is <3 cm in longest diameter, the subject may still be eligible. Central review of the MRI of the target PN is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis. After consenting, please follow instructions in Appendix 6 or the SPM for central review of MRI. Central review will take 3-7 days (please plan accordingly).
- Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) ≥1000/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
  - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
- Subjects with NF-1 and PN will only be eligible if complete tumor resection is not feasible, or if a subject with a surgical option refuses surgery.
  - Since there is no standard effective chemotherapy for subjects with NF-1 and PN, subjects may be treated on this trial without having received prior medical therapy directed at their PN.
  - Must not have received myelosuppressive chemotherapy within prior 4 weeks.
  - Must be at least 2 weeks since undergoing major surgery and must be recovered from effects of surgery.

[redacted]

- Subjects who have received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorefenib, imatinib or vascular endothelial growth factor receptor (VEGFR) or MEK inhibitors are eligible for enrolment if general eligibility criteria are met.
- Subjects who have received therapy for PN that included other MAPK/MEK /RAS inhibitors are eligible for this study.

5. BRAF V600 mutant solid tumors Cohort (B4) Specific Criteria:

- Male or female ≥12 months and <18 years of age at the time of signing the informed consent form;
- BRAF V600 mutation-positive tumor as confirmed in a CLIA-approved laboratory or equivalent. Subjects may be enrolled based on local test results. Note: all subjects must provide archival or fresh tumor tissue at screening for central confirmation of local test derived BRAF V600 mutation status.
- Recurrent disease, refractory disease, or progressive disease after having received at least one standard therapy for their disease;
- NOTE: Subjects with metastatic (and surgically unresectable) melanoma can be enrolled for first-line treatment; Melanoma subjects with CNS involvement may be enrolled.
- Measurable or evaluable tumors.
- Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) ≥1000/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
  - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

5.2.1.4 Specific Eligibility Criteria, Part C

Subjects must meet General Eligibility Criteria.

1. Tumors that have been documented by CLIA or equivalent certified laboratory test to harbor BRAF V600 mutation at diagnosis or relapse.
2. Subjects may be enrolled based on local test results. Note: all subjects must provide archival or fresh tumor tissue at screening for central confirmation of local test derived BRAF V600 mutation status.
3. Measurable or evaluable disease.
4. Adequate bone marrow function defined as:
   - Absolute neutrophil count (ANC) ≥1000/μL;
   - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions);
   - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment).

[redacted]

- PT/INR and PTT ≤ 1.3 x ULN; subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to starting study medication

5.2.1.5 Specific Eligibility Criteria, Part D

Subjects must meet General Eligibility Criteria.

1. Measurable or evaluable disease.
2. Recurrent or refractory BRAF mutant LGG or LCH tumors
3. BRAF V600 mutation confirmed in a CLIA-approved laboratory or equivalent. Subjects may be enrolled based on local test results. Note: all subjects must provide archival or fresh tumor tissue at screening for central confirmation of local test derived BRAF V600 mutation status.
4. Adequate bone marrow function defined as:
   - Absolute neutrophil count (ANC) ≥1000/μL;
   - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions);
   - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment).
   - PT/INR and PTT ≤ 1.3 x ULN; subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to starting study medication

5.2.2 Exclusion Criteria (All Parts)

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

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

1. Lactating or pregnant female.
2. History of another malignancy including resected non-melanomatous skin cancer.
3. Subjects with NF-1 associated optic pathway tumors are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for PN or malignant solid tumor
4. Subjects with a history of NF-1 related cerebral vascular anomaly (such as Moyamoya)
5. Subjects with NF-1 actively receiving therapy for the optic pathway tumor.
6. Subjects with NF-1 and only PN lesions that cannot be evaluated by volumetric analysis (only applicable to Part B).
7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
8. Any prohibited medication(s), currently used or expected to be required, as described in Section 9.2.
9. Any medications for treatment of left ventricular systolic dysfunction

[redacted]

10. Part B, C and D: Previous treatment with dabrafenib or any BRAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor (exception: prior treatment with sorafenib is permitted). Patients who have received prior dabrafenib or another BRAF inhibitor may enrol into Part B4. Patients who have had prior dabrafenib or BRAF inhibitor therapy may enroll in part C or Part D if they have had prior benefit to dabrafenib or BRAF inhibitor monotherapy, as determined by the investigator. (Note: Subjects enrolled in Parts A or B are not eligible to participate in Parts C or D)
11. Administration of an investigational study treatment within 30 days preceding the first dose of study treatment(s) in this study.
12. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment or excipients that contraindicate their participation.
13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or liver metastases).
14. History of hepatic sinusoid obstructive syndrome (venoocculsive disease) within the prior 3 months.
15. History of heparin-induced thrombocytopenia.
16. History of interstitial lung disease or pneumonitis.
17. History or current evidence RVO
18. For subjects with solid tumors that are not primary CNS tumors or NF-1 associated plexiform neurofibromas, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression are excluded.

NOTE: Subjects previously treated for these conditions that have had stable CNS disease (verified with consecutive imaging studies) for >3 months, are asymptomatic and are not currently taking corticosteroids, or are on stable dose or decreasing of corticosteroids for at least 7 days prior to enrolment are permitted.

19. A history of known Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.
20. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v4.03) (NCI 2009) Grade 2 or higher from previous anti-cancer therapy, except alopecia.
21. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs. If clarification is needed as to whether a condition will significantly affect absorption of drugs, contact the Novartis Medical Lead for guidance to enrol the subject.
22. A history or evidence of cardiovascular risk including any of the following:
    - A QT interval corrected for heart rate using the Bazett's formula (QTcB) ≥480 msec;
    - A history or evidence of current clinically significant uncontrolled arrhythmias; **Clarification:** Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible.
    - A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.

[redacted]

- A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines;
- Patients with intra-cardiac defibrillators;
- 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. Subjects with prosthetic valves can be considered eligible provided they meet the criteria as stated above.
- Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg (or above 95th age-specific percentile as listed in Appendix 8), which cannot be controlled by anti-hypertensive therapy;

6 Completion or Withdrawal of Subjects

6.1 Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to Novartis.

6.2 Subject Completion Criteria

A subject will be considered to have completed the study if they discontinued study treatment for reasons listed in Section 6.2 and completed a post-treatment follow-up visit or has died while receiving study treatment.

6.3 Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.12.1. In addition, study treatment may be permanently discontinued for any of the following reasons:

- serious deviation(s) from the protocol that result in a significant risk to the patient's safety;
- subject becomes pregnant;
- request of the subject or proxy (withdrawal of consent by subject or proxy);
- investigator's discretion;
- a dose delay due to study treatment related toxicity of >28 days;
- intercurrent illness that prevents further administration of study treatment(s);
- subject is lost to follow-up;
- sponsor terminates the study.

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

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

[redacted]

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated. All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (see Section 7.1).

Adverse Events must be followed for a minimum of 30 days after the last dose. If it is not practical for the subject to return to the clinic, this data may be collected via telephone from the parent/caregiver/subject (as appropriate).

The discontinuation related safety assessments (same assessments as Final visit in the Time and Events Table) may be completed at any time from the last dose to 30 days after the last dose. Ongoing toxicities should be followed to resolution if at all possible. If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

6.4 Subject Visits and Lost to follow-up Criteria

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance.

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can be appropriately withdrawn from the study. These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

6.5 Study Completion

The study will be considered completed when the last subject enrolled (without disease progression or withdraw from the study for another reason) has been in the study for a minimum of 6 months AND, for those subjects still benefiting from treatment, the rollover protocols are open to enroll pediatric subjects. For subjects entering the rollover study, data from the final study visit may be used for the transition visit into the rollover study

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit.

6.6 Treatment after the End of the Study

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

[redacted]

After study participation in the current study is completed or terminated, subjects may either:

1. Transition to the rollover study if eligible and continue receiving treatment with trametinib or trametinib and dabrafenib

OR

2. Complete a follow-up visit after the last dose of study treatment(s) if the subject:
    - chooses not to enter the roll-over study, or
    - is withdrawn due to an AE considered related to study treatment, or
    - is considered ineligible to enter the rollover study.

Subjects who discontinued treatment with trametinib or dabrafenib will be offered Follow-Up from Novartis consisting of a visit every 3 months (±15 days) for a period of 2 years. At each visit, the following assessments will be performed:

- Brief history and physical exam (a brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated]; brief physical exam to also include dermatologic evaluation, growth, and sexual maturation);
- History to review development;
- History of new malignancies or secondary malignancies, or other significant changes.

Subjects who discontinued dabrafenib treatment will be followed every 3 months for 2 years to monitor for the occurrence of cuSCC and monitored for up to 2 years for non-cutaneous malignancy.

6.7 Withdrawal of Consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data.
    - In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the subject are not allowed unless safety findings require further communication or follow-up.
    - All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

[redacted]

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

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 being performed.

The timing of each assessment is listed in the Time and Events Table (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, PK, PD[redacted] or other assessments. The institutional review board (IRB) or independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 10 mL of blood will be collected at baseline, up to 30 mL for safety and 10-22 mL for PK in the first month (depending on weight), then 6 mL every 4 weeks for the first year, decreasing to every 12 weeks after the first year.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SPM.

7.1 Time and Events Tables

This section consists of the Time and Events Tables to describe assessment windows and sequencing of study-specific assessments and procedures.

[redacted]

Table 7-1 Time and Events, Treatment Phase: Screening through Day 28

All subjects (unless specified) screening- day 28	**STUDY PHASE**	**SCREEN**	**TREATMENT DAYS 1 through 28**				
	VISIT	**Screen**	**Pre-dose Day 1, Week 1**	**Pre-dose Day 8, Week 2**	**Pre-dose Day 15, Week 3**	**Pre-dose Day 22, Week 4**	**Pre-dose Day 28, Week 5**
	VISIT WINDOW (±days)	**-14**	**N/A**	**±2**	**±2**	**±2**	**±2**
Baseline Assessments							
Informed consent/assent		X					
Tumor biopsy or bone marrow aspirate, **Part A**	Optional fresh biopsy or bone marrow aspirate.	X					
Archived tumor biopsy or bone marrow aspirate, **Part B1, B2, and B3**	Archived tissue at screening is required and must be available to be shipped to Novartis; if not available fresh biopsy is acceptable. RAS mutation status does not have to be done within 14 days prior to dosing.	X					
Tumor tissue for V600 testing for those subjects enrolled in **Part B4, Part C and Part D**,	BRAFV600 mutation as per a local result is required for enrolment in the study; the local testing will be subject to subsequent confirmation by centralized testing. Central confirmation can be from archival tissue or if no archival tissue is available, from fresh biopsy. Central confirmation not required within 14 days prior to dosing.	X					
Demographic data	Record date of birth, gender, race and ethnicity	X					
Register subject	Using an interactive voice response system	X	X				
Height and Weight/	Measurements in metric scale.	X	X				X
Tanner Stage		X	X				
Serum pregnancy test	In all menstruating females and according to applicable local requirements and/or regulations, a serum pregnancy test is required at screening (within 7 days of administration of the first dose of study medication). If performed within 7 days of first dose of study drug, does not need to be repeated on Day 1 (pre-dose)	X	X				X
Disease characteristics	Record date of diagnosis, primary tumor type, histology, stage, etc.	X					

[redacted]

All subjects (unless specified) screening- day 28	**STUDY PHASE**	**SCREEN**	**TREATMENT DAYS 1 through 28**				
	VISIT	**Screen**	**Pre-dose Day 1, Week 1**	**Pre-dose Day 8, Week 2**	**Pre-dose Day 15, Week 3**	**Pre-dose Day 22, Week 4**	**Pre-dose Day 28, Week 5**
	VISIT WINDOW (±days)	**-14**	**N/A**	**±2**	**±2**	**±2**	**±2**
Prior anti-cancer therapy & radiation		X					
Prior major surgical procedures		X					
Past and current medical conditions	Medical history will be assessed as related to the eligibility criteria listed in Section 5.2.1. Cardiovascular medical history/risk factors will also be assessed at baseline	X					
Safety/Tolerability Assessments							
Physical examination	Assessment of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities	X	X	X	X	X	X
Dermatologic skin assessment	Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam throughout the study. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits. For subjects enrolled in France, see Appendix 10 for additional follow up.	X				X	
Plain Radiograph of Wrist or Tibial Growth Plate	This procedure scheduled for Day 1 can be done anytime between screening and Day 1		X				
Ophthalmologic examination	Performed by ophthalmologist. See Section 7.3.2 for details.	X					X
ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by personnel with experience in this study population (e.g., pediatric cardiologist).	X					

[redacted]

All subjects (unless specified) screening- day 28	**STUDY PHASE**	**SCREEN**	**TREATMENT DAYS 1 through 28**				
	VISIT	**Screen**	**Pre-dose Day 1, Week 1**	**Pre-dose Day 8, Week 2**	**Pre-dose Day 15, Week 3**	**Pre-dose Day 22, Week 4**	**Pre-dose Day 28, Week 5**
	VISIT WINDOW (±days)	**-14**	**N/A**	**±2**	**±2**	**±2**	**±2**
Echocardiogram (ECHO)	Copies of all ECHOs performed on subjects will be sent to the study sponsor during the study (Additional details in the SPM).	X					X
Vital signs	Blood pressure (at baseline, 3 serial blood pressures; separated by at least 5 minutes see Section 7.3.4; for all other visits, one measure), body temperature, pulse rate, respirations	X	X	X	X	X	X
Urinalysis	Routine Urinalysis (See Table 3-5)		X				
Concomitant medications	See Section 9 for list of prohibited and cautionary medications.	X	X	X	X	X	X
Adverse events	Adverse event assessment should be continuous		X	X	X	X	X
Palatability questionnaire **(subjects receiving oral liquid formulation)**	To be completed after the first dose of study drug and no later than Day 8 (±3 days). See Section 7.3.7 for details. Separate questionnaires are to be used for trametinib and dabrafenib in Part C and part D			X			
Blood Sampling							
Chemistry	Evaluations performed by a local laboratory. Not required on Day 1 if screening assessments were within 72 hr of first dose.	X	X	X	X	X	X
Hematology	Evaluations performed by a local laboratory. Not required on Day 1 if screening assessments were within 72 hr of first dose.	X	X	X	X	X	X
PK sampling	For Part A and Part A extension, trametinib PK sampling is required to be drawn on Day 15 and Day 22. For Part B, trametinib PK sampling is required to be drawn on Day 15 only. For Part C, Part C extension and Part D, trametinib, dabrafenib and dabrafenib metabolites PK sampling is required to be drawn on Study Day 1, Day 15 and Day 22.		X (Parts C and D)		X (All Parts)	X (Parts A, C and D)	

[redacted]

All subjects (unless specified) screening- day 28	**STUDY PHASE**	**SCREEN**	**TREATMENT DAYS 1 through 28**				
	VISIT	**Screen**	**Pre-dose Day 1, Week 1**	**Pre-dose Day 8, Week 2**	**Pre-dose Day 15, Week 3**	**Pre-dose Day 22, Week 4**	**Pre-dose Day 28, Week 5**
	VISIT WINDOW (±days)	**-14**	**N/A**	**±2**	**±2**	**±2**	**±2**
	There is no visit window around these samples. For details, see Table 7-2 and Table 7-3 for PK schedules						
Clinical Activity [redacted]							
Target and non-target lesion assessment	Must be identified at time of screening scan.	X					
Brain MRI (glioma subjects ONLY)	May use brain MRI obtained within 35 days of the first dose. CT with contrast allowed only if brain MRI is contraindicated.	X					
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X	X	X	X
MRI with volumetric assessment for Plexiform Neurofibromas	NF-1 PN Cohort Only. May be performed up to 4 weeks prior to enrollment, and requires central review (see Section 5.2.1.3)	X (Part B)					
Tumor biopsy	Optional fresh biopsy		X		X		
[redacted]							
Study Medication							
Dispense oral study medication and assess compliance	Dispense study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.		X				X
Collection of Scans obtained prior to study							
For patients with a diagnosis of LGG only (enrolled in all parts)	Collection of efficacy assessments (imaging scans, primarily MRI), if available from the most recent prior chemotherapy regimen to include the baseline assessment and a time point closest to 6 months following initiation of that therapy.	This should be collected within 1 month of the patient enrolling in the study, or within 1 month of this amendment being approved, whichever is the later.					
MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram; PK = pharmacokinetic							

[redacted]

Table 7-2 Trametinib Monotherapy PK Sampling: Time and Events for Parts A, A extension and B on Day 15 and Day 22

	Day 15 (Parts A, A extension and B)							Day 22 (Part A and Part A extension only)
Hr	**0**	**1**	**2**	**4**	**7**	**10**	**24**	**0**
COLLECTION WINDOW	**-30 min**	**± 5 min**	**± 5 min**	**± 20 min**	**± 20 min**	**± 2 hr**	**± 20 min**	**-30 min**
Subjects ≥ 25 kg								
PK (2 mL sample)	X	X	X	X	X	X	X	X
Subjects <25 and ≥ 10 kg								
PK (2 mL samples)	X	X	X	X	X	X	X	X
Subjects < 10 kg								
PK (2 mL samples)	X	X	X				X	X

Table 7-3 Trametinib and Dabrafenib Combination PK Sampling: Time and Events for Parts C, C extension and D on Day 1, Day 15 and Day 22

	Day 1			Day 15							Day 22
Hr	**0.5**	**2**	**4**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**0**
COLLECTION WINDOW	**± 5 min**	**± 5 min**	**± 20 min**	**-30 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 20 min**	**± 20 min**	**± 20 min**	**± 20 min**	**-30 min**
Subjects ≥ 25 kg												
Trametinib, dabrafenib and dabrafenib metabolites PK (1 mL sample)	X	X	X	X	X	X	X	X	X	X	X	X
Subjects <25 and ≥ 10 kg												
Trametinib, dabrafenib and dabrafenib metabolites PK (1 mL sample)	X	X	X	X		X	X	X	X		X	X
Subjects < 10 kg												
Trametinib, dabrafenib and dabrafenib metabolites PK (1 mL sample)				X			X		X			X
Plasma concentrations of trametinib, dabrafenib and dabrafenib metabolites will be measured in the 1 mL blood sample.												

[redacted]

Table 7-4 Time and Events, Treatment Phase, Week 9 to Final Visit

(All subjects unless specified) week 9- final visit:	***STUDY PHASE***	**TREATMENT WEEK 9+**							
	Visit	**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 49+ (after 1 year)**	**Final Visit**
	VISIT WINDOW (±days)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Safety Assessments									
Brief Physical examination	Will include height and weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated]	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Dermatologic skin assessment	Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam for the duration of the study to ensure consistency between evaluations. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits.	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Plain radiograph of wrist or tibial growth plate	Only in subjects with open growth plates at screening	X				X	Every 24 weeks (6 months)	Every 48 weeks (12 months)	X
Tanner Stage						X	Every 24 weeks (6 months)	Every 24 weeks	X
Urine Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Ophthalmologic examination	Performed by ophthalmologist. See Section 7.3.2 for details.			X		X	Every 12 weeks	Every 12 weeks	

[redacted]

(All subjects unless specified) week 9- final visit:	***STUDY PHASE***	**TREATMENT WEEK 9+**							
	Visit	**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 49+ (after 1 year)**	**Final Visit**
	VISIT WINDOW (±days)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by personnel with experience in this study population	X		X		X	Every 12 weeks	Every 12 weeks	X
Echocardiogram (ECHO)	Copies of all ECHOs will be collected and sent to the study sponsor during the study. An ECHO does not need to be performed at study discontinuation unless one was not performed within the previous 8 weeks.			X		X	Every 12 weeks	Every 12 weeks	X
Concomitant medications	See Protocol Section 9 for list of prohibited and cautionary medications.	X	X	X	X	X	X	X	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	X	X
Urinalysis	Routine Urinalysis (See Table 7-6)	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Blood Sampling									
Chemistry	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4weeks	Every 12 weeks	X

[redacted]

(All subjects unless specified) week 9- final visit:	***STUDY PHASE***	**TREATMENT WEEK 9+**							
	Visit	**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 49+ (after 1 year)**	**Final Visit**
	VISIT WINDOW (±days)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Clinical Activity [redacted] Assessments									
Part A, Part C and Part D only; for Part B please see Table 7-5									
Target and non-target lesion assessment	Target and non-target lesions identified at time of screening scan must be re-assessed at each restaging scan. If the last radiographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation. For disease specific assessment modality, see Section 7.6	X		X		X	Every 12 weeks	Every 12 weeks (or more frequently per local standard of care)	X
Response (all subjects except LCH subjects)	Complete response/partial response confirmation assessments may take place at Week 13 if initial response was seen at the Week 9 scan. Initial response (complete response/partial response) that is observed at Week 17 or after should be confirmed not less than 4 and not more than 8 weeks after the initial response. For disease specific assessment methodology, refer to Section 7.6 and Appendix 3 to Appendix 7	X		X		X	Every 12 weeks	Every 12 weeks	X
Response (LCH subjects only)	For disease specific assessment methodology, refer to Appendix 7		X			X	Every 12 weeks	Every 12 weeks	X
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X		X	Every 12 weeks	Every 12 weeks	X
Tumor Biopsy	Optional fresh biopsy	Upon disease progression							
[redacted]									

[redacted]

(All subjects unless specified) week 9- final visit:	***STUDY PHASE***	**TREATMENT WEEK 9+**							
	Visit	**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 49+ (after 1 year)**	**Final Visit**
	VISIT WINDOW (±days)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Study Medication									
Dispense oral study medication and assess compliance	Dispense a 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	Every 4 weeks	Every 4-12 weeks	
Post Treatment Follow-up – See Section 6.6									
MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram									

Table 7-5 Time and Events, Part B Clinical Activity Assessments, Week 9 to Final Visit

Additional events Part B week 9- final Visit: STUDY PHASE		**TREATMENT WEEK 4+**							
Visit		**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 49+ (after 1 year)**	**Final Visit**
VISIT WINDOW (±days)		**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Clinical Activity [redacted] Assessments									
Solid Tumor Cohort B1, BRAF Fusion Cohort B2, and BRAF V600 Mutant Solid Tumor Cohort B4									
Target and non-target lesion assessment	Target and non-target lesions identified at time of screening scan must be re-assessed at each restaging scan. If the last radiographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation For disease specific assessment modality, see Section 7.6	X		X		X	Every 12 weeks	Every 12 weeks (or more frequently per local standard of care)	X

[redacted]

Additional events Part B week 9- final Visit: STUDY PHASE		**TREATMENT WEEK 4+**							
	Visit	**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 49+ (after 1 year)**	**Final Visit**
	VISIT WINDOW (±days)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Response	Complete response/partial response confirmation assessments may take place at Week 13 if initial response was seen at the Week 9 scan. Initial response (complete response/partial response) that is observed at Week 17 or after should be confirmed not less than 4 and not more than 8 weeks after the initial response. For disease specific assessment methodology, refer to Section 7.6 and Appendices 3-7	X		X		X	Every 12 weeks	Every 12 weeks	X
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X		X	Every 12 weeks	Every 12 weeks	X
Tumor Biopsy	Optional fresh biopsy	Upon disease progression							
[redacted]									
NF-1 Plexiform Neurofibroma Cohort B3									
MRI with volumetric assessment and/or RECIST 1.1	Visit window of 2 weeks is allowed, central review required for baseline scan (Section 7.6.1)			X			Week 33, 49	Week 73, 97 Then every 24 weeks	X
Response for NF-1	For disease specific assessment methodology, refer to Section 7.6 and Appendices 3-7			X			Week 33, 49	Week 73, 97 Then every 24 weeks	X
Tumor tissue	Optional fresh biopsy	Upon disease progression							
[redacted]									

[redacted]

7.2 Demographic/Medical History and Baseline Assessments

The following demographic parameters will be captured during Screening: date of birth, gender, race and ethnicity.

Medical/medication history assessed as related to the eligibility criteria listed in Section 5.2.

Baseline (Screening) assessments are detailed in the Time and Events Table Section 7.1.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

Additional historic data will be collected, if available, on patients with a diagnosis of LGG enrolled in all study parts. The additional data will consist of efficacy assessments (imaging scans, primarily MRI) from the most recent prior chemotherapy regimen to include the baseline assessment (scan taken just before the initiation of the prior chemotherapy) and a time point closest to 6 months following initiation of that therapy.

7.3 Safety Evaluations

Planned time points for all safety assessments are provided in the Time and Events Table (Section 7.1).

7.3.1 Physical Examinations

A complete physical examination will include assessments of the head, neck, eyes, ears, nose, mouth, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded. Sexual maturation will be assessed using Tanner staging.

A brief physical examination will include assessments of the head, neck, eyes, skin, lungs, cardiovascular system, and abdomen (liver and spleen).

A full body dermatological examination will be performed by a dermatologist (or suitably qualified physician) to identify abnormal skin lesions. All findings will be photographed and identified during screening. Brief skin examinations will be performed as indicated in the Time and Events Table or more frequently as necessitated. Wherever possible, the same physician should perform these examinations. Follow-up skin examinations by a referral dermatologist should be conducted if clinically indicated.

Plain radiographs of the wrist or tibial growth plates (following institutional practice) are required in children with open growth plates at Day 1. Radiograph can be performed anytime between screening and Day 1.

[redacted]

7.3.2 Ophthalmology Examination

An age-appropriate ophthalmologic examination should be performed by an ophthalmologist at screening and at the timepoints specified in the Time and Events Tables (Section 7.1).

During the study, ophthalmologic exams may be repeated as clinically warranted. If any changes are noted during the required age-appropriate exam, or otherwise clinically indicated, a detailed ophthalmologic exam is mandatory (with sedation if necessary).

7.3.3 Performance Status

The performance status will be assessed using Karnofsky and Lansky Scales (Appendix 1) as specified in the Time and Events Table (Section 7.1).

7.3.4 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, temperature, respiration rate and pulse rate. Vital signs should be measured after resting for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs. Baseline blood pressure measurement should be performed in triplicate and for all other occasions, measurement should be performed once.

Baseline blood pressure (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:

1. Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
2. Average the systolic blood pressure from the 2nd and 3rd measurements.
3. Average the diastolic blood pressure from the 2nd and 3rd measurements.
4. The baseline BP is the average of the systolic and average of the diastolic measurements.

7.3.5 Electrocardiogram

Single 12-lead ECGs will be obtained at designated time points during the study using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS, QT, and corrected QT (QTc) intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 10 minute rest.

The QT interval should be corrected for heart rate by Bazett's formula (QTcB). Refer to Section 3.12.1 for QTc stopping criteria. Additional QTc readings may be performed if necessary. Refer to the SPM for details regarding ECG procedures.

7.3.6 Echocardiogram

The ECHOs will be performed to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility and during the study as specified in the Time and Events

[redacted]

Table (Section 7.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF and both right and left-sided valvular lesions.

Copies of all study ECHOs performed will be required to be provided to the sponsor. The ECHOs will not be reviewed in a real-time basis by the sponsor, but rather held for review at a future time point if a cardiac safety signal is identified.

7.3.7 Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 7-6, should be performed according to the Time and Events Table (Section 7.1). Details for the preparation and shipment of samples will be provided in the SPM.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator.

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

All laboratory tests with values that are significantly abnormal (Grade ≥3) during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Table 7-6 List of Clinical Laboratory Tests

Hematology			
Platelet Count		RBC Indices:	Automated WBC Differential:
Red blood cell (RBC) Count		MCV	Neutrophils
White blood cell (WBC) Count (absolute)		MCH	Lymphocytes
Hemoglobin		MCHC	Monocytes
Hematocrit			Eosinophils
HbA1c at baseline (screening) only			Basophils
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin (Bilirubin fractionation recommended if total bilirubin is >2x the upper limit of normal)
Creatinine	Chloride	Alanine aminotransferase (ALT)	Total Protein
Glucose (recheck fasting if >160 mg/dL)	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	**Albumin**
Sodium	Calcium	Alkaline phosphatase (ALP)	
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other screening tests			
Serum pregnancy test			
HVA/VMA in random or 24 hr urine for subjects with neuroblastoma			
In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.			

RBC = Red Blood Cell; WBC = White Blood Cell; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin: MCHC = Mean Corpuscular Hemoglobin Concentration; HVA/VMA = Homovanillic Acid / Vanillylmandelic Acid (ratio); CSF = Cerebrospinal fluid.

Palatability

For subjects ≥12 years of age who receive the dabrafenib suspension or trametinib oral solution, the subject will complete a form (for each drug separately if enrolled in Parts C and D) to evaluate the various properties of the suspension (e.g., bitterness, sweetness, appearance, texture and overall taste). If the subject ≥12 years of age needs assistance completing the questionnaire(s), his/her caregiver (e.g. parent or guardian) will be requested to evaluate the suspension with the child based on verbal and non-verbal feedback. For subjects <12 years of age who receive the suspension, their caregiver (e.g. parent or guardian) will be requested to evaluate the suspension with the child based on verbal and non-verbal feedback. Questionnaires for trametinib and dabrafenib are provided in the SPM. The questionnaire (s) may be completed after the first dose of study drug (s) and must be completed no later than Day 8 (±3 days).

7.3.8 Pregnancy Testing and Reporting

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

If a female subject is of childbearing potential, she must have a serum β-Human Chorionic Gonadotropin (β-HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). 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 during the study until 4 months following the last dose of study treatment(s).

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

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

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

7.4 Pharmacokinetics

PK parameters for study treatment (trametinib,dabrafenib and its metabolites) for subjects in whom the full blood sampling scheme will be used will be calculated with standard non-compartmental methods. The PK parameters calculated with non-compartmental methods include: AUC(0-t), Cmax, Tmax, Cτ, CL/F, and AUC (0-τ) (where τ = 24 hr for trametinib and 12 hr for dabrafenib). For subjects in whom the sparse blood sample collection scheme will be used, AUC(0-τ) and the average steady-state concentration may be estimated with a population PK model. Final PK parameters will be summarized and will be compared to historical adult data.

All trametinib and dabrafenib concentration-time data may be combined and included in a population PK analysis that will examine the influence of demographics (especially age and weight) on the PK of study treatment. Trametinib and dabrafenib PK parameters estimated in the population PK analysis may include: apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and absorption rate (ka) (trametinib only). Data may be pooled with trametinib and/or dabrafenib PK data from all parts of this study and with adult data.

[redacted]

7.4.1 Blood Sample Collection for Pharmacokinetics

Parts A and B:

Blood samples for PK analysis of trametinib will be collected at the time points indicated in the Time and Events Table, Section 7.1. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered to ensure thorough PK monitoring (but the total number of samples and total blood volume collected will not change).

Parts C and D:

Blood samples for PK analysis of trametinib, dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib (GSK2285403, GSK2298683 and GSK2167542, respectively), will be collected at the time points indicated in Time and Events Table, Section 7.1. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered to ensure thorough PK monitoring (but the total number of samples and total blood volume collected will not change).

Liver events and visual changes:

For subjects meeting any of the liver chemistry stopping criteria in Section 3.12.1, blood sample for PK analysis should be drawn as close as possible to the time of the event or within 20 days of the last dose of study treatment(s). Record the date and time of the PK blood sample draw and the date and time of the last dose of study treatment(s) prior the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date or time of the last dose cannot be approximated, or if a PK sample cannot be collected within the 20-day period following the last dose, do not obtain a PK sample.

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.

7.4.2 Pharmacokinetic Sample Analysis

Parts A, B, C and D:

Plasma analysis will be performed under the management of [redacted]. Concentrations of trametinib as well as dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored in the Novartis Archives. [redacted]

Details on PK blood sample collection, processing, storage and shipping procedures are provided in the SPM.

[redacted]

7.5 Translational Research

Performance of these investigations may be conditional on the results of the clinical trial, and samples may be selected for analysis on the basis of the clinical outcome. A table of samples, whether the samples are mandatory or optional, and the primary purpose for collection is provided (see Table 7-7).

Comparative examination of pre-dosing profiles of subjects may uncover known or novel candidate [redacted] profiles which could be used to predict response to treatment with trametinib and dabrafenib or provide new insights into cancer and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate [redacted] profiles and new insights which relate to the action of trametinib and dabrafenib.

All samples may be retained for a maximum of 15 years after the last visit of the last subject.

[redacted]

Table 7-7 List of Samples for Translational Research

Sample Type	Part A	Parts B1, B2 & B3	Parts B4, C and D	Primary Purpose
[redacted]				
Fresh Tissue at Baseline (Day 1) and Day 15	Optional*	Optional *	Optional *	Pharmaco-dynamic Analysis. If sample available, [redacted]
Archival or Fresh Tissue	Optional	Mandatory at screening except in subjects where tumor biopsy is not possible.	Mandatory at Screening for retrospective central confirmation of BRAF V600 status	Central testing/confirmation of BRAFV600 status in relevant cohorts [redacted]
Fresh tissue at radiological progression	Optional	Optional	Optional	Resistance Marker Analysis

*Please note that the same baseline specimen may be used for [redacted] and pharmacodynamic testing

7.5.1 Tumor Tissue for Mutation Testing

7.5.1.1 Part B, Cohorts (B1, B2 and B3)

Archival tissue must be submitted during screening for subsequent confirmation of the Ras pathway activation or mutation status. If archival specimen is not available, subjects will be

[redacted]

required to undergo tumor biopsy prior to participation in the study. If archived tissue is not available and a fresh tumor sample cannot be collected (i.e. subjects with brain tumors) the subject will not be eligible for participation in the study. The only exception will be for those subjects who are exempt from histiologic confirmation. Subjects will also be asked to provide tumor tissue after documented disease progression. However, collection of post-progression tumor tissue is optional and will be collected only from subjects that have provided appropriate consent.

[redacted]

Further details on tissue requirements including amount, sample fixation, and shipment will be provided in the SPM.

7.5.1.2 Parts B (Cohort B4), C and D

Patients may be enrolled in the study on the basis of local test results, but archival tumor tissue sample reflective of the current disease setting will be collected at Screening for central confirmation of the BRAF V600 mutation status. If an archival tumor tissue sample is not available, fresh tumor tissue should be collected (see SPM for further details) to determine the subject's BRAF V600 mutation status. If archived tumor tissue is not available and the collection of a fresh tumor tissue sample is not possible, the subject will not be eligible to participate in Parts B4,C and D of this study. BRAF V600 mutation status must be confirmed in a CLIA or equivalent certified laboratory prior to enrolment, and will be centrally confirmed retrospectively.

[redacted]

Details on sample collection, processing, storage and shipping procedures are provided in the SPM.

7.5.2 Tumor Tissue for Pharmacodynamic Testing

The collection of fresh tumor tissue is optional for PD testing but is strongly recommended. [redacted] The significance of the pharmacodynamic response will be interpreted in the context of pharmacokinetic and clinical endpoints.

[redacted]

[redacted]

[redacted]

7.6 Evaluation of Anti-Cancer Activity

Disease assessment may include imaging (e.g., CT scan, MRI, bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). Disease assessment will be completed within 2 weeks prior to the first dose of study treatment, and then according to the Time and Events Tables (Section 7.1). Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. A window of ±3 days for the first post-baseline assessment and ±7 days for all subsequent assessments is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

Clinical activity will be based on disease specific response criteria provided in Appendix 3 through Appendix 7. Additional details of are provided below in Table 7-8.

[redacted]

Table 7-8 Efficacy Assessment Methods and Measurement Modalities

Disease	Required Response Assessment	Required Response Measurement Modality
Glioma	Response assessed using RANO criteria provided in Appendix 5 by the treating institutions at each response assessment time points listed in Time and Events Table (Section 7.1)	Brain MRI is required at all assessment time points. If a brain MRI is contraindicated, a CT scan with contrast is allowed
NF-1 with PN	For all subjects with NF-1 with PN enrolled in Part A, Part A extension and Part B3, RECIST 1.1 based assessment is required by the treating institution. However, if the institution's standard practice uses volumetric assessment (by Dombi *et al* in Appendix 6), both assessments are required.	For all subjects with NF-1 with PN enrolled in Part A, Part A extension and Part B3, MRI scans that are amenable to volumetric MRI analysis is required at each response assessment time points listed in Time and Events Table (Section 7.1) For Part B3 patients, screening MRI must be centrally reviewed for eligibility prior enrollment
LCH	Response assessed by the treating institutions at each response assessment time points listed in Time and Events Table (Section 7.1) using RECIST 1.1 and the method provided by Histiocyte Society Evaluations and Treatment Guidelines, April 2009 as outlined in Appendix 7. LCH scores described (Donadieu 2004) as outlined in Appendix 7 is also required to be completed by the treating institution	CT Chest, Abdomen and Pelvis (CAP) scan and a brain MRI with and without contrast is required at each response assessment time points listed in Time and Events Table (Section 7.1) Other tests required for LCH scoring system such as blood tests (see Appendix 7) at each response assessment time points listed in Time and Events Table
Neuroblastoma	Patients with neuroblastoma will be evaluated by multiple methodologies by the treating institution. The number of assessments will depend on factors such a presence of MIBG lesions, bone marrow involvement etc. at the time of screening. Please refer to Appendix 4. 1. If subject has measurable disease as a component of their disease burden, response criteria should be assessed according to RECIST v1.1, as well as evaluable disease assessments below as appropriate, to determine overall response. 2. Subjects who had a positive MIBG scan at the start of therapy will be evaluated by response criteria for neuroblastoma subjects with MIBG positive lesions and report the scores for the 9 anatomic regions for the Curie scale, in addition to other assessments if applicable. 3. Subjects who had a positive finding in bone marrow at the start of therapy will be evaluated by the treating institution using the response criteria for neuroblastoma subjects with bone marrow involvement provided in Appendix 4 in addition to other assessments if applicable	MRI or CT scan, MIBG scan, bone marrow biopsy and urine catecholamine levels are mandatory at screening. Each individual scan or test should be performed at subsequent visits if positive at screening.

[redacted]

Disease	Required Response Assessment	Required Response Measurement Modality
Melanoma and other solid tumors	These patients must be assessed using RECIST 1.1 criteria provided in Appendix 3 by the treating institutions at each response assessment time points listed in Time and Events Table (Section 7.1)	Melanoma patients: chest, abdomen and pelvis CT or MRI (with contrast enhancement) is required. Brain CT or MRI is required for subjects with brain metastasis or if clinically indicated and CT or MRI of other metastatic sites (e.g., neck). Other solid tumors not listed above: CT Chest, Abdomen and Pelvis (CAP) scan required.

[redacted]

7.6.1 MRI and/or CT Scan

Magnetic resonance imaging (MRI) will be performed at Screening and at scheduled visits during the study (see Time and Events Table Section 7.1) for subjects with primary brain tumors and subjects with PN. If a brain MRI is contraindicated, a CT scan with contrast is allowed (except for PN subjects in Part B where MRIs are required). Whichever modality is used at screening should be consistently performed during the study.

Scans for neurofibroma will be centrally collected and reviewed. Instructions for image acquisition are included in Appendix 6 and the SPM.

7.6.2 Tumor Marker(s)

For subjects whose disease may be followed by well-characterized tumor markers, such as urine HVA/VMA in neuroblastoma, disease assessments should include results of tumor marker measurements.

Tumor marker values will be recorded in the eCRF.

8 Adverse Events and Serious 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 8.1 and Section 8.2, respectively.

8.1 Definition of an AE

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

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

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

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

[redacted]

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.

8.2 Definition of a SAE

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

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

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect.

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

[redacted]

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 study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (INR) >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: Bilirubin fractionation is performed if testing is available. If testing is not available, 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 ≥2 times ULN, then the event is still reported as a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- Any new primary malignancy with a histology different from the primary tumor.
- LVEF that meets stopping criteria.
- RPED or RVO.

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

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

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

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

8.3.1 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

[redacted]

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation
- Symptomatic LVEF decrease

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported. Any events meeting the definition of SAE should also follow the SAE reporting requirements (Section 8.4.2).

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

8.4 Time Period and Frequency of Detecting AEs and SAEs

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

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

From the time a subject consents to participate in and completes the study (See Section 6), all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to Novartis, as indicated in Table 8-1.

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 AE that they believe possibly related to study treatment.

8.4.1 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?” or for pediatric studies, “How does your child seem to feel?”

"Have you had any (other) medical problems since your last visit/contact?" or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

8.4.2 Prompt Reporting of SAEs and Other Events to Novartis

SAEs, DLTs, pregnancies, and grade ≥ 3 liver function abnormalities, discontinuation of protocol therapy for toxicity, and any grade 5 events that are not related to underlying disease meeting pre-defined criteria will be reported promptly by the investigator to Novartis as described in Table 8-1 once the investigator determines the event meets the protocol definition for that event.

Table 8-1 Reporting of SAEs and Other Events to Novartis

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hr	SAE data collection tool	24 hr	Updated SAE data collection tool
DLTs[d]	24 hr	Email to Sponsor	24 hr	Email to Sponsor
"CV events" and/or "death" [d]	To be completed within one week	CV events" and/or "death" data eCRFs	To be completed within one week	Updated "CV events" and/or "death" data eCRFs
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hr[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hr	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash or 3 times ULN ≥4 weeks	24 hr[a]	Liver Event eCRF[b]	24 hr	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hr[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. Novartis to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible.

[redacted]

c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.
d. If a DLT or "CV event" should also meet the definition of a SAE, the site should also follow the SAE reporting requirements.

Methods for detecting, recording, evaluating, and following up on AEs and serious adverse events (SAEs) are provided in the SPM.

8.4.3 Regulatory reporting requirements for SAEs

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

Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

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

An investigator who receives an investigator safety report describing 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.

9 Concomitant Medications and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by Novartis and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

9.1 Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. 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.

[redacted]

9.2 Prohibited Medications

9.2.1 Prohibited Medications: Parts A & B (Trametinib)

There are no prohibited medications while on treatment in Part A and Part B of this study.

9.2.2 Prohibited Medications: Parts C & D (Dabrafenib)

The following medications or non-drug therapies are prohibited while on treatment in Parts C & D of this study:

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known human immunodeficiency virus (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 9-1) may only be used under special circumstances (e.g., as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval by the 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.

Table 9-1 Prohibited Medications; Parts C and D (Dabrafenib)

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, phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan,
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
Anti-retroviral	Ritonavir, Saquinavir, Atazanavir
Miscellaneous	Conivaptan

9.3 Medications to be Used with Caution; Parts C & D (Dabrafenib)

The following medications should be used with caution in Parts C and D of this study as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

[redacted]

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). **Dabrafenib** is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 9-2 and in the SPM.
- Therapeutic level dosing of warfarin can be used with approval by the Medical Lead and close monitoring of Prothrombin Time/International Normalized Ratio (PT/INR) by the site. Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib-mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued, warfarin exposure may be increased. Thus, warfarin dosing may need to be adjusted based on PT/INR during and after treatment with dabrafenib. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib PK. In an ad-hoc analysis, no differences in Cmax and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

Table 9-2 Medications to be used with Caution; Parts C and D (Dabrafenib)

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin

[redacted]

Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, digoxin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib as exposure to dabrafenib may be decreased	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine

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

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

10 Lifestyle and/or Dietary Restrictions

10.1 Contraception

10.1.1 Female Subjects

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during dosing and for 16 weeks after stopping treatment with trametinib or 2 weeks after stopping treatment with dabrafenib whichever is longer. Highly effective contraception methods include:

a. Total abstinence (when this is 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.
b. 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.

[redacted]

c. Sterilization (at least 6 months prior to screening) for male partners. The vasectomized male partner should be the sole partner for that subject.
d. Trametinib in combination with dabrafenib only: 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.
e. Trametinib monotherapy only: Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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 per Clinical Trial Facilitation Group (CTFG) guidelines (Clinical Trial Facilitation Group 2014).
- Oral contraceptives are not considered as highly effective methods of contraception for patients taking dabrafenib, due to potential drug-drug interactions with dabrafenib.
- 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.

10.1.2 Male Subjects

Male patients (including those that have had a vascetomy) must use a condom during intercourse while taking trametinib and/or dabrafenib and not to father a child during the study and for the period of 16 weeks following stopping of study treatment.

10.2 Lactation Restrictions

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

11 Data Management

For this study subject data will be entered into the eCRF, transmitted electronically to the sponsor or designee and be combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable 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.

In all cases, subject initials will not be collected or transmitted to Novartis according to Novartis policy.

12 Data Analysis and Statistical Considerations

12.1 Hypotheses

12.1.1 Part A: Dose-Escalation Phase

No formal statistical hypotheses are being tested. Analysis of the data obtained from this portion of the study will be focused on comparison between dose cohorts and only descriptive methods will be utilized.

12.1.2 Part B: Expansion Cohort

No formal statistical hypotheses are being tested. Analysis of the data obtained from this portion of the study will be focused on evaluating the safety profile, PK/PD relationship, and anti-cancer activity of trametinib for each disease cohort and only descriptive methods will be used in analysis of the data obtained from this study. The range of response rate and the corresponding exact binomial 95% CI is provided in Section 12.2.2, if any objective response is observed in the Expansion Cohort.

12.1.3 Part C: Combination Cohort

No formal statistical hypotheses are being tested. Analysis of the data obtained from this portion of the study will be focused on comparison between dose cohorts and only descriptive methods will be utilized.

12.1.4 Part D: Expansion Cohort with Combination Therapy

No formal statistical hypotheses are being tested. Analysis of the data obtained from this portion of the study will be focused on evaluating the safety profile, PK/PD relationship, and anti-cancer activity of trametinib in combination with dabrafenib for each disease cohort and only descriptive methods will be used in analysis of the data obtained from this study. The range of response rate and the corresponding exact binomial 95% CI is provided in Section 12.2.4, if any objective response is observed in the Expansion Cohort.

12.2 Sample Size Determination

12.2.1 Part A: Dose-Escalation Phase

The total number of subjects to be enrolled in Part A will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 48 subjects will be enrolled.

[redacted]

Given true incidence rates of DLTs, the associated probability of escalating to the next dose level in a 3+3 scheme are provided for reference below in Table 12-1.

Table 12-1 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

12.2.2 Part B: Expansion Cohort

The sample size for Part B is based on feasibility, practicality, and what would be sufficient for the characterization of the safety of trametinib and the plasma PK for the populations enrolled. Each of the 4 expansion cohorts will enroll at least 10 evaluable subjects, 5 subjects in each cohort will be under the age of 6 years. Therefore, it is estimated that at least 40 subjects will be enrolled into Part B.

If less than 1 response is observed after 10 subjects complete the study, the treatment could be considered to have insufficient clinical activity in that cohort. The estimated sample size (n=10) for the Part B expansion cohorts was further evaluated using exact binominal distribution probabilities, and the details are provided in Table 12-2. For example, if zero responses are observed among 10 subjects in a cohort [if the response rate (RR)=5%], the chance of declaring the cohort as having insufficient clinical activity after 10 subjects is 60%. If the true RR=15% for trametinib in unresectable low grade gliomas subjects, the chance of declaring the cohort as having insufficient clinical activity after 10 subjects is approximately 20%. Table 12-4 provides the corresponding 95% CIs around potential observed objective response rates given N=10 subjects.

Table 12-2 Exact Binomial Probabilities of Observing 0 and 1 (or more) Responses in 10 Subjects

True RR	Probability of Observing 0 responses in 10 Subjects	Probability of Observing ≥1 Responses in 10 Subjects
5%	0.60	0.40
10%	0.35	0.65
15%	0.20	0.80
20%	0.11	0.89
25%	0.056	0.94
30%	0.028	0.97

Table 12-3 Exact Binomial 95% Confidence Intervals Around Potential Observed Objective Responses Rates for 10 Subjects

Observed Objective Response Rate	Exact 95% Confidence Interval (%) (N=10)
10%	0.3, 44.5
20%	2.5, 55.6
30%	6.7, 65.2
40%	12.2, 73.8
50%	18.7, 81.3
60%	26.2, 87.8

[redacted]

Observed Objective Response Rate	Exact 95% Confidence Interval (%) (N=10)
70%	34.8, 93.3

12.2.3 Part C: Combination Cohort

The total number of subjects to be enrolled in Part C will depend on the number of subjects needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 18 subjects will be enrolled.

12.2.4 Part D: Expansion Cohort with Combination Therapy

The sample size for Part D is based on feasibility, practicality, and what would be sufficient for the characterization of the safety and preliminary anti-tumor activity of trametinib/ dabrafenib combination and the plasma PK for the populations enrolled. Similar patient populations have been enrolled into the dabrafenib monotherapy phase 1 study, BRF116013 (see Section 1.3.4.1 of this protocol) where it has been shown that it is more practical to enroll patients with LGG than those with LCH. Thus, approximately 20 subjects with LGG and approximately 10 subjects with LCH will be enrolled. Overall approximately 30 subjects will be enrolled into Part D.

The estimated sample size for the LGG and LCH cohorts in Part D is further evaluated using exact binominal distribution probabilities, and the details are provided in Table 12-4 and Table 12-5. For example, if the true RR=20% for trametinib and dabrafenib combination, the probability of observing < 6 responses out of 20 LGG subjects (observed response rate < 30%) is approximately 80%, and the probability of observing < 3 responses out of 10 LCH subjects (observed response rate < 30%) is approximately 68%. If the true RR=50%, the probability of observing at least 6 responses is > 97% given 20 LGG subjects, and the probability of observing at least 3 responses is > 94% given 10 LCH subjects. Table 12-6 provides the corresponding 95% CIs around potential observed objective response rates given N=20 subjects. The corresponding 95% CIs for potential observed response rates given N=10 is shown in Table 12-3.

Table 12-4 Exact Binomial Probabilities of Observing less than 6 and at least 6 Responses in 20 Subjects

True RR	Probability of Observing < 6 responses in 20 Subjects	Probability of Observing ≥ 6 Responses in 20 Subjects
20%	0.80	0.20
25%	0.62	0.38
30%	0.42	0.58
35%	0.25	0.75
40%	0.13	0.87
45%	0.06	0.94
50%	0.02	0.98
55%	0.01	0.99

[redacted]

Table 12-5 Exact Binomial Probabilities of Observing less than 3 and at least 3 Responses in 10 Subjects

True RR	Probability of Observing < 3 responses in 10 Subjects	Probability of Observing ≥ 3 Responses in 10 Subjects
20%	0.68	0.32
25%	0.53	0.47
30%	0.38	0.62
35%	0.26	0.74
40%	0.17	0.83
45%	0.10	0.90
50%	0.05	0.95
55%	0.03	0.97

Table 12-6 Exact Binomial 95% Confidence Intervals around Potential Observed Objective Responses Rates for 20 Subjects

Observed Objective Response Rate	Exact 95% Confidence Interval (%) (N=20)
20%	5.7, 43.7
30%	11.9, 54.3
40%	19.1, 63.9
50%	27.2, 72.8
60%	36.1, 80.9
70%	45.7, 88.1
80%	56.3, 94.3

12.3 Data Analysis Considerations

12.3.1 Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of study treatment.

This analysis population will be used for summaries of demographic/baseline characteristics and evaluation of anti-cancer activity.

The **Safety Population** consists of all subjects who receive at least one dose of study treatment. Safety will be evaluated based on this analysis population.

The '**DLT Evaluable' population** is defined as those subjects participating in dose determining portion of the study (Part A and 3+3 design portions of Part A extension, Part C and Part C extension) fulfilling the 'All Treated' population criteria and having received an adequate treatment for the first 28 days to enable an appropriate evaluation of study drug related DLTs. Adequate exposure during the first 28 days will be defined as having received >75% of planned study treatment doses, exclusive of missed doses due to treatment-related toxicity. Any subject in the 'All Treated' population who experiences a DLT, as defined in Section 3.2.3, will also be included in the DLT evaluable population regardless of exposure.

The **PK Population** will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

[redacted]

The **Response-evaluable Population** is defined as those subjects fulfilling the All Treated Population criteria with a pre-dose and at least one post-dose disease efficacy assessment. In addition, for patients evaluated by RANO criteria, their disease must be 'measurable' at baseline to be included in the Response-evaluable Population. This population will be used for sensitivity analysis on the efficacy endpoints.

Additional analysis populations may be defined in the Statistical Analysis Plan (SAP).

12.4 Interim Analysis

12.4.1 Part A: Dose-Escalation

While no formal interim analysis is planned for Part A, safety and PK data will be examined on an ongoing basis to support dose escalation decisions. Prior to determining the dose for the next cohort enrolled, [redacted] and the Cτ at steady state. For more details of the dose escalation procedure, see Section 3.2.

12.4.2 Part B: Expansion Cohort

An interim analysis is planned after all subjects have been enrolled in B3 cohort and have completed at least 3 post treatment assessments (Weeks 17, 33 and 49) or have discontinued treatment earlier. The results will be used for decision making for future development options and may be used for publications. At this time, no statistical hypothesis testing is planned, and no decision regarding the conduct of this study will be made.

At this interim analysis, the data for Part A subjects will also be analyzed. The data from other disease cohorts for Part B may also be analyzed. In addition, safety and tolerability will be monitored closely on a continued basis.

12.4.3 Part C: Combination Cohort

Prior to opening Part C the available safety and PK data from Parts A and B will be reviewed. Safety and PK data will be examined on an ongoing basis to support dose escalation decisions. Prior to determining the dose for the next cohort enrolled, [redacted]

12.4.4 Part D: Expansion Cohort with Combination Therapy

An interim analysis is planned after all subjects have been enrolled in LGG cohort and have completed at least 12 months of treatment or have discontinued treatment earlier. The results will be used for decision making for future development options and may be used for publications. At this time, no statistical hypothesis testing is planned, and no decision regarding the conduct of this study will be made.

At this interim analysis, the data for Part A, B, and C subjects will also be analyzed. The data from other disease cohorts for Part D may also be analyzed. In addition, safety and tolerability will be monitored closely on a continued basis.

Details of the interim analysis will be provided in SAP.

[redacted]

12.4.5 Additional Interim Analyses

Additional interim analyses may be performed to support any health authority or publication requests as and when needed. No efficacy or futility conclusions will be drawn based on these interim analyses.

12.5 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.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be information, data from all participating centers will be pooled prior to analysis.

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

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

Demographic and baseline characteristics will be summarized.

Subjects who are intra-subject dose escalated will be summarized in the dose level to which they were initially assigned.

12.5.1 Anti-Cancer Activity Analyses

The All Treated Population will be used for anti-cancer activity analyses. Since this is a Phase I study, anti-cancer activity will be evaluated by investigator assessment based on clinical evidence and response criteria provided in Appendix 3 through Appendix 7. If data warrant, the response data will be summarized by disease cohort and by dose level. Anti-cancer activity analyses will also be performed based on Response-Evaluable population as sensitivity analysis.

In a supportive analysis, for LGG and NF-1 patients, anti-cancer activity will also be evaluated by independent review assessment based on clinical evidence and response criteria provided in Appendix 5 and 6 respectively.

Correlation analysis will be conducted to explore any relationship between the subject's PK or PD evaluations and tumor response based on disease specific response criteria provided in Appendix 3 through Appendix 7.

Full details will be specified in the SAP.

12.5.2 Safety Analyses

The Safety Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points

[redacted]

using a "worst-case" analysis. Complete details of the safety analyses will be provided in the SAP.

12.5.2.1 Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy. Further details will be provided in the SAP.

12.5.2.2 Adverse Events

Adverse events (AEs) 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 v4.03 (NCI 2009).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE v4.03 (NCI 2009) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g., number of occurrences, action taken, grade, etc) of the following AEs of special interest will be summarized separately: rash, diarrhea.

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

Dose-limiting toxicities (DLTs) will be listed for each subject and summarized by dose cohort according to Novartis standards. Further details will be provided in the SAP.

12.5.2.3 Clinical Laboratory Evaluations

Hematology, clinical chemistry and urinalysis data will be summarized using frequencies and proportions according to NCI-CTCAE v4.03 (NCI 2009) For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges and will be summarized using proportions. Further details will be provided in the SAP.

12.5.2.4 Other Safety Measures

Data for vital signs, ECGs, and ECHOs will be summarized based on predetermined criteria identified to be of potential clinical interest. Further details will be provided in the SAP.

12.5.3 Pharmacokinetic Analyses

PK parameters for study treatment (trametinib, dabrafenib and its metabolites) for subjects in whom the full blood sampling scheme will be used will be calculated with standard non-compartmental methods. The PK parameters calculated with non-compartmental methods include; AUC(0-t), Cmax, Tmax, $C\tau$, CL/F, and AUC(0-τ) (where τ = 24 hr for trametinib and 12 hr for dabrafenib). For subjects in whom the sparse blood sample collection scheme will be used, AUC(0-τ) and the average steady-state concentration will be estimated with a population

[redacted]

PK model. Final PK parameters will be summarized and will be compared to historical adult data.

All trametinib and dabrafenib concentration-time data may be combined and included in a population PK analysis that will examine the influence of demographics (especially age and weight) on the PK of study treatment. Trametinib and dabrafenib PK parameters estimated in the population PK analysis will include: apparent clearance following oral dosing (CL/F), central volume of distribution (Vc/F), and absorption rate constants (ka) (trametinib only). Sparse PK data collected for each treatment may be pooled with the rest of the PK data collected for this treatment from all parts of this study and in addition to adult data.

PK analysis will be under the supervision of Novartis. The assay for trametinib, dabrafenib and its metabolites are conducted under GLP conditions and are validated for determination of the PK primary endpoint.

12.5.3.1 Pharmacokinetic Parameters

PK analysis of drug concentration-time data will be conducted by non-compartmental methods under the direction of Novartis. The following PK parameters will be determined if data permit:

- maximum observed plasma concentration (Cmax).
- time to Cmax (tmax).
- area under the plasma concentration-time curve (AUC(0-t), AUC(0-τ) (repeat dosing).
- oral clearance (CL/F).
- Cτ at steady state

Population PK parameters may include the following and are dependent upon the final population PK model for both trametinib and/or dabrafenib: apparent clearance following oral dosing (CL/F), central volume of distribution (Vc/F), absorption rate constants (ka) and MTIME (time when absorption rate changes).

12.5.3.2 Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the PK parameters data will be the responsibility of Novartis with actual analyses being performed by Novartis and/or a designated CRO.

Drug concentration-time data will be listed for each subject and summarized by descriptive statistics at each time point by cohort and by study treatment.

[redacted]

12.5.3.3 Translational Research Analyses

The results of translational research investigations will be reported separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the SAP.

[redacted]

13 Study Conduct Considerations

13.1 Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrollment of subjects begins.

13.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Novartis will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization Good Clinical Practice (ICH 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:

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

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

Written informed consent and assent when applicable must be obtained from each subject or their legally authorized representative prior to participation in the study.

13.3 Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the IRB/IEC is notified.

13.4 Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (GCP) and 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 eCRF will serve as the source document.

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

Novartis (or designated CRO) personnel will monitor the study to ensure that the:

[redacted]

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

13.5 Quality Assurance

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

13.6 Study and Site Closure

The end of the study will be defined as the date of the last visit of the last subject enrolled.

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

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

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

Novartis may also close study sites which fail to recruit subjects within a predefined timeframe.

13.7 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.

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

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

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

Novartis will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis and the clinical study report.

Novartis aims to post a results summary to the Novartis Clinical Trial Results website (novartisclinicaltrials.com) and other publicly available registers no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novaris aims to submit results of the study for publication. When publication is not feasible, please refer to the Novartis Clinical Trial Results website (novartisclinicaltrials.com) for a summary of the trial results.

[redacted]

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15 Appendices

15.1 Appendix 1: Karnofsky and Lansky Performance Scores

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be in multiples of 10			
Karnofsky (age ≥16 years of age)		**Lansky** (age <16 years)	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs of symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort, some signs of symptoms of disease.	80	Active, but tires quickly.
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play, keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.

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15.2 Appendix 2: Dosing Nomograms

Dosing nomograms - Trametinib

	DOSE LEVEL: **0.0125 mg/kg/dose** **SUBJECT WEIGHT:** **≤ 19.4 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** [At this dose level, the 0.05 mg/mL oral solution will be administered to all patients ≤19.4 kg]			
Actual weight* (kg)	Dose	Dose	Dose Reduction	
	mL	mg	mL	mg
2.5 – 3	0.6	0.03	0.4	0.02
3.1-3.6	0.8	0.04	0.6	0.03
3.7-4.3	1	0.05	0.8	0.04
4.4-5.2	1.2	0.06	0.9	0.45
5.3-6.1	1.4	0.07	1.1	0.55
6.2-6.7	1.6	0.08	1.2	0.06
6.8-7.6	1.8	0.09	1.4	0.07
7.7-8.6	2	0.1	1.5	0.075
8.7-9.3	2.2	0.11	1.7	0.085
9.4-10.1	2.4	0.12	1.8	0.09
10.2-10.7	2.6	0.13	2	0.1
10.8-11.3	2.8	0.14	2.1	0.105
11.4-12.2	3	0.15	2.3	0.115
12.3-12.9	3.2	0.16	2.4	0.12
13-13.8	3.4	0.17	2.6	0.13
13.9-14.6	3.6	0.18	2.7	0.135
14.7-15.5	3.8	0.19	2.9	0.145
15.6-16.5	4	0.2	3	0.15
16.6-17.4	4.2	0.21	3.2	0.16
17.5-18	4.4	0.22	3.3	0.165
18.1-18.7	4.6	0.23	3.5	0.175
18.8-19.4	4.8	0.24	3.6	0.18

*weight measured within 7 days of the start of the cycle.

[redacted]

	DOSE LEVEL: **0.0125 mg/kg/dose** **SUBJECT WEIGHT:** **≥ 19.5 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION**			
Actual weight* (kg)	Dose		Dose Reduction	
	mL	mg	mL	mg
19.5- 23.5	5	0.25	3.8	0.19
23.6- 28.5	6	0.3	4	0.2
28.6-34	7.5	0.375	6	0.3
34.1-38	9	0.45	6.8	0.34
38.1-45	10	0.5	7.5	0.375
45.1-55	12.5	0.625	10	0.5
55.1-67	15	0.75	12	0.6
67.1-72	17	0.85	12.5	0.625
≥72.1	20	1.0	15	0.75

*weight measured within 7 days of the start of the cycle

[redacted]

	DOSE LEVEL: **0.025 mg/kg/dose** **SUBJECT WEIGHT:** **< 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** [At this dose level, the 0.05 mg/mL oral solution will be administered to all patients ≤9.9 kg]			
Actual weight* (kg)	Dose		Dose Reduction	
	mL	mg	mL	mg
2-2.5	1	0.05	0.7	0.035
2.6-3.5	1.4	0.07	1.1	0.055
3.6-4.5	2	0.1	1.5	0.075
4.6-5.7	2.5	0.125	2	0.1
5.8-6.9	3	0.15	2.3	0.115
7-9.9	4	0.2	3	0.15

*weight measured within 7 days of the start of the cycle

	DOSE LEVEL: **0.025 mg/kg/dose** **SUBJECT WEIGHT:** **≥ 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION**			
Actual weight* (kg)	Dose		Dose Reduction	
	mL	mg	mL	mg
10-12.5	5	0.25	3.8	0.19
12.6-16.5	7.5	0.375	5	0.25
16.6- 24.5	10	0.5	7.5	0.375
24.6- 35	15	0.75	10	0.5
35.1-45	20	1.0	15.0	0.75
45.1- 55	25	1.25	17.5	0.875
55.1- 68	30	1.5	22.5	1.125
68.1- 72	35	1.75	25	1.25
> 72	40	2	30	1.5

*weight measured within 7 days of the start of the cycle

[redacted]

	DOSE LEVEL: **0.04 mg/kg/dose** **SUBJECT WEIGHT:** **< 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** [At this dose level, the 0.05 mg/mL oral solution will be administered to all patients ≤9.9 kg]			
Actual weight* (kg)	Dose		Dose Reduction	
	mL	mg	mL	mg
2-2.5	1.8	0.09	1.2	0.06
2.6-3.5	2	0.1	1.6	0.08
3.6-4.5	3.2	0.16	2.4	0.12
4.6-5.8	4	0.2	3	0.15
5.9-7.5	5	0.25	3.6	0.18
7.6-9.9	7.5	0.375	5	0.25

*weight measured within 7 days of the start of the cycle

[redacted]

	DOSE LEVEL: **0.04 mg/kg/dose** **SUBJECT WEIGHT:** **≥ 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION**			
Actual weight* (kg)	Dose		Dose Reduction	
	mL	mg	mL	mg
10-14	10	0.5	7.5	0.375
14.1-17	12.5	0.625	9.5	0.475
17.1- 23.5	15	0.75	10	0.5
23.6- 30	20	1.0	15	0.75
30.1-35	25	1.25	17.5	0.875
35.1- 45	30	1.5	20	1.0
45.1- 60	40	2	30	1.5
60.1- 69.9	40	2	30	1.5
≥70	40	2	30	1.5

*weight measured within 7 days of the start of the cycle

[redacted]

	DOSE LEVEL: **0.032 mg/kg/dose** **SUBJECT WEIGHT:** **< 15 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** [At this dose level, the 0.05 mg/mL oral solution will be administered to all patients ≤14.9 kg]		
Actual weight* (kg)	Dose		Dose Reduction
	mL	mg	Please refer to 0.025 mg/kg dosing nomogram ('Dose' column)
2-2.4	1.4	0.07	
2.5-3	1.8	0.09	
3.1-3.7	2.2	0.11	
3.8-4.5	2.7	0.13	
4.6-5.5	3.2	0.16	
5.6-6.7	3.9	0.20	
6.8-8.1	4.8	0.24	
8.2-9.8	5.8	0.29	
9.9-11.9	7.0	0.35	
12-13.9	8.3	0.41	
14-14.9	9.2	0.46	

*weight measured within 7 days of the start of the cycle

	DOSE LEVEL: **0.032 mg/kg/dose** **SUBJECT WEIGHT:** **≥ 15 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION**		
Actual weight* (kg)	Dose		Dose Reduction
	mL	mg	Please refer to 0.025 mg/kg dosing nomogram ('Dose' column)
15-17.9	10.5	0.53	
18-21.5	12.6	0.63	
21.6-25.9	15.2	0.76	
26-31.2	18.3	0.92	
31.3-37.5	22.0	1.10	
37.6-45.1	26.5	1.32	
45.2-54.3	31.8	1.59	
54.4-60	36.6	1.83	
>60	40.0	2	

*weight measured within 7 days of the start of the cycle

[redacted]

Dose and treatment schedule for trametinib tablets for subjects less than 6 years and weight greater or equal to 26kg (0.032 mg/kg/day)

Weight	Dose	Frequency and/or Regimen	Total Daily Dose	Pharmaceutical form and route of administration
26-39.5	2 × 0.5 mg	q.d	1 mg	Tablets for oral administration
39.6-54.5 kg	3 × 0.5 mg	q.d	1.5 mg	Tablets for oral administration
≥ 54.6 kg	1 × 2 mg	q.d	2 mg	Tablets for oral administration

Dose and treatment schedule for trametinib tablets for subjects greater or equal to 6 years and weight greater or equal to 33kg (0.025 mg/kg/day)

Weight	Dose	Frequency and/or Regimen	Total Daily Dose	Pharmaceutical form and route of administration
33-49.5 kg	2 × 0.5 mg	q.d	1 mg	Tablets for oral administration
49.6-69.5 kg	3 × 0.5 mg	q.d	1.5 mg	Tablets for oral administration
≥ 69.6 kg	1 × 2 mg	q.d	2 mg	Tablets for oral administration

[redacted]

Dosing Nomogram – Dabrafenib

1. If a patient's current weight is not a whole number, it should be rounded to its nearest whole number (eg. 12.1 - 12.4 kg is rounded down to 12 and 12.5 – 12.9 is rounded up to 13)
2. Age for daily dose determination in any period during the study is based on the age at enrolment and will remain constant throughout the study.
3. Children < 6 years-old and subjects, regardless of age, with a risk of choking when swallowing capsules will be required to use the dispersible tablet formulation.
4. The investigator or responsible site personnel should instruct the patient and guardians to take or administer the study drug as per protocol (to promote compliance).

[redacted]

Dabrafenib **Capsule** Dosing Nomogram

Dose Level 1 (Starting dose)*					
< 12 year olds			≥ 12 year olds		
Daily dose: 2.63 mg/kg dabrafenib capsule			Daily dose: 2.25 mg/kg dabrafenib capsule		
Body weight (kg)	**Capsules/ dose**	**Total Daily (actual)**	**Body weight (kg)**	**Capsules/ dose**	**Total Daily (actual)**
<32	See dispersible tablet for oral suspension nomogram		**<38**	See dispersible tablet for oral suspension nomogram	
32-47	50 mg	100 mg	**38-55**	50 mg	100 mg
48-71	75 mg	150 mg	**56-83**	75 mg	150 mg
72-94	100 mg	200 mg	**84-111**	100 mg	200 mg
95-118	125 mg	250 mg	**112-138**	125 mg	250 mg
≥ 119	150 mg	300 mg	**≥ 139**	150 mg	300 mg

* No dose reduction is allowed for patients on dose level 2.25 or 2.63 mg/kg/day. If a patient requires dose reduction at this level, dabrafenib treatment must be discontinued

Dose Level 2			
< 12 year olds: 5.25 mg/kg dabrafenib capsule			
Dose			Dose Reduction
Body weight (kg)	**Capsules/ dose**	**Total Daily (actual)**	Please refer to 4.5 mg/kg dabrafenib capsules dosing nomogram ('Dose' column).
<16	See dispersible tablet for oral suspension nomogram		
16-23	50 mg	100 mg	
24-33	75 mg	150 mg	
34-42	100 mg	200 mg	
43-52	125 mg	250 mg	
≥ 53	150 mg	300 mg	

[redacted]

Dose Level 2			
≥ 12 year olds: 4.5 mg/kg dabrafenib capsule			
Dose			Dose Reduction
Body weight (kg)	Capsules/ dose	Total Daily (actual)	Please refer to 3.75 mg/kg dabrafenib capsules dosing nomogram.
<19	See dispersible tablet for oral suspension nomogram		
19-27	50 mg	100 mg	
28-38	75 mg	150 mg	
39-50	100 mg	200 mg	
51-61	125 mg	250 mg	
≥ 62	150 mg	300 mg	

3.75 mg/kg dabrafenib capsule		
Body weight (kg)	Capsules/ dose	Total Daily (actual)
<26	See dispersible tablet for oral suspension nomogram	
26-33	50 mg	100 mg
34-46	75 mg	150 mg
47-59	100 mg	200 mg
60-73	125 mg	250 mg
≥ 74	150 mg	300 mg

Dabrafenib 10mg **Dispersible Tablet** for oral (suspension) Dosing Nomogram

Dose and treatment schedule for dabrafenib (DRB436) 10mg dispersible tablets for patients less than 12 years of age (5.25mg/kg/day)

Weight (kg)	Dose	Frequency and/or Regimen	Total Daily Dose	Pharmaceutical form and route of administration
7-9.5	20 mg	b.i.d	40 mg	Dispersible tablet for oral suspension
9.6-13.5	30 mg	b.i.d	60 mg	Dispersible tablet for oral suspension
13.6-17.5	40 mg	b.i.d	80 mg	Dispersible tablet for oral suspension
17.6-20.5	50 mg	b.i.d	100 mg	Dispersible tablet for oral suspension
20.6-24.5	60 mg	b.i.d	120 mg	Dispersible tablet for oral suspension
24.6-28.5	70 mg	b.i.d	140 mg	Dispersible tablet for oral suspension
28.6-32.5	80 mg	b.i.d	160 mg	Dispersible tablet for oral suspension
32.6-36.5	90 mg	b.i.d	180 mg	Dispersible tablet for oral suspension
36.6-40.5	100 mg	b.i.d.	200 mg	Dispersible tablet for oral suspension

[redacted]

40.6-43.5	110 mg	b.i.d	220 mg	Dispersible tablet for oral suspension
43.6-47.5	120 mg	b.i.d	240 mg	Dispersible tablet for oral suspension
47.6-51.5	130 mg	b.i.d	260 mg	Dispersible tablet for oral suspension
51.6-55.5	140 mg	b.i.d.	280 mg	Dispersible tablet for oral suspension
≥55.6 kg	150 mg	b.i.d	300 mg	Dispersible tablet for oral suspension

Dose and treatment schedule for dabrafenib (DRB436) 10mg dispersible tablet for patients greater than or equal 12 years of age (4.5 mg/kg/day)

Weight (kg)	Dose	Frequency and/or Regimen	Total Daily Dose	Pharmaceutical form and route of administration
10-11.5	20 mg	b.i.d	40 mg	Dispersible tablet for oral suspension
11.6-17.5	30 mg	b.i.d	60 mg	Dispersible tablet for oral suspension
17.6-20.5	40 mg	b.i.d	80 mg	Dispersible tablet for oral suspension
20.6-24.5	50 mg	b.i.d	100 mg	Dispersible tablet for oral suspension
24.6-28.5	60 mg	b.i.d	120 mg	Dispersible tablet for oral suspension
28.6-32.5	70 mg	b.i.d	140 mg	Dispersible tablet for oral suspension
32.6-36.5	80 mg	b.i.d	160 mg	Dispersible tablet for oral suspension
36.6-40.5	90 mg	b.i.d	180 mg	Dispersible tablet for oral suspension
40.6-43.5	100 mg	b.i.d	200 mg	Dispersible tablet for oral suspension
43.6-47.5	110 mg	b.i.d	220 mg	Dispersible tablet for oral suspension
47.6-51.5	120 mg	b.i.d	240 mg	Dispersible tablet for oral suspension
51.6-55.5	130 mg	b.i.d	260 mg	Dispersible tablet for oral suspension
55.6-64.5	140 mg	b.i.d	280 mg	Dispersible tablet for oral suspension
≥64.6	150 mg	b.i.d	300 mg	Dispersible tablet for oral suspension

Please note that the new formulation (DT) applies to only the recommended doses, as the dose-escalation part of the study is already completed.

[redacted]

15.3 Appendix 3: Response Criteria for Solid Tumors (Not Neuroblastoma or PNs or Glioma)

RECIST v1.1 (Eisenhauer 2009) will be used for response evaluation for subjects with solid tumors except neuroblastoma, primary central nervous system tumors, or PN(s).

Subjects with solid tumors may have measurable or evaluable lesions. Measureable lesions are defined as target or non-target lesions. Details of RECIST v1.1 can be found at ctep.cancer.gov/protocolDevelopment/default.htm#protocol_development.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.	
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

[redacted]

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[1]
CR	CR	No	CR	≥4 wks. Confirmation[2]
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation[2]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline[2]
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD[3]	Yes or No	PD	
Any	Any	Yes	PD	

1. See RECIST v1.1 manuscript for further details on what is evidence of a new lesion (Eisenhauer, 2009)
2. Only for non-randomized trials with response as primary endpoint.
3. In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1. Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

[redacted]

15.4 Appendix 4: Response Criteria for Neuroblastoma

Response Criteria for Neuroblastoma Subjects with Measureable Disease

Response evaluations for subjects with neuroblastoma can include measureable disease (by CT/MRI alone) or Evaluable Disease (MIBG alone) and/or in combination with bone marrow, biochemical (urine HVA/VMA).

Response Criteria for Neuroblastoma subjects with measureable disease as a component of their disease burden at enrollment will have measurable disease assessed according to RECIST v1.1 (Eisenhauer 2009) as well as evaluable disease assessments below as appropriate, to determine overall response.

Response Criteria for Neuroblastoma Subjects with MIBG Positive Lesions

Subjects who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of Iodine-123 (^{123}I) for MIBG imaging is recommended for all scans. If the subject has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

The following criteria will be used to report MIBG response by the treating institution:

Complete Response (CR)	Complete resolution of all MIBG positive lesions
Partial Response (PR)	Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable Disease (SD)	No change in MIBG scan in number of positive lesions
Progressive Disease (PD)	Development of new MIBG positive lesions

The response of MIBG lesions will be assessed using the Curie scale (Ady 1995) as outlined below. This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan. In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,

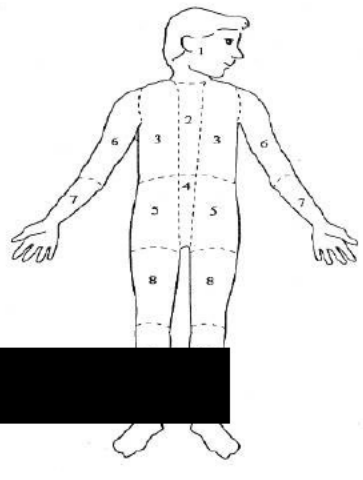
1 = 1 site per segment,

2 = more than one site per segment,

3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:

The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each subject is calculated at each response assessment compared to baseline and classified as below:



- **Complete Response:** all areas of uptake on MIBG scan completely resolved. If

morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.

- **Partial Response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
- **Stable Disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
- **Progressive Disease**: New lesions on MIBG scan.

Response Criteria for Neuroblastoma Subjects with Bone Marrow Involvement

Bone marrow obtained within 28 days (or less if specified by the protocol) prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by Haematoxylin and Eosin (H&E) staining of bilateral bone marrow biopsies and aspirates.

- **Complete Response:** No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.
- **Progressive Disease:** In subjects who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a subject entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a subject entering with 30% tumor must increase to > 60%).

In subjects who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

- **Stable Disease**: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

Overall Best Response Assessment:

Each subject will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response (chart below) is determined from the sequence of the overall response assessments as described above.

Overall Response Evaluation for Subjects Enrolled with Measureable Disease by CT/MRI

CT/MRI	MIBG	Bone Scan/ PET-CT if performed	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD

[redacted]

CT/MRI	MIBG	Bone Scan/ PET-CT if performed	Bone Marrow	Catechol	Overall
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR*

CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; MIBG = Meta-iodobenzylguanidine (scan); PET = Positron Emission Tomography PD = Progressive Disease; SD = Stable Disease; PR = Partial Response; CR = Complete Response.
* If one or more assessments are missing, response will be considered PR

Overall Response Evaluation for Subjects Enrolled with MIBG Positive Disease without Measureable Disease by CT/MRI

Since subjects may be enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered PD.

MIBG	CT/MRI	Bone Scan/ PET-CT if performed	Bone Marrow	HVA/VMA	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR*

CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; MIBG = Meta-iodobenzylguanidine (scan); PET = Positron Emission Tomography PD = Progressive Disease; SD = Stable Disease; PR = Partial Response; CR = Complete Response.
* If one or more assessments are missing, response will be considered PR

References:

Ady N, Zucker JM, Asselain B, et al., A new 123I-MIBG whole body scan scoring method--application to the prediction of the response of metastases to induction chemotherapy in stage IV neuroblastoma. *Eur J Cancer*. 1995; 31A(2): 256-61.

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Fox E, Mosse YP, Meany HM, et al., Time to Disease Progression in Children with Relapsed or Refractory Neuroblastoma Treated with ABT-751: A Report from the Children's Oncology Group (ANBL0621). *Pediatr Blood Cancer* 2014; 61: 990-996.

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Yanik GA, Parisi MT, Shulkin BL, et al., Semiquantitative mIGB Scoring as a Prognostic Indicator in Patients with Stage 4 Neuroblastoma: A Report from the Children's Oncology Group. *J Nucl Med* 2013; 54: 541-548

[redacted]

15.5 Appendix 5: Response Assessment in Neuro-oncology (RANO) Criteria (Glioma Subjects)

Anti-tumor activity will be assessed based on clinical evidence and the Response Assessment in Neuro-Oncology (RANO) criteria for solid tumors (Wen 2010).

NOTE: As part of Protocol Amendment V09, the revised RANO criteria for LGG (RANO-LGG; Wen 2017) will be used for central independent review. This review is in addition to the previously performed review using RANO (2010) These criteria are noted in section 15.5.1.)

All measureable and nonmeasureable lesions should be assessed using the same techniques as at baseline. Ideally, subjects should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Measurable disease is defined as bidimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. As with RECIST version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered nonmeasurable unless there is a nodular component measuring ≥10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

Radiographic response should be determined in comparison to the tumor measurements obtained at pretreatment baseline for determination of response, the smallest tumor measurements at either pretreatment baseline or after initiation of therapy should be used for determination of progression.

- Complete response (CR): Complete disappearance of all enhancing measureable and nonmeasureable disease on contrast enhanced MRI scan sustained for at least 4 weeks, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. In addition, subject must be off steroids or only on physiologic replacement doses. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.
- Partial response (PR): Greater than or equal to a 50% reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasureable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. In addition, subject must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.
- Progressive Disease (PD): Greater than or equal to a 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease)

[redacted]

on stable or increasing doses of corticosteroids, OR a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events, OR the appearance of any new lesions, OR clear progression of nonmeasurable lesions, OR definite clinical deterioration not attributable to other causes apart from tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

- Stable disease : If subject does not qualify for CR, PR, or PD and has stable nonenhancing (T2/FLAIR) lesions on same or lower doses of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging and subsequent follow-up imaging shows that this increase in corticosteroid dose was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Subjects with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Subjects with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 X 9mm lesion [nonmeasurable] increasing to a 10 X 11mm lesion [measurable]). Ideally, the change should be significant (>5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions).

In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression. If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

[redacted]

15.5.1 Response assessment in neuro-oncology (RANO) criteria for low-grade gliomas (LGG) (RANO-LGG)

During the course of the trial, revised RANO criteria specific for LGG have become available (RANO-LGG; Wen, 2017). These criteria will also be used for central independent, review per Protocol Amendment v09.This review is in addition to the previously performed review using RANO (2010).

According the updated RANO-LGG criteria, the definition of measurable disease is modified. Measurable disease is defined as bidimensionally visible lesions on T2 weighted fluid-attenuated inversion recovery (FLAIR) scans with clearly defined margins, with two perpendicular diameters of at least 10 mm (or at least two slice thicknesses with no gaps between slices), visible on two or more axial slices that are preferably, at most, 5 mm apart with 0 mm skip.

Non-measurable disease includes all other lesions, including:

- unidimensionally measurable lesions
- lesions with maximal perpendicular diameter that is both < 10mm and less than two slice thicknesses with no gaps between slices
- lesions with borders that cannot be reproducibly measured
- dural, bony skull metastases
- cystic or necrotic lesions (without a nodular component)
- other measurable lesions that cannot be considered as target lesions

Lesions composed of a tumor around a cyst or a surgical cavity are considered non-measurable unless there is a nodular component that measures 10 mm or more in 2 perpendicular diameters. The cystic or surgical cavity should not be measured for the determination of a response. Non-measurable lesions should all be followed as non-target lesions.

Target lesions should be assessed quantitatively at each of the time points specified in the protocol.

The updated response criteria for LGG are defined in the following tables. Please note that the minor response category is not used in this clinical trial. Patients meeting criteria for minor response will be considered to have stable disease for the purposes of this trial.

Response assessment of target lesions

Response Criteria	Evaluation of target lesions
Complete response (CR)	Complete disappearance of all measurable lesions on T2/FLAIR images sustained for at least 4 weeks.* No new or increased enhancement on T1 images.
Partial response (PR)	≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable lesions on T2/FLAIR sustained for at least 4 weeks.* No new or increased enhancement on T1 images.

[redacted]

Response Criteria	Evaluation of target lesions
Progressive disease (PD)	≥25% increase in sum of the products of perpendicular diameters of measurable lesions on T2/FLAIR images compared to nadir. Increased enhancement on T1 images showing evidence of malignant transformation.
Stable disease (SD)	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. No new or increased enhancement on T1 images.
Not Evaluable (NE)	Not evaluable will be used in exceptional cases where one or more measurable lesions cannot be assessed or have been assessed using a different method than baseline, in absence of progressive disease documentation
* In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.	

Response assessment of non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete response (CR)	Complete disappearance of all non-measurable lesions on T2/FLAIR. No new or increased enhancement on T1 images.
NonCR/NonPD	Persistence of one or more non-measurable lesions on T2/FLAIR. No new or increased enhancement on T1 images.
Progressive disease (PD)	Significant and unequivocal increase of the non-measurable lesions on T2/FLAIR or increase of enhancement on T1 images
Not Evaluable (NE)	Not evaluable will be used in exceptional cases where one or more non-measurable lesions cannot be assessed or have been assessed using a different method than baseline, in absence of progressive disease documentation

A lesion not present at baseline and appearing at any follow-up evaluation timepoint (TP) is considered a New Lesion.

The Investigator/local reader will characterize each new lesion as either equivocal or unequivocal (progressive disease). If unsure of a new lesion, the Investigator/local reader will mark it as equivocal and assess at the next timepoint if the lesion is present. Appearance of an equivocal new lesion does not lead to a determination of PD. If repeat scans confirm the lesion is unequivocal, progression should be retrospectively assigned back to the first observation of the lesion.

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response, the presence of new lesions, corticosteroid use relative to baseline, and clinical status as assessed by investigator and supported by the ECOG/Karnofsky Performance Scale as shown below:

[redacted]

Overall lesion response at each assessment (measurable and non-measurable disease at baseline)

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T2/FLAIR (target lesions)	None	≥50% decrease in SPPD compared to baseline	<50% decrease Compared to baseline but <25% increase in SPPD compared to Nadir	≥25% increase in SPPD compared to Nadir**
T2/FLAIR (non-target lesions)	None	Stable or improved	Stable or improved	Unequivocal PD**
T1 gadolinium enhancing disease	Stable or improved	Stable or improved	Stable or improved	Unequivocal increase**
New Lesions	None	None	None	Present*
Corticosteroids compared to baseline	None	Stable or decreased	Stable or decreased	NA***
Clinical Status compared to baseline	Stable or improved	Stable or improved	Stable or improved	Worsened**
Requirement for Response	All	All	All	Any**

Complete Response (CR):

All of the following criteria must be met:

a. Complete disappearance of the lesion of T2 or FLAIR imaging. . In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease.

b. No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased size of enhancement

c. Participants must be on no steroids or on physiologic replacement doses only.

d. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related

Partial Response (PR):

All of the following criteria must be met:

a. Greater than or equal to 50% in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline.

[redacted]

b. No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased size of enhancement

c. Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.

Stable Disease (SD):

All of the following criteria must be met:

a. Does not qualify for CR, PR, MR or progression.

b. Stable area of non-enhancing abnormalities on T2 or FLAIR imaging

c. No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased size of enhancement

d. Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.

Progressive Disease (PD):

a. A 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with nadir, not attributable to radiation effect or to comorbid events

b. Significant and unequivocal increase of the non-measurable lesions on T2/FLAIR

c. Development of new lesions or increased size of enhancement

d. Definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose

e. Failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

Response Status Unknown: Not Evaluable (NE):

a. Progressive disease has not been documented and one or more target or non-target lesions have not been assessed.

b. Change in method or technique for assessing target and non-target lesions as that used at baseline regardless of the justification of the change; e.g. if a participant develops a contraindication to MRI intravenous (IV) contrast media during the trial, a non-contrast MRI of the brain can be used (if possible); the participants response should only be recorded as not evaluable or progressive disease.

[redacted]

15.6 Appendix 6: Response Criteria for PNs

Prior to starting treatment on this study all known measurable tumors should be imaged with MRI to obtain a baseline. Tumor spread in subjects with NF-1 can be very extensive, and may not allow for all lesions to be followed using 3D-MRI. The goal will therefore be to use 3D-MRI only to follow the inoperable PN (a maximum of three lesions), which will be defined as index lesion(s).

Pre-study radiographic evaluation:

1. Identify and select the inoperable PN (a maximum of three lesions) for 3-D MRI evaluation based on prior imaging studies. Should there be more than 3 inoperable PN, the three most clinically relevant PN will be followed by 3-D MRI analysis.
2. Perform 3-D MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols below.
3. In addition, if possible, perform MRI of all additional measurable PN.
4. Send baseline MRI for central review prior to enrolment (for Part B3 patients).

In Study Part B, central review of the MRI of the target PN is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis.

On study radiographic evaluation:

Unless clinically indicated otherwise obtain MRI of the index lesions only as outlined in the MRI acquisition protocol below prior to cycles 4, 8, 12, and then after every 6 cycles as long as the subject remains on study.

MRI protocols:

Depending on the location of the index lesions the Spine, Head/Neck or Trunk/Extremities protocols outlined in the SPM and imaging guidelines will be used.

Participating institutions may modify the MRI sequences to optimize differentiation of tumor and surrounding tissue. Modifications should be documented in the MRI protocols, and the same imaging protocol, and, if possible, the same MRI scanner, should be used for all subsequent MRI studies. Every attempt should be made to image the entire progressive PN. All MRI data will be analyzed. The MRI data from each scan will be processed to assess the volume of the index PN(s). Each subject's volumetric measurement obtained from the initial MRI will serve as the baseline against which to assess incremental changes in volume that occur during the subsequent intervals. . All MRI studies requested per protocol will be submitted to the imaging vendor via the instructions provided in the SPM.

Response Criteria for NF-1 Associated PNs (Dombi 2013):

Response is assessed at the time that follow-up MRI scans are performed as outlined in Section 7.1. For the purpose of determining the level of response, measurements from the follow-up scans are compared to the tumor size in the pretreatment MRI scan using 3D data analysis.

- Complete Response (CR): A complete resolution of the target plexiform neurofibroma for ≥ 4 weeks

[redacted]

- Partial Response (PR): A ≥20% reduction in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
- Stable Disease (SD): A <20% increase, and < 20% decrease in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
- Progressive Disease (PD): A ≥20% increase in the volume (by 3D-MRI) of the target plexiform neurofibroma compared to the pretreatment volume.
    - The appearance of new discrete subcutaneous neurofibromas does not qualify for disease progression.

Worsening of existing symptoms or the appearance of new symptoms that persist for more than 7 days and that are felt to be definitely related to the plexiform neurofibroma should be evaluated by repeating the MRI. Subjects should not be classified as having progressive disease solely on the basis of new or increased symptoms.

[redacted]

15.7 Appendix 7: Definition of disease state, response criteria and response definition for LCH

Adapted from Histiocyte Society Evaluations and Treatment Guidelines, April 2009.

Definition of Disease State

NON ACTIVE DISEASE (NAD)	no evidence of disease	resolution of all signs or symptoms
ACTIVE DISEASE	regressive disease	regression of signs or symptoms, no new lesions*
	stable disease	persistence of signs of symptoms, no new lesions
	progressive disease	progression of signs or symptoms and/or appearance of new lesions**
*Plus partial or complete response by RECIST (Eisenhauer 2009); and/or pulmonary criteria if applicable */** Isolated pulmonary LCH: improvement in lung function is >10% increase in baseline FEV1 or DLCO at time of disease assessment. Disease progression is >15% decline from baseline FEV1 or DLCO or FVC OR progression of symptoms (dyspnea, cough, constitutional symptoms) that cannot be explained by diagnoses other than pulmonary LCH (infection, heart disease, and/or other clinical issues excluded by careful clinical evaluation and testing) ** Isolated bone disease: progression is defined as appearance of new bone lesions or lesions in other organs		

Response Criteria

BETTER	Complete Resolution	NAD
	Regression	AD Better
INTERMEDIATE	Mixed	New lesions in one site, regression in another site
	Stable	Unchanged
WORSE	Progression	

Response Definition for Efficacy

	3 Month Assessment	6 Month Assessment and beyond (performance relative to 3 month assessment)
Response	NAD or AD Better Mixed Stable	NAD or AD Better or Stable NAD or AD Better NAD or AD Better
Failure	NAD or AD Better NAD or AD Better Mixed or Stable [a] Progression	Mixed Progression Mixed or Stable [a] or Progression N/A
NAD = Non Active Disease AD = Active Disease Stable = Unchanged Mixed = New lesions in one site, regression in another site a. Subjects who are assessed only as stable at the 3 and 6 month assessment are not considered a treatment response; however, they may be considered for continued treatment		

LCH Scoring System (Donadieu 2004)

Variable	Modality	Score
Bone (a)	Pain No Pain	1 0
Bone (b)	Compressing other organs (orbit or spine) No compression	2 0
Fever (>38.5°C)	Yes No	1 0

[redacted]

Variable	Modality	Score
Lung: iconography	Pneumothorax Interstitial lesion on chest x-ray or lung CT Normal chest x-ray or lung CT	2 1 0
Lung: function	Mechanical ventilation or PFT >50% Supplemental oxygen or PFT between 50 and 80% No dysfunction, no cyanosis, no supplemental oxygen	5 2 0
Skin: area	25% 5-25% Below 5%	2 1 0
Soft tissue tumor (including CNS)	5 cm maximum diameter 2-5 cm maximum diameter 0-2 cm maximum diameter	2 1 0
Nodes (>2 cm)	Yes No	1 0
Liver	Below umbilicus Enlarged, above umbilicus Not enlarged	2 1 0
Spleen	Below umbilicus Enlarged, above umbilicus Not enlarged	2 1 0
Liver (enzymes)	>10 ULN 3-10 ULN <3 ULN	2 1 0
Liver (gamma GT)	>10 ULN 3-10 ULN <3 ULN	2 1 0
Albumin	Perfusion required in past week No perfusion but <30 g/L >30 g/L	3 1 0
Platelet: requirements in past week	More than two transfusions 1 or 2 transfusions Low platelet count, no transfusion Normal count	4 3 2 0
Red cells: requirements in past week	More than 2 U 1 or 2 U Hgb below 10 g/dL, no transfusion No transfusion	4 3 1 0

[redacted]

15.8 Appendix 8: Blood Pressure Levels for Children by Age and Height Percentile

Blood pressure (BP) levels for **BOYS**

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age (years)	BP Percentile	Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 3.2.3.1 for definition of dose limiting hypertension, Section 3.13.5 for management and grading of hypertension, and Section 3.13.5 for medical treatment of trametinib related hypertension.

[redacted]

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) for **GIRLS**

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 3.2.3.1 for definition of dose limiting hypertension, Section 3.13.5 for management and grading of hypertension, and Section 3.13.5 for medical treatment of pazopanib related hypertension.

[redacted]

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

[redacted]

15.9 Appendix 9: Dose Escalation based on PK criteria

Number of Subjects with DLT	Number of subjects failing PK criteria	Action
0 out of 3	0 out of 3	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
0 out of 3	One or more	Escalate to next dose level
1 out of 3	0,1,2,or 3	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
0 or 1 out of 6	0 or 1 out of 6	Select dose as PK Target dose
0 or 1 out of 6	2 or more out of 6	Escalate to the next dose level
2 or more		MTD has been exceeded. Expand prior dose level to at least 6 subjects

[redacted]

15.10 Appendix 10: Guidelines for additional dermatological monitoring while on therapy and after IP discontinuation

This Section applies to subjects enrolled in France only.

Cutaneous Squamous Cell Carcinoma (cuSCC) and New primary melanoma

Dermatological examinations should be performed prior to initiation of study treatment, monthly during treatment, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Subjects should be instructed to immediately inform their physician if new lesions develop. Any cuSCC or new primary melanoma should be reported as a protocol specific SAE and treated according to standard clinical practice.

Non-cutaneous secondary/recurrent malignancy

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

[redacted]

15.11 Appendix 11: Protocol Amendment Changes (Amendments 1- 4)

Amendment 1

Where the Amendment Applies

Amendment 1 applies to all sites and is submitted prior to initiation of the study.

Summary of Amendment Changes with Rationale

This amendment was made in response to FDA comments, as well as review from various clinical sites. An internal GSK decision was made to not include patients with leukemia therefore, all references to leukemia were deleted from the protocol. Clarifications were made to the dosing nomogram, response criteria for glioma subjects, age limit for subjects enrolled to dose escalation cohorts, disease status at screening, testing of BRAF mutation status, DLT criteria and reporting. Bone marrow assessments and Tanner staging were added to the Time and Events schedule, and the PK sampling schedule was modified. [redacted]

Protocol synopsis

Study Rationale PREVIOUS TEXT:

Specifically, pediatric patients with recurrent high grade gliomas, and patients with metastatic or recurrent solid tumors, or relapsed leukemia continue to have a poor prognosis and lower rates of long-term survival than patients with localized or non-recurrent disease. Use of second- and third-line cytotoxic chemotherapies, even in dose-intensive regimens, has yet to yield significant impact on progression-free survival or overall survival. Therefore development of new therapeutic options for pediatric cancer patients is needed.

Study Rationale REVISED TEXT:

Specifically, pediatric patients with recurrent high grade gliomas, and patients with metastatic or recurrent solid tumors ~~or relapsed leukemia~~, continue to have a poor prognosis ~~and lower rates of long-term survival than patients with localized or non-recurrent disease.~~ Use of second- and third-line cytotoxic chemotherapies, even in dose-intensive regimens, has yet to yield significant impact on progression-free survival or overall survival. **Increased understanding of the molecular mechanisms of pediatric tumors allows for rationale investigation of agents targeting these mechanisms.** ~~Therefore~~ Development of new therapeutic options for pediatric cancer patients is needed and clinical testing of targeted approaches may provide these options.

PREVIOUS TEXT

[redacted]

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES	Primary Objective: • To determine the safe and tolerable trametinib dose(s) alone or in combination with dabrafenib for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (trough concentration [Cτ]) to the recommended adult dose Secondary Objectives: • To determine the palatability of trametinib in pediatric subjects [redacted]
[redacted]	[redacted]

REVISED TEXT:

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES	Primary Objective: • To determine the safe and tolerable trametinib dose(s) ~~alone or in combination with dabrafenib~~ for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (trough concentration [Cτ]) to the recommended adult dose Secondary Objectives: • To determine the **acceptability and** palatability of trametinib in pediatric subjects [redacted]

PREVIOUS TEXT:

STUDY DESIGN	. • Refractory or relapsed neuroblastoma solid tumors with MAPK pathway activation including but not limited to neuroblastoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors. • Recurrent or unresectable low grade gliomas with serine/threonine kinase B-Raf (BRAF tandem duplication with fusion (without BRAF V600E mutations). • Neurofibromatosis Type -1 associated plexiform neurofibromas that are unresectable and medically significant.

[redacted]

	• Recurrent or refractory leukemia including juvenile myelomonocytic leukemia (JMML) Part C is a limited dose escalation part of the study evaluating the combination of trametinib with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will enroll approximately 18 subjects and will not open to accrual until the dose of dabrafenib in children is established in study BRF116013, the dose trametinib is established in Part A and review of the available safety and PK data of trametinib and dabrafenib monotherapy in children is completed. Part C will require an amendment to this study prior to enrollment to include updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously.

REVISED TEXT:

STUDY DESIGN	• Refractory or relapsed neuroblastoma ~~solid tumors with MAPK pathway activation including but not limited to neuroblastoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors.~~ • Recurrent or unresectable low grade gliomas with ~~serine/threonine kinase B-Raf (~~BRAF tandem duplication with fusion ~~(without BRAF V600E mutations).~~ • Neurofibromatosis Type -1 associated plexiform neurofibromas that are unresectable and medically significant. ~~• Recurrent or refractory leukemia including juvenile myelomonocytic leukemia (JMML)~~ • **BRAF V600 mutant tumors** **Part C** is a limited dose escalation part of the study evaluating the combination of trametinib with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will enroll approximately 18 subjects and will not open to accrual until the dose of dabrafenib in children is established in study BRF116013**, the dose trametinib is established in Part A and review of the available safety and PK data of trametinib and dabrafenib monotherapy in children is completed.** Part C will require an amendment to this study prior to enrollment to include updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously.

PREVIOUS TEXT:

INCLUSION/ EXCLUSION CRITERIA	**General Inclusion Criteria for All Parts** (for complete details and further eligibility criteria for specific parts please see full protocol):
	1. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form
	2. Part C between 12 months and <18 years of age, inclusive;
	5. Females of child-bearing potential must be willing to practice acceptable methods of birth control. Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment;
	General Exclusion Criteria for All Parts:
	17. History or Current evidence / risk of retinal vein occlusion (RVO) or retinal pigment epithelium detachment (RPED):
	• History of RVO or RPED, or predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease(s) such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).
	• Visible retinal pathology as assessed by ophthalmic exam performed within 1 month of enrollment that is considered a risk factor for RVO or RPED such as:
	  • Evidence of new optic disc cupping
	  • Evidence of new visual field defects
	  • Intraocular pressure >21mm Hg
	19. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.

[redacted]

REVISED TEXT:

INCLUSION/ EXCLUSION CRITERIA	**General Inclusion Criteria for All Parts** (for complete details and further eligibility criteria for specific parts please see full protocol): 1. Male or female between one month and **<** 18 years of age (inclusive) at the time of signing the informed consent form 2. Part C between 12 months and **<**18 years of age, inclusive; **3. (added text) Part A subjects < 2 years of age will not be include in the initial dose escalation** 5. Females of child-bearing potential must be willing to practice acceptable methods of birth control. Additionally, females of childbearing potential must have a negative serum pregnancy test within ~~7~~**14** days prior to enrollment; **General Exclusion Criteria for All Parts**: 17. ~~History or~~ Current evidence ~~/ risk~~ of retinal vein occlusion (RVO) or retinal pigment epithelium detachment (RPED): • History of RVO or RPED~~, or predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease(s) such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).~~ ~~• Visible retinal pathology as assessed by ophthalmic exam performed within 1 month of enrollment that is considered a risk factor for RVO or RPED such as:~~ ~~• Evidence of new optic disc cupping~~ ~~• Evidence of new visual field defects~~ ~~• Intraocular pressure >21mm Hg~~ 19. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. ~~Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.~~

PREVIOUS TEXT, 1st paragraph, last sentence:

STUDY TREATMENT DOSE/ROUTE/ REGIMEN	When taken together, trametinib should be taken with the morning dose of dabrafenib.

REVISED TEXT, 1st paragraph, last sentence:

[redacted]

STUDY TREATMENT DOSE/ROUTE/ REGIMEN	When taken together, trametinib should be taken **consistently** with **either** the morning **or evening** dose of dabrafenib.

PREVIOUS TEXT, 1st paragraph, 2nd sentence

TRANSLATIONAL RESEARCH	[redacted]

REVISED TEXT, 1st paragraph, 2nd sentence

TRANSLATIONAL RESEARCH	[redacted]

Section 1.2 Trametinib DELETEDTEXT:

~~Trametinib potently inhibited proliferation (concentration causing 50% growth inhibition [gIC50] values <200 nM) of 87% (13 of 15) of cancer cell lines of acute monocytic/myelogenous leukemia (AML) origin and 83% (5 of 6) of cell lines of chronic myelogenous leukemia (CML) origin.~~

Section 1.3.4 Dabrafenib Pediatric Experience DELETED TEXT:

~~As of Feb 2013, 3 subjects <18 years of age with melanoma have received dabrafenib on a compassionate use basis.~~ [redacted]

Section 1.4 Combination of Trametinib and Dabrafenib ADDED TEXT:

Please refer to the most current version of the GSK1120212+GSK2118436 Investigator Brochure for the most current safety information and additional details [GlaxoSmithKline Document Number 2011N126811/01].

Section 1.5 Rationale for BRAF and MEK inhibitors in Pediatric Cancers PREVIOUS TEXT

- Solid tumors including neuroblastoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors (NF-1 related and sporadic).
- Recurrent or unresectable low grade gliomas with serine/threonine kinase B-Raf BRAF tandem duplication with fusion
- Neurofibromatosis (NF)-related PNs.
- Leukemias with activation of the Ras/MAPK pathway including juvenile myelomonocytic leukemia (JMML). Leukemias with known wild type Ras mutation will be excluded

[redacted]

The safety and activity of the combination of dabrafenib with trametinib in adults with BRAF V600 mutation positive melanoma has been demonstrated. Once the dose of dabrafenib is determined in children and adolescents, a treatment arm to evaluate the safety of dabrafenib in combination with trametinib in children and adolescents will be opened.

Section 1.5 Rationale for BRAF and MEK inhibitors in Pediatric Cancers REVISED TEXT

- Relapsed or refractory neuroblastoma
- Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion
- Neurofibromatosis (NF)-related PNs.
- BRAF V600 mutant tumors

The safety and activity of the combination of dabrafenib with trametinib in adults with BRAF V600 mutation positive melanoma has been demonstrated. Once the **doses of dabrafenib and trametinib monotherapy are** determined in children and adolescents, a treatment arm to evaluate the safety of dabrafenib in combination with trametinib in children and adolescents will be opened.

Section 1.6 Malignant Solid Tumors in Infants, Children, and Adolescents DELETED TEXT

~~Rhabdomyosarcoma is the most common malignant soft tissue tumor in children. Alveolar rhabdomyosarcoma frequently harbor chromosomal rearrangements. Recent investigations indicate that 20% of embryonal rhabdomyosarcomas have somatic *NRAS* mutations and dysregulation of RAS signaling may contribute to pathogenesis of this cancer [Martinelli, 2009]. Concomitant activation of Ras/MEK/ERK and PI3K/protein kinase B (AKT)/mTOR in rhabdomyosarcoma may require combination therapy [Guenther, 2013].~~

~~Malignant peripheral nerve sheath tumors are rare malignant tumors that can be sporadic or associated with NF-1 [Stucky, 2011]. Malignant peripheral nerve sheath tumors comprise approximately 3-10% of all soft tissue sarcomas [Zou, 2009] and develop in the cells surrounding the peripheral nerves. MPNSTs generally occur in adulthood (between 20 and 50 years), but approximately 10-20% of cases have been reported to occur in the first 2 decades of life [Minovi, 2007; Ferrari, 2007a; Ferrari, 2007b]. The incidence of MPNST in NF-1 patients may be as high as 8% to 12% [Zou, 2009]. In a recent analysis, disease-specific survival (DSS) was similar in patients with NF-1 related MPNST and sporadic MPNST. Subjects in this retrospective analysis had newly diagnosed high grade MPNST (n=105) and 70% had negative margins after primary resection. The 3-year DSS was 64% and median DSS was 8 years [LaFemina, 2013]. Prognosis is poor for patients with unresectable, metastatic or recurrent MPNST (< 10-20% 5-year OS). MPNST is considered to be a sarcoma with complex genetic alterations [Yang, 2013]. NF-1 associated MPNST have been associated with molecular heterogeneity among tumors as well as intra-tumor molecular heterogeneity [Thomas, 2012]. In addition, studies in animal models indicate that other sarcomas with NF-1 deletions may be sensitive to MEK inhibition by direct effects on proliferation of tumor cells and indirectly by changes in the tumor microenvironment [Dodd, 2013].~~

[redacted]

Section 1.7 Relapsed or Recurrent Leukemia including JMML in Infants, Children and Adolescents was DELETED; all subsequent sections numbering was updated.

Previously Section 1.9.1 Predicted Toxicities for Trametinib, PREVIOUS TEXT

Ocular effects: Visual impairments, including chorioretinopathy, retinal pigment epithelium detachment (RPED), and retinal vein occlusion (RVO), were reported with trametinib. Cases of ocular toxicities were reported with other MEK inhibitors in clinical development. Subjects with a history of RVO ~~or risk factors of RVO~~, should not receive trametinib. Subjects with the following visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO should not receive trametinib:

Evidence of optic disc cupping.

- Evidence of new visual field defects on perimetry.
- Intraocular pressure > 21 mm Hg as measured by tonography.

Section 1.8.1 Predicted Toxicities for Trametinib, REVISED TEXT

Ocular effects: Visual impairments, including chorioretinopathy, retinal pigment epithelium detachment (RPED), and retinal vein occlusion (RVO), were reported with trametinib. Cases of ocular toxicities were reported with other MEK inhibitors in clinical development. Subjects with a history of RVO ~~or risk factors of RVO~~, should not receive trametinib. ~~Subjects with the following visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO should not receive trametinib:~~

~~Evidence of optic disc cupping.~~

- ~~Evidence of new visual field defects on perimetry.~~
- ~~Intraocular pressure > 21 mm Hg as measured by tonography~~.

[redacted]

Previously Section 1.9.2 Predicted Toxicities for Combination of Trametinib and Dabrafenib; ADDED TEXT

Hemorrhage: Major hemorrhagic events can occur in patients receiving dabrafenib in combination with trametinib. Monitor for signs and symptoms of bleeding.

Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving dabrafenib in combination with trametinib.

Interstitial lung disease (ILD)/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 if clinically indicated.

Pancreatitis – Pancreatitis has been observed in subjects receiving dabrafenib. Subjects will be monitored for abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis.

Hyperglycemia: Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Serum glucose levels will be monitored as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia.

Hepatic Events:

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib.

Ocular effects: Both trametinib and dabrafenib have been associated with ocular toxicities which appear to be class effects, including papilledema, RPED, and RVO, uveitis and iritis associated with trametinib, ~~and uveitis (including chorioretinitis, choroiditis, retinitis, vitritis, cyclitis, iridocyclitis, iritis, and uveitis)~~ associated with dabrafenib. Please refer to Section 1.8.1 and Section 3.13.3.

Section 2 Objectives, Endpoints, Hypothesis(es) PREVIOUS TEXT

Objective	Endpoint	Hypothesis(es)
Primary		
To determine the safe and tolerable trametinib dose(s) alone or in combination with dabrafenib for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures ($C\tau$) to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state $C\tau$ of trametinib	Infants, children and adolescents will tolerate doses of trametinib alone or in combination with dabrafenib that achieve steady state trough concentrations associated with clinical benefit in adults

Objective	Endpoint	Hypothesis(es)
Secondary		
To determine the acceptability and palatability of trametinib in pediatric subjects		
[redacted]		

Section 2 Objectives, Endpoints, Hypothesis(es) REVISEDTEXT

Objective	Endpoint	Hypothesis(es)
Primary		
To determine the safe and tolerable trametinib dose(s) ~~alone or in combination with dabrafenib~~ for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (Cτ) to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib	Infants, children and adolescents will tolerate doses of trametinib ~~alone or in combination with dabrafenib~~ that achieve steady state trough concentrations associated with clinical benefit in adults
Secondary		
To determine the **acceptability and** palatability of trametinib in pediatric subjects		
[redacted]		

[redacted]

Section 3.1 Discussion of Study Design, PREVIOUS TEXT

- **Part A** will be a pharmacokinetically driven limited dose escalation study in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase.
- **Part B** will be an expansion study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of Ras/MAPK activation in childhood solid tumors. Forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts.
    - Refractory or relapsed solid tumors with Ras/MAPK pathway activation including but not limited to neuroblastoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors.
    - Recurrent or unresectable low grade gliomas (without BRAF V600E mutations)
    - Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant.
    - Recurrent or refractory leukemia harboring Ras pathway activation, including JMML
- **Part C** is a limited dose escalation study-of the combination of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study, with a planned enrollment of up to 18 subjects, will not open until the dose of dabrafenib in children is established in study BRF116013. Part C will require an amendment to this study prior to enrollment to include updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously.

Subjects may not participate-in more than one part of the study.

Section 3.1 Discussion of Study Design, REVISED TEXT

- **Part A** will be a pharmacokinetically driven limited dose escalation ~~study~~ in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase **(subjects less than 2 years of age will not be included in the initial dose escalation (approximately 6-12 subjects) is complete and the age specific cohorts are opened)** and 18 subjects to the age expansion phase.
- **Part B** will be an expansion ~~study~~ to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of Ras/MAPK activation in childhood solid tumors. Forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts.

[redacted]

- B1: Refractory or relapsed neuroblastoma ~~solid tumors with Ras/MAPK pathway activation including but not limited to neuroblastoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors~~.
- B2: Recurrent or unresectable low grade gliomas with ~~serine/threonine kinase B-Raf (~~BRAF tandem duplication with fusion
- B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant.
- ~~Recurrent or refractory leukemia harboring Ras pathway activation, including JMML~~
- B4: BRAF V600 mutant tumors.

- **Part C** is a limited dose escalation ~~study~~ of the combination of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study, with a planned enrollment of up to 18 subjects, will not open until the dose of dabrafenib in children is established in study BRF116013, **the dose of trametinib monotherapy is established in Part A and all available PK and safety data is reviewed.** Part C will require an amendment ~~to this study~~ prior to enrollment to include updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously.

Subjects may not ~~participate~~ **enroll** in more than one part of the study.

Section 3.2 Part A: Trametinib Dose-Escalation Determination DELETED TEXT, 2nd paragraph

During dose escalation, children will be closely monitored for drug-related toxicity. If MTD is determined ~~dose limiting toxicity (DLT) is observed in 2 or more patients (or >33%) at a dose level,~~ the RP2D will be defined by the MTD rather than by PK criteria.

Section 3.2.2 Trametinib Dose Escalation PREVIOUS TEXT, 3rd bullet, and last paragraph

- If 2 or more of the initial 3-6 subjects enrolled at the starting dose experience DLT, accrual will be suspended and the MTD will have been exceeded.

Detailed PK sampling will be required on Day 15 for trametinib (see Section 7.4.1). In addition, PK trough blood samples (immediately prior to dosing and approximately 24 hr after prior dose) will be required on Day 15 and Day 22 in all subjects. The Day 15 trametinib $C\tau$ of all subjects in a dose level cohort will be compared to the target $C\tau$ (10 ng/mL) in adults who were treated with the recommended dose in adults. If Dose Level 3 is reached without exceeding the MTD, additional subjects may be enrolled if necessary to determine $C\tau$. In the absence of an MTD, the PK target dose defined as the dose that meets the PK criteria for adequate exposure (Day 15 trametinib $C\tau \geq 10$ ng/mL in at least 80% of subjects in a cohort of at least 6 subjects (i.e.; 5/6 subjects treated at that dose level).

Section 3.2.2 Trametinib Dose Escalation REVISED TEXT, 3rd bullet, and last paragraph

- If 2 or more of the initial 3-6 subjects enrolled at **a dose level** ~~the starting dose~~ experience DLT, accrual will be suspended and the MTD will have been exceeded.

[redacted]

PK Criteria for Escalation:

Detailed PK sampling will be required on Day 15 for trametinib (see Section 7.4.1). **Subjects who have a day 15 trametinib Cτ <10 ng/mL will be considered to have failed to reach the PK target. If more than 1 out of 3 to 6 patients at a dose level have failed to reach the PK target, and MTD criteria have not been met, dose escalation will continue.** ~~In addition, PK trough blood samples (immediately prior to dosing and approximately 24 hr after prior dose) will be required on Day 15 and Day 22 in all subjects.~~ The Day 15 trametinib Cτ of all subjects in a dose level cohort will be compared to the target Cτ (10 ng/mL) in adults who were treated with the recommended dose in adults. ~~If Dose Level 3 is reached without exceeding the MTD, additional subjects may be enrolled if necessary to determine Cτ.~~ In the absence of an MTD, **the RP2D will be** the PK target dose defined as the dose that meets the PK criteria for adequate exposure (Day 15 trametinib Cτ ≥10 ng/mL in at least 80% of subjects in a cohort of at least 6 subjects (i.e.; 5/6 subjects) treated at that dose level **(Apppendix 8).**

Section 3.2.3 Dose Limiting Toxicity Definitions ADDED TEXT, paragraphs 2 and 3

If a subject is withdrawn before completing at least 75% of doses (at least 21 doses during the first 28 days of study treatment), for any reason other than toxicity, the subject will be replaced with the next available subject if escalation or de-escalation rules have not been fulfilled.

An AE will be considered a DLT if it is considered by the investigator to be **at least possibly** related to study treatment and **also meets any of the criteria listed in Section 3.2.3.1 or Section 3.2.3.2. DLTs will be reported to GSK using the procedures outlined for reporting of SAEs (Section 8.4.2).**

Section 3.2.3.1 Non-Hematological Dose Limiting Toxicity DELETED and ADDEDTEXT

~~Grade 3 elevation in alanine aminotransferase (ALT) (see Section 3.11.1).~~

- **Dose limiting hypertension will be considered as the following:**
  - **Grade 4 hypertension**
  - **A blood pressure >25 mmHg above the 95th percentile for age, height, and gender (see Appendix 7) confirmed by repeated measurement (See Section 13.3.3.1 and Section 13.3.3.2)**

Section 3.2.3.2 Hematological Dose Limiting Toxicity DELETED and ADDED TEXT

~~Note: Participants enrolled on Part B with compromised bone marrow function and a neutrophil count < 1.5 x 10^9/L or platelet count < 100 x 10^9/L secondary to tumor infiltration of the bone marrow or prior therapy are not evaluable for hematologic toxicity, and the criteria for hematologic DLT will not be dose-limiting toxicity in this population.~~

- **Grade 4 anemia**
- **Grade 3 or 4 hemolysis**

[redacted]

Figure 1 and Figure 2 were updated to reflect changes in the protocol

Section 3.8.2 Rationale for Populations PREVIOUS TEXT, paragraph 1, last sentence

These include tumors positive for BRAF gene duplication (e.g., juvenile pilocytic astrocytoma, low grade gliomas); NF-1 related PN; and selected solid tumors with Ras/MEK pathway activation including but not limited to neuroblastoma, rhabdomyosarcoma, peripheral nerve sheath tumors.

Section 3.8.2 Rationale for Populations REVISEDTEXT, paragraph 1, last sentence

These include tumors positive for **BRAF V600 mutation**, BRAF gene duplication (e.g., juvenile pilocytic astrocytoma, low grade gliomas); NF-1 related PN; and ~~selected solid tumors with Ras/MEK pathway activation including but not limited to~~ neuroblastoma, ~~rhabdomyosarcoma, peripheral nerve sheath tumors.~~

Section 3.8.4 Rationale for Endpoints, 2nd paragraph, DELETED TEXT

~~In the absence of dose limiting toxicity at the 0.025 mg/kg dose level (equivalent to therecommended dose in adults), if target Day 15 C in at least 80% of subjects is≥10 ng/mL, trametinib dose escalation will stop. However, in the absence of doselimiting toxicity, if Day 15 Cτ is less than 10 ng/mL in 20% or more of subjects, the dose will be escalated to 0.04 mg/kg.~~

Section 3.10.1 Trametinib, PREVIOUS TEXT, 4th paragraph, 4th sentence

However, subject can take the missed dose immediately if the next scheduled dose is at least 16 hours later.

Section 3.10.1 Trametinib, REVISED TEXT, 4th paragraph, 4th sentence

However, subject can take the missed dose immediately if the next scheduled dose is at least **12** hours later.

Section 3.10.3 Meals and Dietary Restrictions ADDED TEXT, first bullet

- If it is not possible for a subject to tolerate the fasting conditions noted above, trametinib can be administered with a small non-fat meal (e.g., small amount of apple juice/sauce, a piece of dry toast). **Children that are breastfeeding may continue to breast feed on demand. If child is breast fed during collection of PK samples the time of breastfeeding should be recorded.**

Section 3.12 Dose Delay and Modification for Events Considered Related to Trametinib ADDED TEXT

A maximum of one trametinib dose reductions is allowed. If a second dose level reduction is required, treatment will be permanently discontinued.

Trametinib dose modification guidelines are outlined in Table 4 for clinically significant toxicities that are deemed related to trametinib (i.e. peripheral and periorbital edema) with exception for following events of special interest:

rash (Section 3.13.1)

diarrhea (Section 3.13.2),

[redacted]

ejection fraction changes (Section 3.11.3.1),
hypertension (Section 3.13.3)
prolonged QTc (Section 3.11.2)
pneumonitis (Section 3.13.4),
visual changes (Section 3.13.3),
liver chemistry elevation (Section 3.11.1)

For these refer to the relevant sections for dose modification guidelines for adverse events of special interest as stated above.

Table 5 Dose Delay and Modification for Events Considered Related to Trametinib

CTCAE Grade	Action and Dose Modification
Grade 1 and tolerable Grade 2	• Continue trametinib at current dose level • Monitor closely • Provide supportive care according to institutional standards
Intolerable Grade 2 and Grade 3	• Interrupt trametinib ~~if clinically indicated~~ • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by one dose level** • If the intolerable Grade 2 or Grade 3 toxicity recurs, ~~interrupt trametinib~~ permanently discontinue trametinib • ~~When toxicity resolves to Grade 1 or baseline, restart trametinib reduced by another dose level~~
Grade 4	• Interrupt trametinib • Monitor closely • Provide supportive care according to institutional standards • If event resolves to Grade 1 or baseline discuss potential continuation of trametinib with GSK Medical Monitor; if continuation of treatment agreed then restart trametinib at dose **reduced by one dose l**evel • **If event does not resolve permanently discontinue trametinib**

Abbreviation: GSK = GlaxoSmithKline

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

[redacted]

Table 5 Management of Rash ADDED TEXT

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% crean
c. Approval of GSK medical monitor is required to re-start study treatment after >4 weeks of interruption
d. Escalation of trametinib to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

Section 3.13.3 Hypertension

The algorithm in Figure 4 will be used to grade and manage trametinib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine,) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 3.13.3.2

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section.3.13.3.1.

3.13.3.1 Baseline Blood Pressure

[redacted]

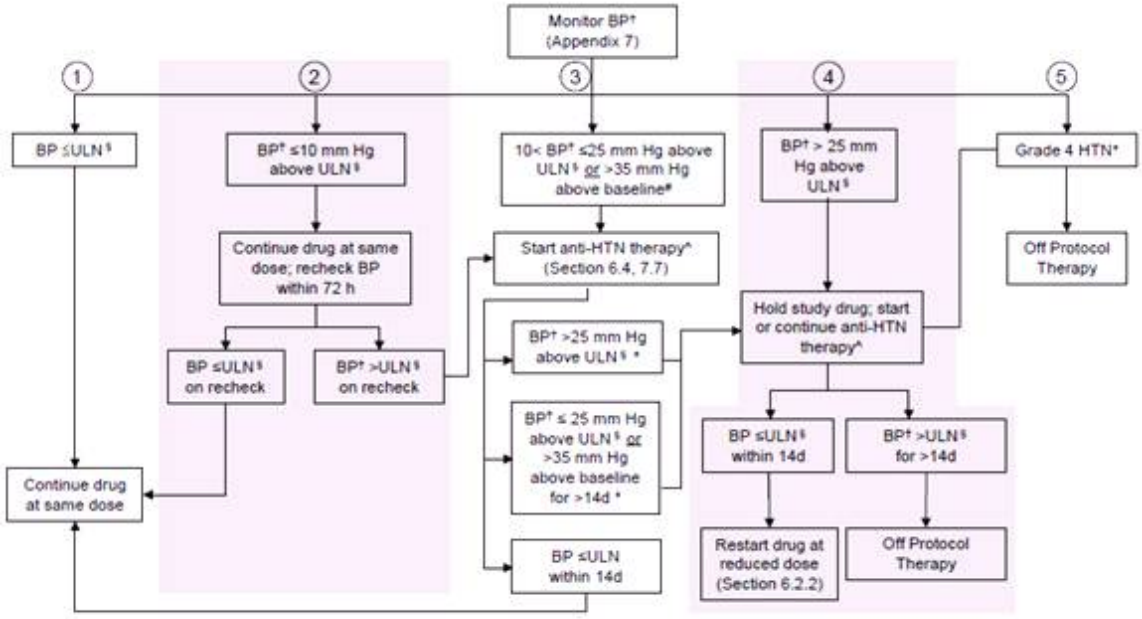
- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:
  1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
  2) Average the systolic blood pressure from the 2nd and 3rd measurements.
  3) Average the diastolic blood pressure from the 2nd and 3rd measurements.
  4) The baseline BP is the average of the systolic and average of the diastolic measurements.

3.13.3.2 Management of Hypertension

- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. (Appendix 7)
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with an elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage trametinib related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

[redacted]

Figure 4 Algorithm For Management of Trametinib-Related Hypertension



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix 7)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 3.13.3.1.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95%ile for age, height, and gender: continue trametinib at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue trametinib at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue trametinib at the same dose.
  - If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start/adjust anti-hypertensive therapy and continue trametinib at the same dose. Monitor BP at least twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue trametinib at the same dose and continue anti-hypertensive therapy.
  - If the BP remains elevated ≥ 25 mm Hg above the ULN or > 35 mm Hg above baseline for more than 14 days after the institution/adjustment of anti-hypertensive therapy, **hold trametinib**, monitor BP at least every 3 days, and

[redacted]

follow Arm 4 of the algorithm from the point that trametinib is held. The anti-hypertensive therapy should be continued until the BP is less than the ULN.

- If the BP returns to ≤ ULN within 14 days, restart trametinib at a reduced dose.
- If the BP remains > ULN for more than 14 days, patient must be removed from protocol therapy.

    - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, hold trametinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that trametinib is held.
- If the BP is ≤ULN within 14 days, trametinib may be restarted at a reduced dose
- If the BP is > ULN for > 14 days, the patient must be removed from protocol therapy (Section 6.3)

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN **hold trametinib**, monitor BP, and administer/adjust anti-hypertensive therapy as clinically indicated.
    - If the BP returns to ≤ ULN within 14 days, trametinib may be restarted at a reduced dose.
    - If the BP is > ULN for >14 days, the patient must be removed from protocol therapy (Section 6.3).

Arm 5 of algorithm:

If the participant develops Grade 4 hypertension, discontinue trametinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 6.3).

Section 3.13.4 Visual Changes ADDED TEXT

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. 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. 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 (Section 7.1 for PK sample volume).

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided in Table 7.

[redacted]

Table 7 Management and Dose Modification Guidelines for Visual Changes

NCI-CTCAE v4.03 [a]	Adverse Event Management	Action and Dose Modification
Grade 1	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification Table 7 below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue study treatment and report as SAE**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib	• If RPED and RVO excluded, restart trametinib at same dose level • If RPED diagnosed, see RPED dose modification Table 8 below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue study treatment and report as SAE**
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib • Report as an SAE	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • **If RPED or RVO diagnosed, permanently discontinue trametinib**

Abbreviations: NCI-CTCAE v4.03 = National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03; RPED=retinal pigment epithelium detachment; RVO = retinal vein occlusion; SAE = serious adverse event

a. Refers to NCI-CTCAE v4.03 'Eye disorders – Other, specify

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

[redacted]

Table 8 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'

Section 5.1 Number of Subjects PREVIOUS TEXT, sentence 3

In Part B every attempt will be made to enrol a minimum of 10 subjects in each group.

Section 5.1 Number of Subjects REVISEDTEXT, sentence 3

In **Part B a minimum of 10 subjects will be enrolled in each group with at least 4 in each cohort under the age of 6.** ~~every attempt will be made to enrol a minimum of 10 subjects in each group.~~

Section 5.2.1.1 General Eligibility Criteria (All Parts) ADDED and REVISED TEXT

2. Male or female between one month and **< 18 years** of age (inclusive) at the time of signing the informed consent form (Part C between 12 months and **< 18 years** of age, inclusive).

3. **Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or have a disease for which there are no standard treatment regimens that are potentially curative.**

1. **6.** Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 10.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within **14** days prior to enrollment**, throughout treatment period and for 4 months after last dose of study drug.**

9. **Adequate Blood Pressure Control defined as:**
   - **Blood pressure ≤ the 95th percentile for age, height, and gender (Appendix 7) measured as described in Section 3.13.3.1.**

Section 5.2.1.2 Specific Eligibility Criteria, Part A REVISED and ADDED TEXT

1. **For the initial dose escalation to identify the maximum tolerable or PK target dose, age between 2 years and < 18 years (inclusive) at the time of signing the informed consent form. Children between 1 mo and < 2 years of age will be enrolled once the age specific expansion cohorts are open.**

[redacted]

2. Histologically confirmed solid tumors, **which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, and primary brain tumors. In subjects with brain stem gliomas the requirement for histological confirmation can be waived if a biopsy was not performed.**

3. Measurable or evaluable tumors. Subjects with neuroblastoma that is only detectable by MIBG scan are eligible. ~~and considered to have measurable disease using the Curie scale.~~ Subjects with neuroblastoma that is only detected by bone marrow aspirate/biopsy or elevated homovanillic acid / vanillylmandelic acid (HVA/VMA) are not eligible.

Section 5.2.1.3 Specific Eligibility Criteria, Part B ADDED and DELETED TEXT

1. Tumor tissue (archived or fresh) is required and must be available to be shipped to GSK **or site specific laboratory.**

2. **Solid Tumor Cohort (B1) Specific Criteria**:

   - Histologically confirmed **neuroblastoma** which have been associated with MAPK/RAS/MEK activation, ~~which may include but are not limited to recurrent or refractory rhabdomyosarcoma,~~ neuroblastoma~~, or unresectable, recurrent, or refractory malignant peripheral nerve sheath tumors (NF-1 associated or sporadic)~~. Histological confirmation may be at diagnosis or recurrence. Laboratory documentation of pathway activation is not required; however, archival tissue is requested at the time of enrollment.

5. BRAF V600 mutant solid tumors Cohort (B4) Specific Criteria:

- **Male or female ≥12 months and <18 years of age at the time of signing the informed consent form;**
- **BRAF V600 mutation-positive tumor as confirmed in a CLIA-approved laboratory or equivalent (the local BRAF testing may be subject to subsequent verification by centralized testing; centralized testing can confirm V600E and V600K mutations only)**
- **Recurrent disease, refractory disease, or progressive disease after having received at least one standard therapy for their disease;**

  NOTE: Subjects with metastatic (and surgically unresectable) melanoma can be enrolled for first-line treatment; Melanoma subjects with CNS involvement may be enrolled.
- **Measurable or evaluable tumors.**
- **Adequate hematologic function defined as:**
  - **Absolute neutrophil count (ANC) ≥1000/µL;**
  - **Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)**
  - **Platelets ≥75,000/µL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)**

Section 5.2.2 Exclusion Criteria (All Parts) ADDED and DELETED TEXT

[redacted]

3. Subjects with NF-1 **associated optic pathway tumors** are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for PN or malignant solid tumor (Subjects with NF-1 and **isolated optic pathway tumors as only site of evaluable tumor are not eligible for enrollment)**.

5. **Subjects with NF-1 and active optic glioma are excluded**.

10. Part B and Part C only: Previous treatment with dabrafenib (cohort B4), trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted)

17. History or current evidence ~~/ risk of~~ RVO or RPED:

- History of RVO or RPED~~, or predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease(s) such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).~~
- ~~Visible retinal pathology as assessed by ophthalmic exam performed within 1 month of enrollment that is considered a risk factor for RVO or RPED such as:~~
    - ~~Evidence of new optic disc cupping~~
    - ~~Evidence of new visual field defects~~
    - ~~Intraocular pressure >21mm Hg~~

Section 6.6 Treatment after the End of the Study ADDED TEXT, last paragraph

Subjects who discontinued dabrafenib treatment will be followed every 3 months for 2 years to monitor for the occurrence of SCC and monitored for up to 2 years for non-cutaneous malignancy.

Section 7.1, Time and Events Tables

Table 11, Screening through Day 28:

Archived tumor biopsy or bone marrow aspirate, Part B	Archived tissue at screening is required and must be available to be shipped to GSK; if not available f**resh biopsy is acceptab**le. ~~Central confirmation of~~ RAS mutation status does not have to be done within 14 days prior to dosing.
Tumor tissue for V600 testing, Part B4 and Part C	**Local BRAF testing required for enrolment in the study**; the local testing will be subject to subsequent confirmation by centralized testing. Central confirmation can be from archival tissue or if no archival tissue is available, from fresh biopsy. **Central confirmation not required** within 14 days prior to dosing.
Vital signs	Blood pressure (3 serial blood pressues; separated by at least 5 minutes see Section 3.13.3.1), body temperature, pulse rate, respirations

Tumor biopsy ~~or bone marrow aspirate~~	Optional fresh biopsy ~~or bone marrow aspirate~~
[redacted]	[redacted]

[redacted]

Table 12, PREVIOUS TEXT

	Day 15 (Parts A, B, and C)						
hr	**0**	**1**	**2**	**4**	**8**	**12**	**24**
COLLECTION WINDOW	-30 min	± 5 min	± 5 min	± 20 min	± 20 min	± 20 min	± 20 min

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~):

	Day 15 (Parts A, B, and C)						
hr	**0**	**1**	**2**	**4**	**7**	**10**	**24**
COLLECTION WINDOW	-30 min	± 5 min	± 5 min	± 20 min	± 20 min	**± 2 hr**	± 20 min

Table 14, Week 9 to Final Visit

Tanner Stage						**X**	**Every 24 weeks (6 months)**	**Every 24 weeks**	**X**

Table 16, List of Clinical Laboratory Tests:
Added HbA1c

[redacted]

Section 7.5 Translational Research

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~):

Table 17 List of Samples for Translational Research

Study Part	Sample type	Mandatory/Optional	Primary Purpose
Part A	**Archival or fresh tumor tissue**	**Mandatory at screening. If unavailable, the subject is not eligible to participate in the study.**	**Retrospective analysis RAS mutation status**
Part B	Archival or fresh tumor tissue	Mandatory at screening. If unavailable, the subject is not eligible to participate in the study	**Retrospective analysis of RAS mutation status**
Part B4 and Part C	Archival or fresh tumor tissue	Mandatory at screening	Central confirmation of *BRAF* V600 mutation status

[redacted]

[redacted]

Section 7.5.1.1 Part B, All Cohorts

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~):

Patients may be enrolled in the study on the basis on local test results, but archival tissue must be submitted during screening for subsequent confirmation of the Ras pathway activation or mutation status ~~using a validated assay~~. If archival specimen is not available, subjects will be required to undergo tumor biopsy **prior to participation in the study. If archived tissue is not available and a fresh tumor sample cannot be collected (i.e. subjects with brain tumors) the subject will not be eligible for participation in the study**…..

Section 7.5.1.2 Part C, ~~Subjects with Melanoma~~

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~):

Patients may be enrolled in the study on the basis of local test results, Archival tumor tissue sample reflective of the current disease setting will be collected at Screening for central confirmation of the BRAF V600E mutation status. If an archival tumor tissue sample is not available, fresh tumor tissue should be collected (see SPM for further details) to determine the subject's BRAF V600E mutation status. ~~Submission of archival tumor tissue is optional for Parts A and B.~~**If archived tumor tissue is not available and the collection of a fresh tumor tissue sample is not possible the subject will not be eligible to participate in the study.**

Section 7.5.2 Tumor Tissue for Pharmacodynamic Testing

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~):

The collection of fresh tumor tissue is optional **for PD testing** but…

[redacted]

Section 8.4.2 Prompt Reporting of SAEs and Other Events to GSK

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~):

SAEs, **DLTs**, pregnancies….

All SAEs **and DLTs**	24 hr	SAE data collection tool	24 hr	Updated SAE data collection tool

Changes to Appendices:

Appendix 2 Dosing Nomogram was updated to include dose in mg

Appendix 5 Response Criteria for CNS tumors was replaced with Response Assessment in Neuro-oncology (RANO) Criteria (Glioma Subjects)

Appendix 6 – Country Specific Amendment was deleted

Appendix 7 (added) Blood Pressure Levels for Children by Age and Height Percentile

[redacted]

Appendix 8 (added) Dose Escalation Based on PK Criteria

[redacted]

Amendment 2

Amendment 2

Where the Amendment Applies

Amendment 2 applies to all sites.

Summary of Amendment Changes with Rationale

This amendment was made in response to MHRA comments, as well as review from clinical sites.

Section 1.6.3 Langerhans Cell Histiocytosis—new section

LCH is a rare proliferative disorder of unknown etiology that primarily affects children. It is distinguished by the clonal proliferation of pathologic histiocytes with the morphologic characteristics of Langerhans cells. Langerhans cells are bone-marrow derived dendritic cells, characterized by the expression of CD1a, S100 and the production of Birbeck granules. The pathogenesis of LCH is poorly understood. Clinical manifestations are related to the pattern of infiltration or organ involvement [Stockschlaeder, 2006; Arico, 1998]. The clinical presentation is heterogeneous, can involve single or multiple organs, and can be associated with varying, often unpredictable outcomes ranging from spontaneous regression to multiple episodes of reactivation, long term debilitating sequelae, rapid progression, and death.

Patients with localized (single system) disease in 'low risk' organs typically have good prognosis and may require minimal treatment (for example, isolated bone lesion). On the other hand, multisystem disease, especially disease involving key 'high risk' organs (hematopoietic, spleen, liver, lung), carries higher risk of poor outcomes and recurrent events (reactivation disease) after initial therapy.

LCH occurs at an estimated rate of 2 to 10 per million children/adolescents under the age of 15 years [NCI, 2012; Stalemark, 2008], as compared to approximately 1 to 2 cases per million in adults. Approximately 76% of cases occur in children less than 10 years old. Risk of morbidity and mortality increases substantially when multifocal or multi-organ disease is present [Satter, 2008].

In a recent report, which is also the first to show activation of any oncogenic signalling pathway in LCH, BRAF V600E mutations were identified in nearly 60% of a cohort of archival lesion samples obtained from children and adults with LCH [Badalian-Very, 2010]. The identification of BRAF V600E mutations in LCH has been confirmed in a recently published second report [Satoh, 2012].

Mutational analysis of BRAF V600 wild type LCH tumors has very recently revealed a second pathway activating alteration, MAP2K1 [Brown , 2014]. Of the roughly half of LCH specimens lacking the BRAF V600E mutation, half (about 25% overall) were found to have activation mutations of MAP2K1. This finding reinforces the important role of this pathway in the genesis of LCH and related diseases, and provides a rationale for additional investigation of inhibition of this pathway at more downstream positions, including that provided by inhibitors of MEK1/2.

Section 3.1 Discussion of study design PREVIOUS TEXT

Discussion of Study Design

[redacted]

This is a 3-part (Part A, Part B, Part C), Phase I/IIa, multi-center, open label study in pediatric subjects with refractory or recurrent tumors likely to have pathway activation and thus more likely to benefit from therapy. The overall goal of this trial is to efficiently establish safe, pharmacologically relevant dose of trametinib in infants, children and adolescents and determine preliminary activity of trametinib monotherapy in selected recurrent, refractory or unresectable childhood tumors. In addition, Part C of the study is designed to establish the safety, tolerability and activity of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAFV600E mutated tumors.

- **Part A** will be a pharmacokinetically driven limited dose escalation in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase (subjects less than 2 years of age will not be included in the initial dose escalation (approximately 6-12 subjects) is complete and the age specific cohorts are opened) and 18 subjects to the age expansion phase

Section 3.1 Discussion of Design REVISED TEXT

This is a 3-part (Part A, Part B, Part C), Phase I/IIa, multi-center, open label study in pediatric subjects with refractory or recurrent tumors likely to have pathway activation and thus more likely to benefit from therapy. The overall goal of this trial is to efficiently establish safe, pharmacologically relevant dose of trametinib in infants, children and adolescents and determine preliminary activity of trametinib monotherapy in selected recurrent, refractory or unresectable childhood tumors. In addition, Part C of the study is designed to establish the safety, tolerability and activity of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAFV600E mutated tumors.

- **Part A** will be a pharmacokinetically driven limited dose escalation in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase ~~(subjects less than 2 years of age will not be included in the initial dose escalation (approximately 6-12 subjects) is complete and the age specific cohorts are opened)~~ and 18 subjects to the age expansion phase (**subjects less than 2 years of age will not be included in the initial dose escalation until the age specific cohorts are opened).**

Section 3.2.4 Part A: Age Group Expansion PREVIOUS TEXT

Following the initial 3+3 dose escalation (Section 3.2.2), the dose will be confirmed and evaluated in the following specific age groups:

- Infants and toddlers (age 1 month to <2 years).
- Children (age 2 to ≤12 years).
- Adolescents (age >12 years to <18 years).

[redacted]

Section 3.2.4 Part A: Age Group Expansion REVISED TEXT

Following the initial 3+3 dose escalation (Section 3.2.2), the dose will be confirmed and evaluated in the following specific age groups **(age on day of consent)**:

- Infants and toddlers (age 1 month to <2 years).
- Children (age 2 to ≤12 years).
- Adolescents (age >12 years to <18 years).

Note: For the purposes of this study, age 12 is considered to be the day of a subject's 12th birthday. The day after the 12th birthday, a subject is considered to be greater than 12 years.

SECTION 3.3 Part B: Tumor-Specific Expansion PREVIOUS TEXT

Part B will evaluate the preliminary activity of trametinib monotherapy in 4 disease-specific cohorts of subjects. Each cohort will enroll at least 10 response-evaluable subjects (evaluable for response is defined as a subject with a pre-dose and at least 1 post–dose disease assessment or clinical assessment of progression of disease).

PK samples will be collected on Day 15 only. Archived or fresh tumor tissue to confirm Ras pathway activation is required from all subjects at screening.

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Trametinib will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

[redacted]

SECTION 3.3 Part B: Tumor-Specific Expansion REVISED TEXT

Part B will evaluate the preliminary activity of trametinib monotherapy in 4 disease-specific cohorts of subjects. Each cohort will enroll at least 10 response-evaluable subjects (evaluable for response is defined as a subject with a pre-dose and at least 1 post–dose disease assessment or clinical assessment of progression of disease).

PK samples will be collected on Day 15 only.

Archived or fresh tumor tissue to confirm **BRAF V600 or** Ras pathway activation is required from all subjects at screening, **unless the patient is specifically exempt from the requirement for histologic confirmation (e.g. NF-1, some brainstem gliomas (refer to inclusion criteria)). If tissue is unavailable, from non-exempt patients, then enrollment is not permitted.**

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Trametinib will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

SECTION 3.7 Study Schematics PREVIOUS FIGURES

Figure 2 Trametinib Disease Specific Expansion

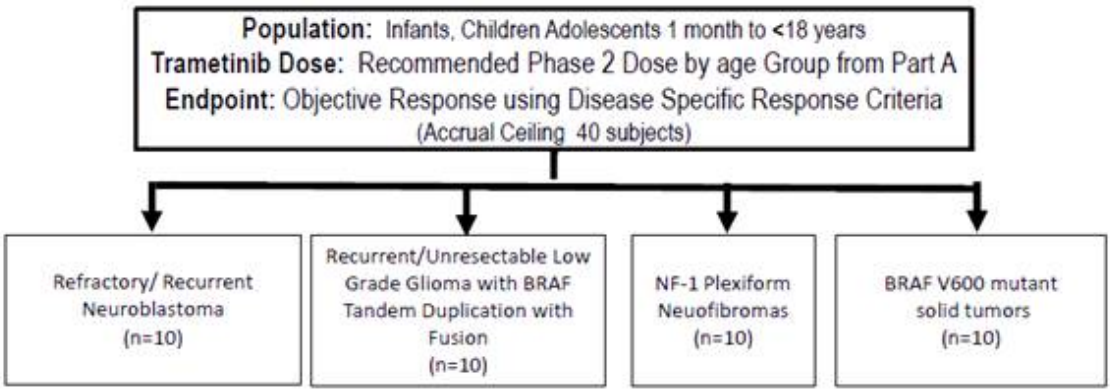
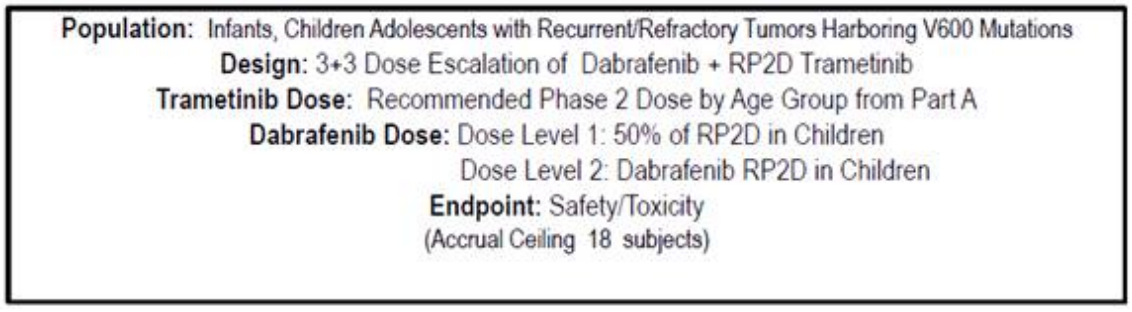


Figure 3 Trametinib in Combination with Dabrafenib



[redacted]

SECTION 3.7 Study Schematics REVISED FIGURES

(added clarification note to each Figure for age requirements)

Figure 2 Trametinib Disease Specific Expansion

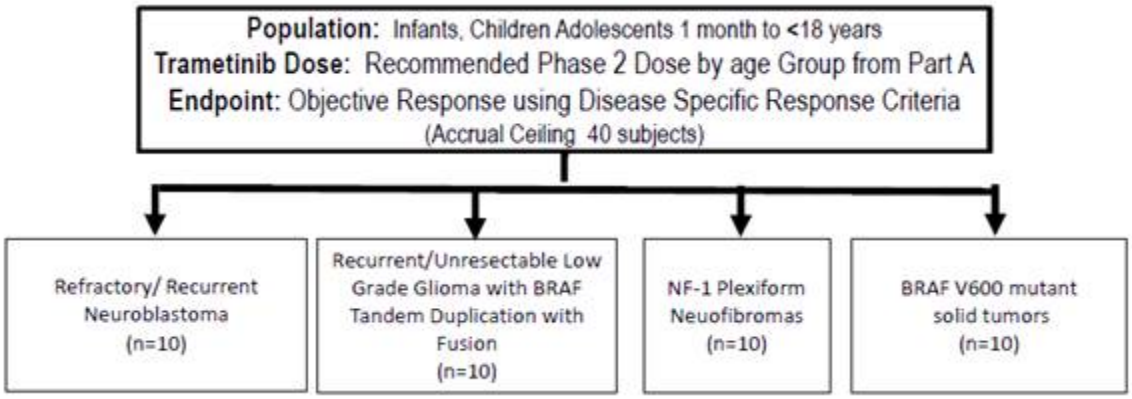


FIGURE 2 Note: A minimum of four subjects age younger than 6 years old is required in each of the four groups.

Figure 3 Trametinib in Combination with Dabrafenib

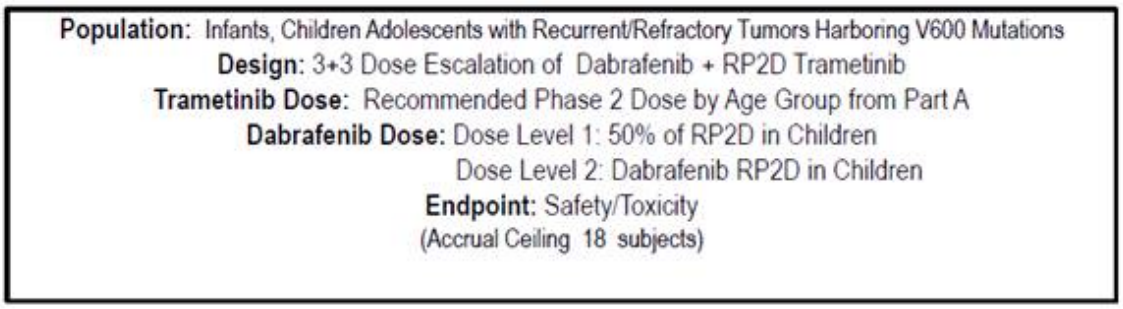


Figure 3 Notes:

1. Allowable ages are between 12 months and less than 18 years inclusive.

2. There is no specific age-expansion in Part C, however study goal is to enroll at least four subjects age younger than 12.

Section 3.11.3.1 LVEF stopping Criteria PREVIOUS TEXT

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 (Section 7.1). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 3.

ECHO should be performed at baseline and at follow up visit(s). Electronic copies of all ECHO scans will be collected by GSK for review. Instructions for submission of ECHO scans are provided in the Study Procedures Manual (SPM).

[redacted]

Table 3 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

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

[redacted]

Clinical Observation	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	• **Permanently discontinue trametinib.** • **Discontinue dabrafenib[d]** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[e]
	Grade 4: resting LVEF <20%	

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

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
b. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
c. If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult medical monitor.
d. Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.
e. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with GSK medical monitor.

Section 3.11.3.1 LVEF stopping Criteria Revised TEXT

(added Grade 2 note to Table 3, Asymptomatic Clinical Observation)

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 (Section 7.1). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 3.

ECHO should be performed at baseline and at follow up visit(s). Electronic copies of all ECHO scans will be collected by GSK for review. Instructions for submission of ECHO scans are provided in the Study Procedures Manual (SPM).

[redacted]

Table 3 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinical Observation	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Grade 2: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• Interrupt trametinib and dabrafenib and repeat ECHO within 2 weeks[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) • Consult with the GSK medical monitor and request approval for restart • Restart treatment with trametinib reduced by one dose level • Restart dabrafenib at previous dose level[b] Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter • If LVEF **does not recover** within 4 weeks • Consult with cardiologist • **Permanently discontinue trametinib** • Report as an SAE • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution • Consult with GSK medical monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib.** • **Discontinue dabrafenib** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[e]

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

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

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

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

[redacted]

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

d. Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.

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

[redacted]

SECTION 3.13.1.2 Reactive Management PREVIOUS TEXT

Table 5 Management of Rash

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of GSK medical monitor is required to re-start study treatment after >4 weeks of interruption
d. Escalation of trametinib to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

[redacted]

SECTION 3.13.1.2 Reactive Management REVISED TEXT (added reference to Appendix 2 Dose nomogram throughout)

Table 5 Management of Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	Initiate prophylactic and symptomatic treatment measures[a] Use moderate strength topical steroid[b] Reassess after 2 weeks;	Continue trametinib If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level** (Appendix 2).
Grade 2	Initiate prophylactic and symptomatic treatment measures[a] Use moderate strength topical steroid[b] Reassess after 2 weeks.	**Reduce trametinib by one dose level** (Appendix 2). Reassess after 2 weeks: • 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 trametinib until recovery to ≤grade 1, restart trametinib at reduced dose level
Grade ≥3	Use moderate strength topical steroids[b] (PLUS methylprednisolone dose pack. Consult dermatologist	• Interrupt trametinib until rash recovers to Grade ≤1 • **Restart[c] with trametinib reduced by one dose level[d]** (Appendix 2) If no recovery to grade ≤2 within 4 weeks, **permanently discontinue trametinib.**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of GSK medical monitor is required to re-start study treatment after >4 weeks of interruption
d. Escalation of trametinib to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

SECTION 3.13.3 Hypertension PREVIOUS TEXT

The algorithm in Figure 4 will be used to grade and manage trametinib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine,) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 3.11.3.2

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-

[redacted]

hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section 3.13.3.1.

Baseline Blood Pressure

- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:
  1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
  2) Average the systolic blood pressure from the 2nd and 3rd measurements.
  3) Average the diastolic blood pressure from the 2nd and 3rd measurements.
  4) The baseline BP is the average of the systolic and average of the diastolic measurements.

SECTION 3.13.3 Hypertension REVISED TEXT

(moved text to Section 7.3.4 Vital Signs to be more accessible to Investigators during safety evaluation as information is applicable there instead of stopping criteria section)

The algorithm in Figure 4 will be used to grade and manage trametinib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine,) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 3.11.3.2

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section. 3.13.3.1. **See requirements for Baseline blood pressure measurements in Section 7.3.4.**

~~**Baseline Blood Pressure**~~

- ~~**Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:~~
  ~~1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.~~
  ~~2) Average the systolic blood pressure from the 2nd and 3rd measurements.~~
  ~~3) Average the diastolic blood pressure from the 2nd and 3rd measurements.~~
  ~~4) The baseline BP is the average of the systolic and average of the diastolic measurements.~~

SECTION 5.2.1.1 General Eligibility Criteria (All Parts) PREVIOUS TEXT

[redacted]

1. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including pharmacokinetics sampling will be obtained according to institutional guidelines.
2. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form (Part C between 12 months and < 18 years of age, inclusive).
3. . Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or have a disease for which there are no standard treatment regimens that are potentially curative.
4. Prior therapy: The subject's cancer (not NF-1 with PN) must have relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. All subjects (including NF-1 with PN) must have recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.

- *Myelosuppressive chemotherapy*: The last dose of all myelosuppressive anticancer drugs must be at least 21 days prior to enrollment.
- *Differentiating Agents/ Biologic response modifiers (small molecules, antibodies, viral therapies) (anti-cancer agent)*: The last dose *of all biologic agents for the treatment of the subject's cancer (such as retinoids) must be at least 7 days prior t*o study entry. The last dose of monoclonal antibodies, immunotherapy, or viral therapy must be at least 30 days prior to enrollment.
- *Non-myelosuppressive anticancer agents*: (antiangiogenic agents, tyrosine kinase inhibitors): The last dose of non-investigational agent that is not cytotoxic must be at least 2 weeks prior to enrollment.
- *Investigational agent*: The last dose of all investigational agents must be at least 30 days prior to study entry.
- *Radiation therapy*: The last dose of radiation (including therapeutic Iodine-131-meta-iodobenzylguanidine [MIBG]) to more than 25% of marrow containing bones (pelvis, spine, skull) must be at least 28 days prior to enrollment. The last dose of all other local palliative (limited port) radiation must be at least 14 days prior to enrollment.
- *Stem Cell Transplantation or Infusion*. Subjects must be at least 2 months post-autologous transplant or stem cell infusion and must have recovered from toxicities. Subjects must be at least 6 months post- allogeneic transplant, must have recovered from toxicities, and must have no evidence of active graft-versus-host disease. Subjects must also have been off of immunosuppressive treatment at least 30 days.
- *Number of prior treatment regimens*: No limitation on the number of prior systemic or local treatment modalities that the subject may have received prior to study entry.
- *Colony stimulating factors*: The last dose of colony stimulating factors, such as filgrastim, sargramostim, and epoetin, must be at least 48 hr prior to study entry, and the last dose of

[redacted]

long-acting colony stimulating factors, such as pegfilgrastim, must be at least 10 days prior to study entry.

- *Corticosteroids* in subjects with solid tumors are permitted if the dose of corticosteroids is stable or decreasing for at least 7 days prior to enrollment. .

5. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale [Yates, 1980] (Appendix 1).
6. Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 10.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment, throughout treatment period and for 4 months after last dose of study drug.
7. Must have adequate organ function as defined by the following values:

- Renal function: 24 hr creatinine clearance (revised Schwartz formula), or radioisotope glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2; or a serum creatinine ≤ ULN for age and gender as defined in the following table:

Age (Years)	**Upper Limit of Normal Serum Creatinine** (mg/dl)	
	Male	Female
Less than 6 months	0.4	0.4
6 months to less than 1 year	0.5	0.5
1 year to less than 2 years	0.6	0.6
2 to less than 6 years	0.8	0.8
6 to less than 10 years	1	1
10 to less than 13 years	1.2	1.2
13 years to less than 16 years	1.5	1.4
Greater than 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR [Schwartz, 1985] utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

- Liver function defined as:
  - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age
  - ALT ≤2.5 x ULN; for the purposes of enrollment and toxicity monitoring the ULN for ALT will be 45 U/L.
- Cardiac function defined as:
  - Corrected QT (QTcB) interval <480 msec
  - LVEF ≥LLN by ECHO

8. Able to swallow and retain enterally (PO or nasogastric or gastric tube) administered medication and does not have any clinically significant gastrointestinal abnormalities

[redacted]

that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

9. Adequate Blood Pressure Control defined as:
    a. Blood pressure ≤ the 95th percentile for age, height, and gender) measured as described in Section7.3.4.
10. **French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Section 5.2.1.1 General Eligibility Criteria (All Parts) REVISED TEXT

(Updated to clarify population for the trial and at the request of regulatory to shorten timeframe for pregnancy testing prior to enrollment from 14 to 7 days in applicable subjects)

1. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including pharmacokinetics sampling will be obtained according to institutional guidelines.
2. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form (Part C between 12 months and < 18 years of age, inclusive).
3. Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or **must have a current disease for which there is no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life** ~~have a disease for which there are no standard treatment regimens that are potentially curative~~
4. Prior therapy: The subject's ~~cancer~~ **disease (i.e. cancer**, ~~(not~~ NF-1 with PN, **or LCH)** must have relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. All subjects ~~(including NF-1 with PN)~~ must have recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.

- *Myelosuppressive chemotherapy*: The last dose of all myelosuppressive anticancer drugs must be at least 21 days prior to enrollment.
- *Differentiating Agents/ Biologic response modifiers (small molecules, antibodies, viral therapies) (anti-cancer agent)*: The last dose *of all biologic agents for the treatment of the subject's cancer (such as retinoids) must be at least 7 days prior t*o study entry. The last dose of monoclonal antibodies, immunotherapy, or viral therapy must be at least 30 days prior to enrollment.
- *Non-myelosuppressive anticancer agents*: (antiangiogenic agents, tyrosine kinase inhibitors): The last dose of non-investigational agent that is not cytotoxic must be at least 2 weeks prior to enrollment.

[redacted]

- *Investigational agent*: The last dose of all investigational agents must be at least 30 days prior to study entry.
- *Radiation therapy*: The last dose of radiation (including therapeutic Iodine-131-meta-iodobenzylguanidine [MIBG]) to more than 25% of marrow containing bones (pelvis, spine, skull) must be at least 28 days prior to enrollment. The last dose of all other local palliative (limited port) radiation must be at least 14 days prior to enrollment.
- *Stem Cell Transplantation or Infusion*. Subjects must be at least 2 months post-autologous transplant or stem cell infusion and must have recovered from toxicities. Subjects must be at least 6 months post- allogeneic transplant, must have recovered from toxicities, and must have no evidence of active graft-versus-host disease. Subjects must also have been off of immunosuppressive treatment at least 30 days.
- *Number of prior treatment regimens*: No limitation on the number of prior systemic or local treatment modalities that the subject may have received prior to study entry.
- *Colony stimulating factors*: The last dose of colony stimulating factors, such as filgrastim, sargramostim, and epoetin, must be at least 48 hr prior to study entry, and the last dose of long-acting colony stimulating factors, such as pegfilgrastim, must be at least 10 days prior to study entry.
- *Corticosteroids* in subjects with solid tumors are permitted if the dose of corticosteroids is stable or decreasing for at least 7 days prior to enrollment. .

5. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale [Yates, 1980] (Appendix 1).
6. Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 10.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within **7** ~~14~~ days prior to **start of study drugs**, throughout treatment period and for 4 months after last dose of study drug.
7. Must have adequate organ function as defined by the following values:

- Renal function: 24 hr creatinine clearance (revised Schwartz formula), or radioisotope glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2; or a serum creatinine ≤ ULN for age and gender as defined in the following table:

Age (Years)	**Upper Limit of Normal Serum Creatinine** (mg/dl)	
	Male	Female
Less than 6 months	0.4	0.4
6 months to less than 1 year	0.5	0.5
1 year to less than 2 years	0.6	0.6
2 to less than 6 years	0.8	0.8
6 to less than 10 years	1	1
10 to less than 13 years	1.2	1.2
13 years to less than 16 years	1.5	1.4

[redacted]

Greater than 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR [Schwartz, 1985] utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

- Liver function defined as:
  - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age
  - ALT ≤2.5 x ULN; for the purposes of enrollment and toxicity monitoring the ULN for ALT will be 45 U/L.
- Cardiac function defined as:
  - Corrected QT (QTcB) interval <480 msec
  - LVEF ≥LLN by ECHO

8. Able to swallow and retain enterally (PO or nasogastric or gastric tube) administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

9. Adequate Blood Pressure Control defined as:
   - Blood pressure ≤ the 95th percentile for age, height, and gender) measured as described in Section 7.3.4.

10. French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Section 5.2.1.2 Specific Eligibility Criteria, Part A PREVIOUS TEXT

Subjects must meet General Eligibility Criteria. The specific eligibility criteria listed here will apply to subjects enrolling to Part A.

1. For the initial dose escalation to identify the maximum tolerable or PK target dose, age between 2 years and < 18 years (inclusive) at the time of signing the informed consent form. Children < 2 years of age will be enrolled once the age specific expansion cohorts are open.
2. Histologically confirmed solid tumors, which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, and primary brain tumors. In subjects with brain stem gliomas the requirement for histological confirmation can be waived if a biopsy was not performed.
3. Measurable or evaluable tumors. Subjects with neuroblastoma that is only detectable by MIBG scan are eligible. Subjects with neuroblastoma that is only detected by bone marrow aspirate/biopsy or elevated homovanillic acid / vanillylmandelic acid (HVA/VMA) are not eligible.
4. Adequate bone marrow function defined as:
   - Absolute neutrophil count (ANC) ≥1000/μL;
   - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)

[redacted]

- Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

Section 5.2.1.2 Specific Eligibility Criteria, Part A REVISED TEXT (updated #2 criteria to make clear to investigators that subjects with NF-1 associated PNs and Subjects with LCH are eligible and to clarify tumor assessments)

Subjects must meet General Eligibility Criteria. ~~In cases of conflict, the~~ The specific eligibility criteria listed here will apply to subjects enrolling to Part A.

1. For the initial dose escalation to identify the maximum tolerable or PK target dose, age between 2 years and < 18 years (inclusive) at the time of signing the informed consent form. Children < 2 years of age will be enrolled once the age specific expansion cohorts are open.
2. Histologically confirmed solid tumors, which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, ~~and~~ primary brain tumors, **NF-1 associated plexiform neurofibromas, and Langerhans Cell histocytosis (LCH).** In subjects with brain stem gliomas the requirement for histological confirmation can be waived if a biopsy was not performed. **For plexiform neurofibromas, histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiological findings, but should be considered if malignant degeneration of a PN is clinically suspected**.
3. Measurable or evaluable tumors. Subjects with neuroblastoma that is only detectable by MIBG scan are eligible. Subjects with neuroblastoma that is only detected by bone marrow aspirate/biopsy or elevated homovanillic acid / vanillylmandelic acid (HVA/VMA) are not eligible.
4. Adequate bone marrow function defined as:
   - Absolute neutrophil count (ANC) ≥1000/μL;
   - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
   - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

SECTION 5.2.2 Exclusion Criteria (All Parts) PREVIOUS TEXT

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

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

1. Lactating or pregnant female.
2. History of another malignancy including resected non-melanomatous skin cancer.
3. Subjects with NF-1 associated optic pathway tumors are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for PN or malignant

[redacted]

solid tumor (Subjects with NF-1 and isolated optic pathway tumors as only site of evaluable tumor are not eligible for enrollment).

4. Subjects with a history of NF-1 related cerebral vascular anomaly are excluded.
5. Subjects with NF-1 and active optic glioma are excluded.
6. Subjects with NF-1 and PN that cannot be evaluated by volumetric analysis.
7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
8. Any prohibited medication(s), currently used or expected to be required, as described in Section 9.2.
9. Any medications for treatment of left ventricular systolic dysfunction
10. Part B and Part C only: Previous treatment with dabrafenib (cohort B4), trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted)
11. Administration of an investigational study treatment within 30 days preceding the first dose of study treatment(s) in this study.
12. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment or excipients that contraindicate their participation.
13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or liver metastases).
14. History of hepatic sinusoid obstructive syndrome (venoocculsive disease) within the prior 3 months.
15. History of sensitivity to heparin or heparin-induced thrombocytopenia.
16. History of interstitial lung disease or pneumonitis.
18. History or current evidence RVO or RPED
19. For subjects with solid tumors that are not primary CNS tumors, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression are excluded.

NOTE: Subjects previously treated for these conditions that have had stable CNS disease (verified with consecutive imaging studies) for >3 months, are asymptomatic and are not currently taking corticosteroids, or are on stable dose or decreasing of corticosteroids for at least 7 days prior to enrolment are permitted.

20. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.
21. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia.

[redacted]

22. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs. If clarification is needed as to whether a condition will significantly affect absorption of drugs, contact the GlaxoSmithKline (GSK) medical monitor for guidance to enrol the subject.
23. A history or evidence of cardiovascular disease
    - **Part C only,** Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram. Subjects with moderate valvular thickening should not be entered on study;

SECTION 5.2.2 Exclusion Criteria (All Parts) REVISED TEXT

- (updated #3, 4,5,6,15,18,19,23; Changed to exclude only optic pathway tumors that are being actively treated This is because GSK now understands that the NF1 academic community prefers to enroll such patients (NF-1 associated optic gliomas as only site of disease) into MEK inhibitor trials. Previously, our understanding was that such patients should not be treated on this study, and perhaps be treated in different investigational trials; Cardiovascular exclusion criteria were updated to be consistent with requirements in other trametinib and dabrafenib studies; Removal of RPED (retinal pigment epithelium detachment) as an exclusion criterion, based on current safety data that only requires history of RVO (retinal vein occlusion) as an exclusion; Removal of heparin-sensitivity as an exclusion as there are no known drug-drug interactions between heparin and trametinib or dabrafenib. Heparin-induced thrombocytopenia remains as an exclusion.)

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

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

1. Lactating or pregnant female.
2. History of another malignancy including resected non-melanomatous skin cancer.
3. Subjects with NF-1 associated optic pathway tumors are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for PN or malignant solid tumor ~~(Subjects with NF-1 and isolated optic pathway tumors as only site of evaluable tumor are not eligible for enrollment).~~
4. Subjects with a history of NF-1 related cerebral vascular anomaly (**such as Moyamoya)** are excluded.
5. **Subjects with NF-1 actively receiving therapy for the optic pathway tumor** ~~Subjects with NF-1 and active optic glioma are excluded.~~
6. Subjects with NF-1 and **only** PN **lesions** that cannot be evaluated by volumetric analysis.
7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.

[redacted]

8. Any prohibited medication(s), currently used or expected to be required, as described in Section 9.2.
9. Any medications for treatment of left ventricular systolic dysfunction
10. Part B and Part C only: Previous treatment with dabrafenib (cohort B4), trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted)
11. Administration of an investigational study treatment within 30 days preceding the first dose of study treatment(s) in this study.
12. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment or excipients that contraindicate their participation.
13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or liver metastases).
14. History of hepatic sinusoid obstructive syndrome (venoocculsive disease) within the prior 3 months.
15. History of ~~sensitivity to heparin or~~ heparin-induced thrombocytopenia.
16. History of interstitial lung disease or pneumonitis.
18. History or current evidence RVO ~~or RPED~~
19. For subjects with solid tumors that are not primary CNS tumors **or NF-1 associated plexiform neurofibromas**, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression are excluded.

NOTE: Subjects previously treated for these conditions that have had stable CNS disease (verified with consecutive imaging studies) for >3 months, are asymptomatic and are not currently taking corticosteroids, or are on stable dose or decreasing of corticosteroids for at least 7 days prior to enrolment are permitted.

20. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.
21. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia.
22. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs. If clarification is needed as to whether a condition will significantly affect absorption of drugs, contact the GlaxoSmithKline (GSK) medical monitor for guidance to enrol the subject.
23. A history or evidence of cardiovascular ~~disease~~ **risk including any of the following:**
    - **A QT interval corrected for heart rate using the Bazett's formula (QTcB) ≥480 msec;**

[redacted]

- **A history or evidence of current clinically significant uncontrolled arrhythmias; Clarification: Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible.**
- **A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.**
- **A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines;**
- **Patients with intra-cardiac defibrillators;**
- **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. Subjects with prosthetic valves can be considered eligible provided they meet the criteria as stated above.**
- **Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg (or above 95th age-specific percentile as listed in Appendix 8), which cannot be controlled by anti-hypertensive therapy;**
- ~~**Part C only,** Abnormal cardiac valve morphology (≥Grade 2) documented by echocardiogram. Subjects with moderate valvular thickening should not be entered on study;~~

Section 6.3 Permanent Discontinuation from Study Treatment Previous Text

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.11.1. In addition, study treatment may be permanently discontinued for any of the following reasons:

- serious deviation(s) from the protocol;
- subject becomes pregnant;
- request of the subject or proxy (withdrawal of consent by subject or proxy);
- investigator's discretion;
- a dose delay due to administrative, scheduling or study treatment related toxicity of >28 days;
- intercurrent illness that prevents further administration of study treatment(s);
- subject is lost to follow-up;
- sponsor terminates the study.

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

Subjects who require permanent discontinuation of one of the study treatments in a given treatment combination must permanently discontinue both treatments in that combination and the reason for discontinuation must be recorded.

[redacted]

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

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated. All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (see Section 7.1).

Section 6.3 Permanent Discontinuation from Study Treatment REVISED TEXT

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.11.1. In addition, study treatment may be permanently discontinued for any of the following reasons:

- serious deviation(s) from the protocol;
- subject becomes pregnant;
- request of the subject or proxy (withdrawal of consent by subject or proxy);
- investigator's discretion;
- a dose delay due to administrative, scheduling or study treatment related toxicity of >28 days;
- intercurrent illness that prevents further administration of study treatment(s);
- subject is lost to follow-up;
- sponsor terminates the study.

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

Subjects who require permanent discontinuation of one of the study treatments in a given treatment combination must permanently discontinue both treatments in that combination and the reason for discontinuation must be recorded.

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

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated. All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (see Section 7.1).

Adverse Events must be followed for a minimum of 28days after the last dose. If it is not practical for the subject to return to the clinic, this data may be collected via telephone from the parent/caregiver/subject (as appropriate).

The discontinuation related safety assessments (same assessments as Final visit in the Time and Events Table 14) may be completed at any time from the last dose to 28 days after the last dose. Ongoing toxicities should be followed to resolution if at all possible.

[redacted]

Section 7.1 Time and Events PREVIOUS TEXT

Please refer to Section 7.1 of Protocol Amendment 01 for the prior T&Es in Table 11-Table 15.

SECTION 7.1 Time and Events REVISED TEXT

Table 11

Updated comments in ECHO line item,

Added baseline urinalysis (missing before due to error),

Added comment to PK line item for Day 15 and Day 22 samples

Table 14

Updated comments in ECHO line item (same as in Table 11),

Added LCH Response assessment timing as is different from some other tumor types. ,

Changed header visit reference for the visits after one year from Weeks 52+ to Weeks 53+ to align with odd week visit schedule in the rest of the protocol.

Table 15

Changed header visit reference for the visits after one year from Weeks 52+ to Weeks 53+ to align with odd week visit schedule in the rest of the protocol.

Table 11 Time and Events, Treatment Phase: Screening through Day 28

All subjects (unless specified) screening- day 28 STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 28				
VISIT		Screen	Pre-dose Day 1, Week 1	Pre-dose Day 8, Week 2	Pre-dose Day 15, Week 3	Pre-dose Day 22, Week 4	Pre-dose Day 28, Week 5
VISIT WINDOW (±days		-14	N/A	±2	±2	±2	±2
Baseline Assessments							
Informed consent/assent		X					
Tumor biopsy or bone marrow aspirate, **Part A**	Optional fresh biopsy or bone marrow aspirate.	X					
Archived tumor biopsy or bone marrow aspirate, **Part B**	Archived tissue at screening is required and must be available to be shipped to GSK; if not available fresh biopsy is acceptable. RAS mutation status does not have to be done within 14 days prior to dosing..	X					

[redacted]

All subjects (unless specified) screening- day 28 STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 28				
VISIT		Screen	Pre-dose Day 1, Week 1	Pre-dose Day 8, Week 2	Pre-dose Day 15, Week 3	Pre-dose Day 22, Week 4	Pre-dose Day 28, Week 5
VISIT WINDOW (±days		-14	N/A	±2	±2	±2	±2
Tumor tissue for V600 testing for those subjects enrolled in **Part B4 and Part C**,	Local BRAF testing required for enrolment in the study; the local testing will be subject to subsequent confirmation by centralized testing. Central confirmation can be from archival tissue or if no archival tissue is available, from fresh biopsy. Central confirmation not required within 14 days prior to dosing.	X					
Demographic data	Record date of birth, gender, race and ethnicity	X					
Register subject	Using an interactive voice response system	X	X				
Height/Weight/tanner stage	Measurements in metric scale.	X	X				
Serum pregnancy test	In all menstruating females and according to applicable local requirements and/or regulations, a serum pregnancy test is required at screening (within 7 days of administration of the first dose of study medication). If performed within 7 days of first dose of study drug, does not need to be repeated on Day 1 (pre-dose)	X	X				X
Disease characteristics	Record date of diagnosis, primary tumor type, histology, stage, etc.	X					
Prior anti-cancer therapy & radiation		X					
Prior major surgical procedures		X					
Past and current medical conditions	Medical history will be assessed as related to the eligibility criteria listed in Section 5.2.1. Cardiovascular medical history/risk factors will also be assessed at baseline	X					

[redacted]

All subjects (unless specified) screening- day 28 STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 28				
VISIT		Screen	Pre-dose Day 1, Week 1	Pre-dose Day 8, Week 2	Pre-dose Day 15, Week 3	Pre-dose Day 22, Week 4	Pre-dose Day 28, Week 5
VISIT WINDOW (±days		-14	N/A	±2	±2	±2	±2
Safety/Tolerability Assessments							
Physical examination	Assessment of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities	X	X	X	X	X	X
Dermatologic skin assessment	Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam throughout the study. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits.	X				X	
Plain Radiograph of Wrist and Tibial Growth Plate			X				
Ophthalmologic examination	Performed by ophthalmologist. See Section 7.3.2 for details.	X					X
ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by personnel with experience in this study population (e.g., pediatric cardiologist).	X					
Echocardiogram (ECHO)	Copies of all ECHOs and cardiology consultations performed on subjects **will be sent to the study sponsor during the study (Additional details in the SPM)** ~~who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is less than the institution's LLN will be collected for possible central review~~	X					X
Vital signs	Blood pressure (3 serial blood ~~pressues~~**pressures**; separated by at least 5 minutes see Section 7.3.4), body temperature, pulse rate, respirations	X	X	X	X	X	X
Urinalysis	**Routine Urinalysis (See Table 16)**		**X**				
Concomitant medications	See Section 9 for list of prohibited and cautionary medications.	X	X	X	X	X	X

[redacted]

All subjects (unless specified) screening- day 28 STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 28				
VISIT		Screen	Pre-dose Day 1, Week 1	Pre-dose Day 8, Week 2	Pre-dose Day 15, Week 3	Pre-dose Day 22, Week 4	Pre-dose Day 28, Week 5
VISIT WINDOW (±days		-14	N/A	±2	±2	±2	±2
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X
Palatability questionnaire **(subjects receiving oral liquid formulation)**	To be completed after the first dose of study drug and no later than Day 8 (±3 days). See Section 7.3.7 for details.			X			
Blood Sampling							
Chemistry	Evaluations performed by a local laboratory. Not required on Day 1 if screening assessments were within 72 hr of first dose.	X	X	X	X	X	X
Hematology	Evaluations performed by a local laboratory. Not required on Day 1 if screening assessments were within 72 hr of first dose.	X	X	X	X	X	X
PK sampling	**PK sampling is required to be drawn on Study Day 15 and Day 22 in Parts A & C and on Study Day 15 in Part B, there is no visit window around these samples.** For details, see Table 12 for trametinib; Table 13 for dabrafenib		X (Parts C)		X (Parts A, B, C)	X (Parts A, C)	
Clinical Activity [redacted]							
Target and non-target lesion assessment	Must be identified at time of screening scan.	X					
Brain MRI (**glioma subjects ONLY)**	May use brain MRI obtained within 35 days of the first dose. CT with contrast allowed only if brain MRI is contraindicated.	X					
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X	X	X	X
MRI with volumetric assessment for **Plexiform Neurofibromas**	NF-1 PN Cohort Only. May be performed up to 4 weeks prior to enrollment, and requires central review (see Section 5.2.1.3)	X					
Tumor biopsy	Optional fresh biopsy		X		X		
[redacted]							
Study Medication							
Dispense oral study medication and assess compliance	Dispense study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.		X				X

MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram; PK = pharmacokinetic

[redacted]

Table 14 Time and Events, Treatment Phase, Week 9 to Final Visit

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Safety Assessments									
Brief Physical examination	Will include height and weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated]	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Dermatologic skin assessment	Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam for the duration of the study to ensure consistency between evaluations. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits.	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Plain radiograph of wrist and tibial growth plate	Only in subjects with open growth plates at screening	X				X	Every 24 weeks (6 months)	Every 52 weeks (12 months)	X
Tanner Stage						X	Every 24 weeks (6 months)	Every 24 weeks	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Urine Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Ophthalmologic examination	Performed by ophthalmologist. See Section 7.3.2 for details.			X		X	Every 12 weeks	Every 12 weeks	
ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by personnel with experience in this study population	X		X		X	Every 12 weeks	Every 12 weeks	X
Echocardiogram (ECHO)	Copies of all ECHOs **will be collected and sent to the study sponsor during the study** ~~and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is less than the institution's LLN will be collected for possible central review~~ (additional details are provided in the SPM). An ECHO does not need to be performed at study discontinuation unless one was not performed within the previous 8 weeks.			X		X	Every 12 weeks	Every 12 weeks	X
Concomitant medications	See Protocol Section 9 for list of prohibited and cautionary medications.	X	X	X	X	X	X	X	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	X	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Blood Sampling									
Chemistry	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4weeks	Every 12 weeks	X
Clinical Activity [redacted] ***Assessments***									
Part A and Part C only; for Part B please see Table 15									
Target and non-target lesion assessment	Target and non-target lesions identified at time of screening scan must be re-assessed at each restaging scan. If the last radiographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation	X		X		X	Every 12 weeks	Every 12 weeks (or more frequently per local standard of care)	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		**TREATMENT WEEK 9+**							
Visit		**Week 9**	**Week 13**	**Week 17**	**Week 21**	**Week 25**	**Weeks 25+ (after 6 months)**	**Weeks 53+ (after 1 year)**	**Final Visit**
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Response	Complete response/partial response confirmation assessments may take place at Week 13 if initial response was seen at the Week 9 scan. Initial response (complete response/partial response) that is observed at Week 17 or after should be confirmed not less than 4 and not more than 8 weeks after the initial response. **LCH assessment: ONLY required at Week 13 and Week 25, then every 12 weeks**	X	**X (LCH only)**	X		X **+LCH**	Every 12 weeks	Every 12 weeks	X
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X		X	Every 12 weeks	Every 12 weeks	X
Tumor Biopsy	Optional fresh biopsy	Upon disease progression							
[redacted]									
Study Medication									
Dispense oral study medication and assess compliance	Dispense a 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	Every 4 weeks	Every 4 weeks	
Post Treatment Follow-up – See Section 6.6									

MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram

[redacted]

Table 15 Time and Events, Part B Clinical Activity Assessments, Week 9 to Final Visit

Additional events Part B week 9- final Visit: STUDY PHASE		TREATMENT WEEK 4+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Clinical Activity [redacted] Assessments									
Solid Tumor Cohort B1 and BRAF Fusion Cohort B2									
Target and non-target lesion assessment	Target and non-target lesions identified at time of screening scan must be re-assessed at each restaging scan. If the last radiographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation	X		X		X	Every 12 weeks	Every 12 weeks (or more frequently per local standard of care)	X
Response	Complete response/partial response confirmation assessments may take place at Week 12 if initial response was seen at the Week 8 scan. Initial response (complete response/partial response) that is observed at Week 16 or after should be confirmed not less than 4 and not more than 8 weeks after the initial response.	X		X		X	Every 12 weeks	Every 12 weeks	X
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X		X	Every 12 weeks	Every 12 weeks	X
Tumor Biopsy	Optional fresh biopsy	Upon disease progression							
[redacted]									
NF-1 Plexiform Neurofibroma Cohort B3									
MRI with volumetric assessment	Visit window of 2 weeks is allowed, central review required (Section 7.6.1			X			Week 32, 48,	Week 72, 96 Then every 24 weeks	
Tumor tissue	Optional fresh biopsy	Upon disease progression							
[redacted]									

SECTION 7.3.4 Vital Signs PREVIOUS TEXT

[redacted]

Vital sign measurements will include systolic and diastolic blood pressure (see Section 3.13.3.1) temperature, respiration rate and pulse rate. Vital signs should be measured after resting for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs.

SECTION 7.3.4 Vital Signs REVISED TEXT (moved text from Section 3.13.3.1 to this section)

Vital sign measurements will include systolic and diastolic blood pressure ~~(See Section 3.13.3.1)~~, temperature, respiration rate and pulse rate. Vital signs should be measured after resting for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs.

Baseline blood pressure (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:

1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.

2) Average the systolic blood pressure from the 2nd and 3rd measurements.

3) Average the diastolic blood pressure from the 2nd and 3rd measurements.

4) The baseline BP is the average of the systolic and average of the diastolic measurements.

SECTION 7.3.6 Echocardiogram PREVIOUS TEXT

The ECHOs will be performed to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility and during the study as specified in the Time and Events Table (Section 7.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF and both right and left-sided valvular lesions.

Copies of all ECHOs performed on subjects who experience grade ≥2 LVEF decrease, valvular regurgitation/stenosis or left ventricular systolic dysfunction that requires interruption, modification or discontinuation of study treatment may be required by GSK for review.

SECTION 7.3.6 Echocardiogram REVISED TEXT (updated to reflect all ECHOs will need to be provided to sponsor)

The ECHOs will be performed to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility and during the study as specified in the Time and Events Table (Section 7.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF and both right and left-sided valvular lesions.

Copies of all **study** ECHOs performed will be required to be provided to the sponsor. **The ECHOs will not be reviewed in a real-time basis by the sponsor, but rather held for**

[redacted]

review at a future time point.~~on subjects who experience grade ≥2 LVEF decrease, valvular regurgitation/stenosis or left ventricular systolic dysfunction that requires interruption, modification or discontinuation of study treatment may be required by GSK for review.~~

SECTION 7.3.7 Laboratory Assessments

Table 16 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	MCV	Neutrophils	
White blood cell (WBC) Count (absolute)	MCH	Lymphocytes	
Hemoglobin	MCHC	Monocytes	
Hematocrit		Eosinophils	
HbA1c		Basophils	
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin (Bilirubin fractionation recommended if total bilirubin is >2x the upper limit of normal)
Creatinine	Chloride	Alanine aminotransferase (ALT)	Total Protein
Glucose (recheck fasting if >160 mg/dL)	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	**Albumin**
Sodium	Calcium	Alkaline phosphatase (ALP)	
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Urine Protein Creatinine – Part C only			
Other screening tests			
Urine or serum pregnancy test			
HVA/VMA in random or 24 hr urine for subjects with neuroblastoma			
In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.			

RBC = Red Blood Cell; WBC = White Blood Cell; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin: MCHC = Mean Corpuscular Hemoglobin Concentration; HVA/VMA = Homovanillic Acid / Vanillylmandelic Acid (ratio); CSF = Cerebrospinal fluid.

[redacted]

SECTION 7.3.7 Laboratory Assessments REVISED TEXT (changed to only allow Serum Pregnancy Test)

Table 16 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	MCV	Neutrophils	
White blood cell (WBC) Count (absolute)	MCH	Lymphocytes	
Hemoglobin	MCHC	Monocytes	
Hematocrit		Eosinophils	
HbA1c		Basophils	
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin (Bilirubin fractionation recommended if total bilirubin is >2x the upper limit of normal)
Creatinine	Chloride	Alanine aminotransferase (ALT)	Total Protein
Glucose (recheck fasting if >160 mg/dL)	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	**Albumin**
Sodium	Calcium	Alkaline phosphatase (ALP)	
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Urine Protein Creatinine – Part C only			
Other screening tests			
~~Urine or~~ serum pregnancy test			
HVA/VMA in random or 24 hr urine for subjects with neuroblastoma			
In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.			

RBC = Red Blood Cell; WBC = White Blood Cell; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin: MCHC = Mean Corpuscular Hemoglobin Concentration; HVA/VMA = Homovanillic Acid / Vanillylmandelic Acid (ratio); CSF = Cerebrospinal fluid.

SECTION 7.3.8 Pregnancy Testing and Reporting PREVIOUS TEXT

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

If a female subject is of childbearing potential, she must have a serum β-Human Chorionic Gonadotropin (β-HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). 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 during the study until 30 days following the last dose of study treatment(s).

[redacted]

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

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

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

SECTION 7.3.8 Pregnancy Testing and Reporting REVISED TEXT

(Lengthened requirement to 4 months for contraception use after last dose at request of regulatory authority)

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

If a female subject is of childbearing potential, she must have a serum β-Human Chorionic Gonadotropin (β-HCG) pregnancy test performed within 7 days prior to the first dose of study treatment(s). 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 during the study until ~~30 days~~**4 months** following the last dose of study treatment(s).

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

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

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

SECTION 7.5 Translation Research PREVIOUS TEXT

[redacted]

Table 17 List of Samples for Translational Research

Study Part	Sample type	Mandatory/Optional	Primary Purpose
Part A	Archival or fresh tumor tissue	Mandatory at screening. If unavailable, the subject is not eligible to participate in the study.	For retrospective analysis for RAS mutation status
Part B	Archival or fresh tumor tissue	Mandatory at screening. If unavailable, the subject is not eligible to participate in the study	For retrospective analysis for RAS mutation status
Part B4 and Part C	Archival or fresh tumor tissue	Mandatory at screening	Central confirmation of *BRAF* V600 mutation status
All Parts	Fresh tissue at baseline	Optional (please note that the same baseline specimen may be used for [redacted] pharmacodynamic testing)	[redacted]
All Parts	Fresh tissue at radiological progression	Optional	Resistance marker analysis
All Parts	Fresh tissue at baseline	Optional (please note that the same baseline specimen may be used for [redacted] pharmacodynamic testing)	Pharmacodynamic testing
Part A,	Fresh tissue at baseline and Day 28		
[redacted]			

[redacted]

SECTION 7.5 Translational Research REVISED TEXT (updated to correct the optional samples and reformatted for clarity)

Table 17 List of Samples for Translational Research

Sample Type	Part A	Parts B1, B2 & B3	Part B4	Part C	Primary Purpose
[redacted]					
Fresh Tissue at Baseline (Day 1) and Day 15	Optional *	Optional *	Optional *	Optional *	Pharmaco-dynamic Analysis. [redacted]
Archival or Fresh Tissue	Optional	For subjects that must have RAS or BRAF V600 confirmed, this is mandatory at screening. If unavailable, the subject is not eligible to participate in the study	Mandatory at Screening	Mandatory at Screening	For prospective testing of RAS mutation in Part B4 and retrospective Analysis for RAS/BRAF mutation. Central testing/confirmation of BRFV600
Fresh tissue at radiological progression	Optional	Optional	Optional	Optional	Resistance Marker Analysis

*Please note that the same baseline specimen may be used for [redacted] and pharmacodynamic testing

SECTION 7.5.1.1 Part B, Cohorts (B1, B2, and B3) PREVIOUS TEXT

Archival tissue must be submitted during screening for subsequent confirmation of the Ras pathway activation or mutation status. If archival specimen is not available, subjects will be required to undergo tumor biopsy prior to participation in the study. If archived tissue is not available and a fresh tumor sample cannot be collected (i.e. subjects with brain tumors) the subject will not be eligible for participation in the study. Subjects will also be asked to

[redacted]

provide tumor tissue after documented disease progression. However, collection of post-progression tumor tissue is optional and will be collected only from subjects that have provided appropriate consent.

[redacted]

Further details on tissue requirements including amount, sample fixation, and shipment will be provided in the SPM.

SECTION 7.5.1.1 Part B, Cohorts (B1, B2, and B3) REVISED TEXT

Archival tissue must be submitted during screening for subsequent confirmation of the Ras pathway activation or mutation status. If archival specimen is not available, subjects will be required to undergo tumor biopsy prior to participation in the study. If archived tissue is not available and a fresh tumor sample cannot be collected (i.e. subjects with brain tumors) the subject will not be eligible for participation in the study. **The only exception will be for those patients who are exempt from histologic confirmation.** Subjects will also be asked to provide tumor tissue after documented disease progression. However, collection of post-progression tumor tissue is optional and will be collected only from subjects that have provided appropriate consent.

[redacted]

Further details on tissue requirements including amount, sample fixation, and shipment will be provided in the SPM.

SECTION 7.6.1 MRI and/or CT Scan PREVIOUS TEXT

Magnetic resonance imaging (MRI) will be performed at Screening and at scheduled visits during the study (see Time and Events Table Section 7.1) for subjects with primary brain tumors and subjects with PN. If a brain MRI is contraindicated, a CT scan with contrast is allowed. Whichever modality is used at screening should be consistently performed during the study.

Scans for neurofibroma will be centrally collected and reviewed. Instructions for image acquisition are included in Appendix 6 and the SPM.

SECTION 7.6.1 MRI and/or CT Scan REVISED TEXT (updated to reflect MRIs are required in Part B for PN subjects, this is to allow for required Volumetric Analysis)

Magnetic resonance imaging (MRI) will be performed at Screening and at scheduled visits during the study (see Time and Events Table Section 7.1) for subjects with primary brain tumors and subjects with PN. If a brain MRI is contraindicated, a CT scan with contrast is allowed **(except for PN subjects in Part B where MRIs are required).** Whichever modality is used at screening should be consistently performed during the study.

Scans for neurofibroma will be centrally collected and reviewed. Instructions for image acquisition are included in Appendix 6 and the SPM.

SECTION 9.2 Prohibited Medications; Part C (Dabrafenib) PREVIOUS TEXT

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

- Other anti-cancer therapies;
- Other investigational drugs;

[redacted]

- Antiretroviral drugs (Note: Subjects with known human immunodeficiency virus (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 19) may only be used under special circumstances (e.g., as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data. Refer to the SPM for the most current list.

SECTION 9.2 Prohibited Medications REVISED TEXT (updated for clarity that there are no prohibited medications in Parts A & B)

9.2.1 Prohibited Medications Parts A & B

There are no prohibited medications while on treatment in Part A and Part B of this study.

9.2.2 Prohibited Medications; Part C (Dabrafenib)

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known human immunodeficiency virus (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 19) may only be used under special circumstances (e.g., as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data. Refer to the SPM for the most current list.

SECTION 9.3 PREVIOUS TEXT

Table 19 Medications to be used with Caution: Part C (Dabrafenib)

Section 9.3 REVISED TEXT

~~Table 19~~ Table 20 Medications to be used with Caution: Part C (Dabrafenib)

SECTION 12.2.1 PREVIOUS TEXT

Table 20 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

[redacted]

Section 12.2.1 REVISED TEXT

~~Table 20~~ Table 21 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

SECTION 10.1.1 Female Subjects PREVIOUS TEXT

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

In questionable cases, consider obtaining follicle stimulating hormone (FSH) and estradiol values (FSH must be >40 mIU/mL and estradiol <40pg/mL [<140 pmol/L] for non-childbearing potential).

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

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%.

[redacted]

Abstinence

Sexual inactivity by abstinence must be consistent 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.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 28 days after the last dose of study treatment.

SECTION 10.1.1 Female Subjects REVISED TEXT (updated with same rationale as Section 7.3.8)

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

In questionable cases, consider obtaining follicle stimulating hormone (FSH) and estradiol values (FSH must be >40 mIU/mL and estradiol <40pg/mL [<140 pmol/L] for non-childbearing potential).

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

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%.

Abstinence

Sexual inactivity by abstinence must be consistent 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.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least ~~28 days~~ **4 months** after the last dose of study treatment.

SECTION 12.2.1 PREVIOUS TEXT

Table 20 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

Section 12.2.1 REVISED TEXT

~~Table 20~~ Table 21 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

[redacted]

SECTION 12.2.2 PREVIOUS TEXT

Table 21 Exact Binomial Probabilities of Observing 0 and 1 (or more) Responses in 10 Subjects

Section 12.2.2 REVISED TEXT

~~Table 21~~ Table 22 Exact Binomial Probabilities of Observing 0 and 1 (or more) Responses in 10 Subjects

SECTION: APPENDIX 6: Response Criteria for PNs PREVIOUS TEXT

Prior to starting treatment on this study all known measurable tumors should be imaged with MRI to obtain a baseline. Tumor spread in subjects with NF-1 can be very extensive, and may not allow for all lesions to be followed using 3D-MRI. The goal will therefore be to use 3D-MRI only to follow the inoperable PN (a maximum of three lesions), which will be defined as index lesion(s).

Pre-study radiographic evaluation:

1. Identify and select the inoperable PN (a maximum of three lesions) for 3-D MRI evaluation based on prior imaging studies. Should there be more than 3 inoperable PN, the three most clinically relevant PN will be followed by 3-D MRI analysis.
2. Perform 3-D MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols below.
3. In addition, if possible, perform MRI of all additional measurable PN.
4. Send baseline MRI to address below for central review prior to enrolment.

On study radiographic evaluation:

Unless clinically indicated otherwise obtain MRI of the index lesions only as outlined in the MRI acquisition protocol below prior to cycles 4, 8, 12, and then after every 6 cycles as long as the subject remains on study.

MRI protocols:

Depending on the location of the index lesions the Spine, Head/Neck or Trunk/Extremities protocols outlined on the following pages will be used.

Participating institutions may modify the MRI sequences to optimize differentiation of tumor and surrounding tissue. Modifications should be documented in the MRI protocols, and the same imaging protocol, and, if possible, the same MRI scanner should be used for all subsequent MRI studies. Every attempt should be made to image the entire progressive PN. All MRI studies requested per protocol will be submitted to the NCI Pediatric Oncology Branch (POB) within 2 weeks of acquisition for volume analysis. The studies have to be sent on Compact Disk in uncompressed Digital Imaging and Communications in Medicine (DICOM) format. At the same time, a copy of the MRI protocol and the institutional radiology report will be sent to the NCI POB.

For technical support, please contact:

[redacted], M.D. (phone [redacted], e-mail: [redacted]

Send MRI studies and protocols used to obtain studies and radiology reports to:

[redacted]

[redacted]

[redacted]

Phone: [redacted], fax: [redacted], e-mail: [redacted]

All MRI data will be analyzed at the POB of the NCI. The MRI data from each scan will be processed to assess the volume of the index PN(s). Each subject's volumetric measurement obtained from the initial MRI will serve as the baseline against which to assess incremental changes in volume that occur during the subsequent intervals. The NCI POB will inform participating investigators about the results of the MRI study by written report. MRI results will be transferred to GSK or GSK contracted third party imaging vendor.

MRI Protocol- Spine STUDY ID NUMBER: _____

Note: Only the series outlined below are required for volumetric analysis of PNs and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.

1. AXIAL FAST SPIN ECHO-INVERSION RECOVERY (FSEIR)

Axial FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	5 mm		
Skip	0		
Matrix	256x256		
FOV	22 cm		
NEX	1		
Frequency Direction	R→L		
Options	Tailored RF, FC, PC, 0.75 FOV		

[redacted]

2. CORONAL FSEIR

Coronal FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	5 mm		
Skip	0		
Matrix	256x256		
FOV	22 cm		
NEX	1		
Frequency Direction	S→I		
Options	Tailored RF, FC, PC		

Date:_____Signature (responsible MRI technician):_____

[redacted]

3. Axial T2

Axial T2	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	16		
TR	3000-6000		
TE	100		
Slice Thickness	5 mm		
Skip	0		
Matrix	320x256		
FOV	18 cm		
NEX	3		
Options	Tailored RF, NPW		

4. Sagittal T2

Coronal FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	16		
TR	3000-6000		
TE	100		
Slice Thickness	5 mm		
Skip	0		
Matrix	320x256		
FOV	24 cm		
NEX	3		
Options	Tailored RF, NPW		

Date:_____Signature (responsible MRI technician):_____

MRI Protocol- Head/Neck STUDY ID NUMBER: _____

Note: Only the series outlined below are required for volumetric analysis of PNs and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.

[redacted]

1. AXIAL FSEIR

Axial FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	54 mm		
Skip	0		
Matrix	256x256		
FOV	22 cm		
NEX	1		
Frequency Direction	A→P		
Options	Tailored RF, FC, 0.75 FOV		

2. CORONAL FSEIR

Coronal FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	5 mm		
Skip	0 mm		
Matrix	256x192		
FOV	22 cm		
NEX	1		
Frequency Direction	S→I		
Options	Tailored RF, PC		

Date:_____Signature (responsible MRI technician):_____

MRI Protocol-Trunk/Extremities STUDY ID NUMBER: _____

Note: Only the series outlined below are required for volumetric analysis of PNs and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.

1. AXIAL PLANE-STIR

Axial Plane STIR	Protocol Specifications	Actual Specifications	Reason For Change

[redacted]

Coil: Body			
Sequence: Fast Spin Echo (Turbo) FSEIR			
Echo Train Length	5		
TR	6000		
TE	15		
TI	150		
Slice Thickness	10 mm		
Skip	0		
Matrix	512x160		
FOV	40x30		
No. of Excitations/ Sequence	0.5		
No. of Acquisitions	1		
Saturation	None		

2. CORONAL PLANE STIR

Coronal Plane STIR	Protocol Specifications	Actual Specifications	Reason For Change
Coil: Body			
Sequence: Fast Spin Echo (Turbo) FSEIR			
Echo Train Length	5		
TR	3400		
TE	15		
TI	150		
Slice Thickness	5 mm		
Skip	0		
Matrix	512x160		
FOV	48x48		
No. of Excitations/ Sequence	1		
No. of Acquisitions	1		
Saturation	None		

Date:_____Signature (responsible MRI technician):_____

[redacted]

Response Criteria for NF-1 Associated PNs:

Response is assessed at the time that follow-up MRI scans are performed as outlined in Section7.1. For the purpose of determining the level of response, measurements from the follow-up scans are compared to the tumor size in the pretreatment MRI scan using 3D data analysis.

- Complete Response (CR): A complete resolution of the target plexiform neurofibroma for ≥ 4 weeks
- Partial Response (PR): A ≥20% reduction in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
- Stable Disease (SD): A <20% increase, and < 20% decrease in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
- Progressive Disease (PD): A ≥20% increase in the volume (by 3D-MRI) of the target plexiform neurofibroma compared to the pretreatment volume.
    - The appearance of new discrete subcutaneous neurofibromas does not qualify for disease progression.

Worsening of existing symptoms or the appearance of new symptoms that persist for more than 7 days and that are felt to be definitely related to the plexiform neurofibroma should be evaluated by repeating the MRI. Subjects should not be classified as having progressive disease solely on the basis of new or increased symptoms without discussing the case with the protocol Principal Investigator.

SECTION: Appendix 6: Response Criteria for PNs REVISED TEXT (Updated to reflect procedural changes)

Prior to starting treatment on this study all known measurable tumors should be imaged with MRI to obtain a baseline. Tumor spread in subjects with NF-1 can be very extensive, and may not allow for all lesions to be followed using 3D-MRI. The goal will therefore be to use 3D-MRI only to follow the inoperable PN (a maximum of three lesions), which will be defined as index lesion(s).

Pre-study radiographic evaluation:

1. Identify and select the inoperable PN (a maximum of three lesions) for 3-D MRI evaluation based on prior imaging studies. Should there be more than 3 inoperable PN, the three most clinically relevant PN will be followed by 3-D MRI analysis.
2. Perform 3-D MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols below.
3. In addition, if possible, perform MRI of all additional measurable PN.
4. Send baseline MRI ~~to address below~~ for central review prior to enrolment.

In Study Part B, central review of the MRI of the target PN is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis.

On study radiographic evaluation:

[redacted]

Unless clinically indicated otherwise obtain MRI of the index lesions only as outlined in the MRI acquisition protocol below prior to cycles 4, 8, 12, and then after every 6 cycles as long as the subject remains on study.

MRI protocols:

Depending on the location of the index lesions the Spine, Head/Neck or Trunk/Extremities protocols outlined ~~on the following~~ **in the SPM**~~pages~~ will be used.

Participating institutions may modify the MRI sequences to optimize differentiation of tumor and surrounding tissue. Modifications should be documented in the MRI protocols, and the same imaging protocol, and, if possible, the same MRI scanner should be used for all subsequent MRI studies. Every attempt should be made to image the entire progressive PN. All MRI studies requested per protocol will be submitted ~~to the NCI Pediatric Oncology Branch (POB)~~ within 2 weeks of acquisition for volume analysis **to the study central reader via the instructions provided in the SPM**. ~~The studies have to be sent on Compact Disk in uncompressed Digital Imaging and Communications in Medicine (DICOM) format. At the same time, a copy of the MRI protocol and the institutional radiology report will be sent to the NCI POB.~~

~~For technical support, please contact:~~

[redacted] ~~M.D. (phone~~ [redacted] ~~, e-mail:~~ [redacted]

~~Send MRI studies and protocols used to obtain studies and radiology reports to:~~

[redacted] ~~, M.D.~~

[redacted]

~~Phone:~~ [redacted] ~~, fax:~~ [redacted] ~~, e-mail:~~ [redacted]

All MRI data will be analyzed~~at the POB of the NCI~~. The MRI data from each scan will be processed to assess the volume of the index PN(s). Each subject's volumetric measurement obtained from the initial MRI will serve as the baseline against which to assess incremental changes in volume that occur during the subsequent intervals. The ~~NCI POB~~ **central reader** will inform participating investigators about the results of the MRI study by written report. MRI results will be transferred to GSK or GSK contracted third party imaging vendor.

~~MRI Protocol Spine STUDY ID NUMBER: _____~~

~~**Note:** Only the series outlined below are required for volumetric analysis of PNs and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.~~

[redacted]

Response Criteria for NF-1 Associated PNs [Dombi, 2013]**:**

Response is assessed at the time that follow-up MRI scans are performed as outlined in Section 7.1. For the purpose of determining the level of response, measurements from the follow-up scans are compared to the tumor size in the pretreatment MRI scan using 3D data analysis.

- Complete Response (CR): A complete resolution of the target plexiform neurofibroma for ≥ 4 weeks
- Partial Response (PR): A ≥20% reduction in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
- Stable Disease (SD): A <20% increase, and < 20% decrease in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
- Progressive Disease (PD): A ≥20% increase in the volume (by 3D-MRI) of the target plexiform neurofibroma compared to the pretreatment volume.
    - The appearance of new discrete subcutaneous neurofibromas does not qualify for disease progression.

Worsening of existing symptoms or the appearance of new symptoms that persist for more than 7 days and that are felt to be definitely related to the plexiform neurofibroma should be evaluated by repeating the MRI. Subjects should not be classified as having progressive disease solely on the basis of new or increased symptoms without discussing the case with the protocol Principal Investigator.

SECTION: APPENDIX 7 Definition of disease state, response criteria and response definition for LCH (NEW appendix, later Appendices renumbered)

Adapted from Histiocyte Society Evaluations and Treatment Guidelines, April 2009.

[redacted]

Definition of Disease State

NON ACTIVE DISEASE (NAD)	no evidence of disease	resolution of all signs or symptoms
ACTIVE DISEASE	regressive disease	regression of signs or symptoms, no new lesions*
	stable disease	persistence of signs of symptoms, no new lesions
	progressive disease	progression of signs or symptoms and/or appearance of new lesions**

*Plus partial or complete response by RECIST [Eisenhauer, 2009]; and/or pulmonary criteria if applicable

*/** Isolated pulmonary LCH: improvement in lung function is >10% increase in baseline FEV1 or DLCO at time of disease assessment. Disease progression is >15% decline from baseline FEV1 or DLCO or FVC OR progression of symptoms (dyspnea, cough, constitutional symptoms) that cannot be explained by diagnoses other than pulmonary LCH (infection, heart disease, and/or other clinical issues excluded by careful clinical evaluation and testing)

** Isolated bone disease: progression is defined as appearance of new bone lesions or lesions in other organs

Response Criteria

BETTER	Complete Resolution	NAD
	Regression	AD Better
INTERMEDIATE	Mixed	New lesions in one site, regression in another site
	Stable	Unchanged
WORSE	Progression	

[redacted]

Response Definition for Efficacy

	3 Month Assessment	6 Month Assessment (performance relative to 3 month assessment)
Response	NAD or AD Better	NAD or AD Better or Stable
	Mixed	NAD or AD Better
	Stable	NAD or AD Better
Failure	NAD or AD Better	Mixed
	NAD or AD Better	Progression
	Mixed or Stable [a]	Mixed or Stable [a] or Progression
	Progression	N/A

NAD = Non Active Disease

AD = Active Disease

Stable = Unchanged

Mixed = New lesions in one site, regression in another site

f. Subjects who are assessed only as stable at the 3 and 6 month assessment are not considered a treatment response; however, they may be considered for continued treatment

LCH Scoring System [Donadieu, 2004]

Variable	Modality	Score
Bone (a)	Pain	1
	No Pain	0
Bone (b)	Compressing other organs (orbit or spine)	2
	No compression	0
Fever (>38.5°C)	Yes	1
	No	0
Lung: iconography	Pneumothorax	2
	Interstitial lesion on chest x-ray or lung CT	1
	Normal chest x-ray or lung CT	0
Lung: function	Mechanical ventilation or PFT >50%	5
	Supplemental oxygen or PFT between 50 and 80%	2
	No dysfunction, no cyanosis, no supplemental oxygen	0
Skin: area	25%	2
	5-25%	1
	Below 5%	0
Soft tissue tumor (including CNS)	5 cm maximum diameter	2
	2-5 cm maximum diameter	1
	0-2 cm maximum diameter	0
Nodes (>2 cm)	Yes	1
	No	0
Liver	Below umbilicus	2
	Enlarged, above umbilicus	1
	Not enlarged	0

[redacted]

Variable	Modality	Score
Spleen	Below umbilicus	2
	Enlarged, above umbilicus	1
	Not enlarged	0
Liver (enzymes)	>10 ULN	2
	3-10 ULN	1
	<3 ULN	0
Liver (gamma GT)	>10 ULN	2
	3-10 ULN	1
	<3 ULN	0
Albumin	Perfusion required in past week	3
	No perfusion but <30 g/L	1
	>30 g/L	0
Platelet: requirements in past week	More than two transfusions	4
	1 or 2 transfusions	3
	Low platelet count, no transfusion	2
	Normal count	0
Red cells: requirements in past week	More than 2 U	4
	1 or 2 U	3
	Hgb below 10 g/dL, no transfusion	1
	No transfusion	0

[redacted]

AMENDMENT 3

Amendment 3

Where the Amendment Applies

Amendment 3 applies to all sites.

Summary of Amendment Changes with Rationale

This amendment was generated to expand the description of Part C to include the dabrafenib recommended phase II dose levels and rationale along with the observed safety in pediatric patients on dabrafenib monotherapy. Updated safety information from adult combination studies is included.

Title Page

Authors PREVIOUS TEXT

Author (s):

[redacted] [redacted] GSK Oncology Medicines Development

[redacted] [redacted] GSK Oncology Medicines Development

[redacted] GSK Oncology Precision Medicine and Diagnostics

Authors REVISED TEXT

[redacted] [redacted] Novartis Oncology Global Development
Novartis Oncology Global Development
Novartis Oncology Global Development
Novartis Oncology Global Development

[redacted]

PROTOCOL SYNOPSIS
PREVIOUS TEXT

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES	Primary Objective: • To determine the safe and tolerable trametinib dose(s) for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (trough concentration [Cτ]) to the recommended adult dose Secondary Objectives: • To characterize the pharmacokinetics of trametinib • To characterize the safety and tolerability of trametinib • To assess any preliminary anti-tumor activity of trametinib • To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach • To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination • To determine the acceptability and palatability of trametinib in pediatric subjects [redacted] Primary Endpoint(s): • Adverse Events (AEs); electrocardiograms (ECGs); echocardiograms (ECHOs); changes in laboratory values and vital signs. Steady state Cτ of trametinib Secondary Endpoint(s): • Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax) and half-life (t½) of trametinib, as appropriate

[redacted]

	• AEs; ECG; changes in laboratory values and vital signs • Tumor response as defined in Appendix 3 through Appendix 7. • CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates • Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and t½ of trametinib and dabrafenib when administered in combination Hypothesis: • Infants, children and adolescents will tolerate doses of trametinib alone or in combination with dabrafenib that achieve steady state trough concentrations associated with clinical benefit in adults.
STUDY DESIGN	This is a 3-part (Part A, Part B, Part C), Phase I/IIa, multi-center, open label, study in pediatric subjects with refractory or recurrent tumors. **Part A** will be a pharmacokinetically driven limited dose escalation in subjects and will include an expansion for safety, tolerability, and pharmacokinetics (PK) in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase. **Part B** will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of proto-oncogene RAS (Ras)/ mitogen-activated protein kinase (MAPK) activation in childhood solid tumors. Forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts. • Refractory or relapsed neuroblastoma • Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion • Neurofibromatosis Type -1 associated plexiform neurofibromas that are unresectable and medically significant. • BRAF V600 mutant tumors

	Part C is a limited dose escalation part of the study evaluating the combination of trametinib with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will enroll approximately 18 subjects and will not open to accrual until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib is established in Part A and review of the available safety and PK data of trametinib and dabrafenib monotherapy in children is completed. Part C will require an amendment to this study prior to enrollment to include updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously. Subjects may not enroll in more than one part of the study. Subjects will receive study treatment until disease progression, death or unacceptable toxicity. All parts of the study will use trametinib tablet strengths (0.125, 0.5, and 2 mg tablets) for children who are able to reliably swallow tablets. In addition, an oral solution formulation (0.05 mg/mL) is available. Doses will be calculated using body weight and prescribed using a dosing nomogram. Rules for dose modifications in response to toxicity are provided in the protocol. For Part C of the study dabrafenib capsules (10, 25, 50, 75 mg) or suspension (10 mg/ml) will be used.
INCLUSION/ EXCLUSION CRITERIA	**General Inclusion Criteria for All Parts** (for complete details and further eligibility criteria for specific parts please see full protocol): 1. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including pharmacokinetics sampling will be obtained according to institutional guidelines; 2. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form 3. Part C between 12 months and <18 years of age, inclusive; 4. Part A subjects < 2 years of age will not be include in the initial dose escalation 5. Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or must have a current

	disease for which there is no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life. 6. Prior therapy: The subject's disease (i.e. cancer, NF-1 with Plexiform Neurofibromas, or Langerhans Cell Histiocytosis [LCH]) must have relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. Subjects must have recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment. 7. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale [Yates, 1980]. 8. Females of child-bearing potential must be willing to practice acceptable methods of birth control. Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment; 9. Must have adequate organ function. 10. In France, subjects will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category. **General Exclusion Criteria for All Parts**: 1. Lactating or pregnant female. 2. History of another malignancy including resected non-melanomatous skin cancer. 3. Subjects with Neurofibromatosis Type-1 (NF-1) associated optic pathway tumors are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for Plexiform Neurofibroma or malignant solid tumor. 4. Subjects with a history of NF-1 related cerebral vascular anomaly (such as Moyamoya). 5. Subjects with NF-1 actively receiving therapy for the optic pathway tumor 6. Subjects with NF-1 and only Plexiform Neurofibroma (PN) lesions that cannot be evaluated by volumetric analysis.

	7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures. 8. Any prohibited medication(s) as described in Section 9.2. 9. Any medications for treatment of left ventricular systolic dysfunction 10. **Part B and Part C only**: Previous treatment with dabrafenib (cohort B4) trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted) 11. Administration of an investigational study treatment within 30 days preceding the first dose of study treatment(s) in this study. 12. Have a known hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment or excipients that contraindicate their participation. 13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or liver metastases). 14. History of hepatic sinusoid obstructive syndrome (Venoocculsive disease) within the prior 3 months. 15. History of heparin-induced thrombocytopenia. 16. History of interstitial lung disease or pneumonitis. 17. History of or current evidence of retinal vein occlusion (RVO) 18. For subjects with solid tumors that are not primary central nervous system (CNS) tumors or NF-1 associated plexiform neurofibromas, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression are excluded. 19. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. 20. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI

	CTCAE v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia. 21. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs. If clarification is needed as to whether a condition will significantly affect absorption of drugs, contact the GlaxoSmithKline (GSK) medical monitor for guidance to enrol the subject. 22. A history or evidence of cardiovascular risk (as detailed in protocol Section 5.2.2)

REVISED TEXT

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES	Primary Objective: • To determine the safe and tolerable trametinib dose(s) for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (trough concentration [Cτ]) to the recommended adult dose Secondary Objectives: • To characterize the pharmacokinetics of trametinib • To characterize the safety and tolerability of trametinib • To assess any preliminary anti-tumor activity of trametinib • To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach • To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination • **To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination** • **To determine the safe and tolerable dabrafenib dose(s) when administered in combination with the recommended trametinib dose for chronic continuous daily dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (trough concentration [Cτ]) to the recommended adult dose** • To determine the acceptability and palatability of trametinib in pediatric subjects

	[redacted]  Primary Endpoint(s): • Adverse Events (AEs); electrocardiograms (ECGs); echocardiograms (ECHOs); changes in laboratory values and vital signs. Steady state Cτ of trametinib Secondary Endpoint(s): • Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax) and half-life (t½) of trametinib, as appropriate • AEs; ECG; changes in laboratory values and vital signs • Tumor response as defined in Appendix 3 through Appendix 7. • CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates • Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and t½ of trametinib and dabrafenib when administered in combination Hypothesis: • Infants, children and adolescents will tolerate doses of trametinib alone or in combination with dabrafenib that achieve steady state trough concentrations associated with clinical benefit in adults.
STUDY DESIGN	This is a 3-part (Part A, Part B, Part C), Phase I/IIa, multi-center, open label, study in pediatric subjects with refractory or recurrent tumors. **Part A** will be a pharmacokinetically driven limited dose escalation in subjects and will include an expansion for safety, tolerability, and pharmacokinetics (PK) in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose

[redacted]

(RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase.

Part B will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of proto-oncogene RAS (Ras)/ mitogen-activated protein kinase (MAPK) activation in childhood solid tumors. **At least forty** subjects are planned for Part B, 10 subjects in each of 4 disease cohorts.

- Refractory or relapsed neuroblastoma
- Recurrent or unresectable low grade gliomas **associated** with BRAF tandem duplication with fusion, **or NF1 subjects with gliomas, not suitable for the NF1 with PN cohort**
- Neurofibromatosis Type -1 associated plexiform neurofibromas that are unresectable and medically significant.
- BRAF V600 mutant tumors

Part C is a limited dose escalation part of the study evaluating the combination of trametinib with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will enroll approximately 18 subjects **(including up to 6 adolescent subjects with BRAF V600 mutant metastatic melanoma)** and will not open to accrual until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib is established in Part A and review of the available safety and PK data of trametinib and dabrafenib monotherapy in children is completed. ~~Part C will require an amendment to this study prior to enrollment to include~~. **Amendment 3 provides the** updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously. **Patients who have had prior dabrafenib therapy may enroll in part C if they have had prior benefit to dabrafenib monotherapy, as determined by the investigator**.

Subjects may not enroll in more than one part of the study. Subjects will receive study treatment until disease progression, death or unacceptable toxicity.

All parts of the study will use trametinib tablet strengths (0.125, 0.5, and 2 mg tablets) for children who are able to reliably swallow tablets.

[redacted]

	In addition, an oral solution formulation (0.05 mg/mL) is available. Doses will be calculated using body weight and prescribed using a dosing nomogram. Rules for dose modifications in response to toxicity are provided in the protocol. For Part C of the study dabrafenib capsules (~~10, 25~~, 50, 75 mg) or suspension (10 mg/ml) will be used.
INCLUSION/ EXCLUSION CRITERIA	**General Inclusion Criteria for All Parts** (for complete details and further eligibility criteria for specific parts please see full protocol): 11. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including pharmacokinetics sampling will be obtained according to institutional guidelines; 12. Male or female between one month and < 18 years of age (inclusive) at the time of signing the informed consent form 13. Part C between 12 months and <18 years of age, inclusive; 14. Part A subjects < 2 years of age will not be ~~include~~**included** in the initial dose escalation 15. Must have a disease that is relapsed/refractory to all potentially curative standard treatment regimens or must have a current disease for which there is no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life. 16. Prior therapy: The subject's disease (i.e. cancer, NF-1 with Plexiform Neurofibromas, or Langerhans Cell Histiocytosis [LCH]) must have relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. Subjects must have recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment. 17. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale [Yates, 1980]. 18. Females of child-bearing potential must be willing to practice acceptable methods of birth control. Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment;

[redacted]

	19. Must have adequate **multi** organ function. 20. In France, subjects will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category. **General Exclusion Criteria for All Parts**: 23. Lactating or pregnant female. 24. History of another malignancy including resected non-melanomatous skin cancer. 25. Subjects with Neurofibromatosis Type-1 (NF-1) associated optic pathway tumors are excluded if they are actively receiving therapy for the optic pathway tumor or do not meet criteria for Plexiform Neurofibroma or malignant solid tumor. 26. Subjects with a history of NF-1 related cerebral vascular anomaly (such as Moyamoya). 27. Subjects with NF-1 actively receiving therapy for the optic pathway tumor 28. Subjects with NF-1 and only Plexiform Neurofibroma (PN) lesions that cannot be evaluated by volumetric analysis. 29. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures. 30. Any prohibited medication(s) as described in Section 9.2. 31. Any medications for treatment of left ventricular systolic dysfunction 32. **Part B cohorts 1, 2 and** ~~Part C only~~**3**: Previous treatment with dabrafenib~~(cohort B4)~~ trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted). **Patients who have had prior dabrafenib therapy may enroll into cohort B4. Patients who have had prior dabrafenib therapy and had benefit from that therapy as determined by the investigator, are allowed in Part C)** 33. Administration of an investigational study treatment within 30 days preceding the first dose of study treatment(s) in this study.

	34. Have a known hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment or excipients that contraindicate their participation. 35. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or liver metastases). 36. History of hepatic sinusoid obstructive syndrome (Venoocculsive disease) within the prior 3 months. 37. History of heparin-induced thrombocytopenia. 38. History of interstitial lung disease or pneumonitis. 39. History of or current evidence of retinal vein occlusion (RVO) 40. For subjects with solid tumors that are not primary central nervous system (CNS) tumors or NF-1 associated plexiform neurofibromas, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression are excluded. 41. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. 42. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, except alopecia. 43. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs. If clarification is needed as to whether a condition will significantly affect absorption of drugs, contact the ~~GlaxoSmithKline (GSK)~~ medical monitor for guidance to enrol the subject. 44. A history or evidence of cardiovascular risk (as detailed in protocol Section 5.2.2)

Section 1.2.1 Pharmacokinetics of Trametinib in Humans
Additional new text added

[redacted]

In the adult population PK model, trametinib CL/F was estimated as 5.07 L/hr and was dependent on gender and weight. The typical CL/F of trametinib in male subjects was 24% higher than that observed in female subjects. The effect of body weight at the minimum and maximum weight observed was within 16% of the typical CL/F value. Although smaller female subjects will tend to have higher exposure than heavier male subjects, no dosage adjustment is warranted in this population.

Section 1.2.2 Clinical Safety and Efficacy of Trametinib

PREVIOUS TEXT

Based on the adverse events (AEs) observed in the dose escalation phase of the early phase trials, the Maximum Tolerated Dose (MTD) of trametinib was 3 mg once daily, and the recommended Phase II dose of trametinib was 2 mg once daily. Five monotherapy studies have administered trametinib 2 mg daily to 499 subjects. Adverse events have been reported by 50% to 100% of subjects, with the most common being rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. In these studies up to 32% of subjects reported serious AEs (SAEs), and up to 13% permanently discontinued study treatment due to AEs.

Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (i.e., were observed with other MEK inhibitors) or potentially life-threatening. Please refer to the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] for the most current safety information and additional details.

REVISED TEXT

Based on the adverse events (AEs) observed in the dose escalation phase of the early phase trials **in adults**, the Maximum Tolerated Dose (MTD) of trametinib was 3 mg once daily, and the recommended Phase II dose of trametinib was 2 mg once daily. Five monotherapy studies have administered trametinib 2 mg daily to 499 subjects. Adverse events have been reported by 50% to 100% of subjects, with the most common being rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. In these studies up to 32% of subjects reported serious AEs (SAEs), and up to 13% permanently discontinued study treatment due to AEs.

Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs,**hypertension, bleeding events, edema** and pneumonitis are considered AEs of special interest **for trametinib** because they are either known class effects (i.e., were observed with other MEK inhibitors) or potentially life-threatening. Please refer to the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] for the most current safety information and additional details.

1.2.4 Trametinib Pediatric Experience

PREVIOUS TEXT

[redacted]

As of September 2013, no subject under the age of 18 has received trametinib monotherapy in a GSK sponsored clinical trial.

REVISED TEXT

~~As of September 2013~~, **prior to the initiation of this trial**, no subject under the age of 18 has received trametinib monotherapy in a GSK sponsored clinical trial.

1.3.1 Pharmacokinetics of Dabrafenib in Humans

New text added

In the adult population PK model for dabrafenib, body weight also impacted oral volume of distribution (Vc/F) and distributional clearance (Q/F). The difference between female and male subjects (9%) and between subjects with low (50 kg) or high (140 kg) body weight relative to a typical body weight of 80 kg (<20%) was not considered clinically relevant.

1.3.2 Clinical Safety and Efficacy of Dabrafenib

PREVIOUS TEXT

As of 25 June 2012, 586 subjects had received at least one dose of dabrafenib 150 mg BID. Integrated safety data from these subjects showed that 97% had experienced AEs, the most common (≥20%) being hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, alopecia, skin papilloma, and rash. A total of 174 (30%) subjects experienced any serious adverse event (SAE), and 114 (19%) subjects had treatment-related SAEs. The proportion of subjects who experienced AEs leading to discontinuation of study treatment was low (3%). [GlaxoSmithKline Document Number CM2010/00010/03]

In the pivotal Phase III study BRF113683 (BREAK-3), dabrafenib was associated with a 70% reduction in the risk of progression or death compared with dacarbazine with a hazard ratio (HR) of 0.30 (95% CI: 0.18, 0.51; p<0.0001) in subjects with BRAF V600E mutation positive melanoma and no brain metastases [Hauschild, 2012]. Dabrafenib provided a clear and meaningful benefit in subjects with BRAF V600E mutation-positive melanoma with brain metastases as demonstrated by overall intracranial response rate (OIRR) over 30% and median OS exceeding 7 months in study BRF113929 (BREAK-MB). Subjects with BRAF V600E mutation positive melanoma also benefit from dabrafenib treatment, with a confirmed response rate of 13% and the median duration of response of 5.3 months (BRF113710, BREAK-2).

Dabrafenib (TAFINLAR™) was approved by the FDA on 29 May 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with the BRAF V600E mutation.

Combination of Trametinib and Dabrafenib

As of ~~25~~**22** June ~~2012, 586 subjects had~~ **2015, approximately 2,000 patients with various cancers have** received ~~at least one dose of~~ dabrafenib ~~150 mg BID~~ **for up to 6 years and approximately 3,200 subjects have received trametinib in combination with dabrafenib for up to 5 years in GSK-sponsored ongoing or completed studies and compassionate care programs. Cumulative postmarketing exposure to dabrafenib through 31 March 2015 is estimated to be 3,546.16 patient-years.**

[redacted]

Integrated safety data from ~~these~~subjects **(N=586) receiving 150 mg BID** showed that 97% had experienced AEs, the most common (≥20%) being hyperkeratosis **(32%),** headache **(30%),** pyrexia **(30%),** arthralgia **(29%),** fatigue **(26%),** nausea **(25%),** alopecia **(23%),** skin papilloma **(21%),** and rash **(20%).** A total of 174 (30%) subjects experienced any serious adverse event (SAE), and 114 (19%) subjects had treatment-related SAEs. The proportion of subjects who experienced AEs leading to discontinuation of study treatment was low (3%). [GlaxoSmithKline Document Number CM2010/00010/03]

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Dabrafenib (TAFINLAR™) was **first** approved by the FDA on 29 May 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with the BRAF V600E mutation.

1.3.4 Dabrafenib Pediatric Experience

New section added 1.3.4.1

1.3.4.1 Background data from part 1 of study BRF116013

Twenty seven subjects were enrolled, with a median age of 9.0 years, ranging from 11 months -17 years old; 56% were male. Most subjects (89%) were caucasian. Most subjects (21 subjects, 78%) had measurable disease at baseline per the investigator, and all were previously treated for this tumor. Dose escalation was pharmacokinetically driven, to achieve exposures (measured as AUC 0-12) in pediatric patients that is similar to that seen in adults treated at recommended doses. Note that an MTD has not been determined in adults.

Similar to the experience in adults, a maximally tolerated dose was not identified in this study. Based on the doses in part 1 that achieved target exposures (AUCs 0-12 hours > 4000 ng*hr/mL, parent molecule) there are currently separate phase II dose recommendations for those under 12 years of age (5.25mg/kg/day), and those 12 and older (4.5mg/kg/day). The doses will be further defined based on modelling and simulation of all available data at the time of finalizing the protocol.

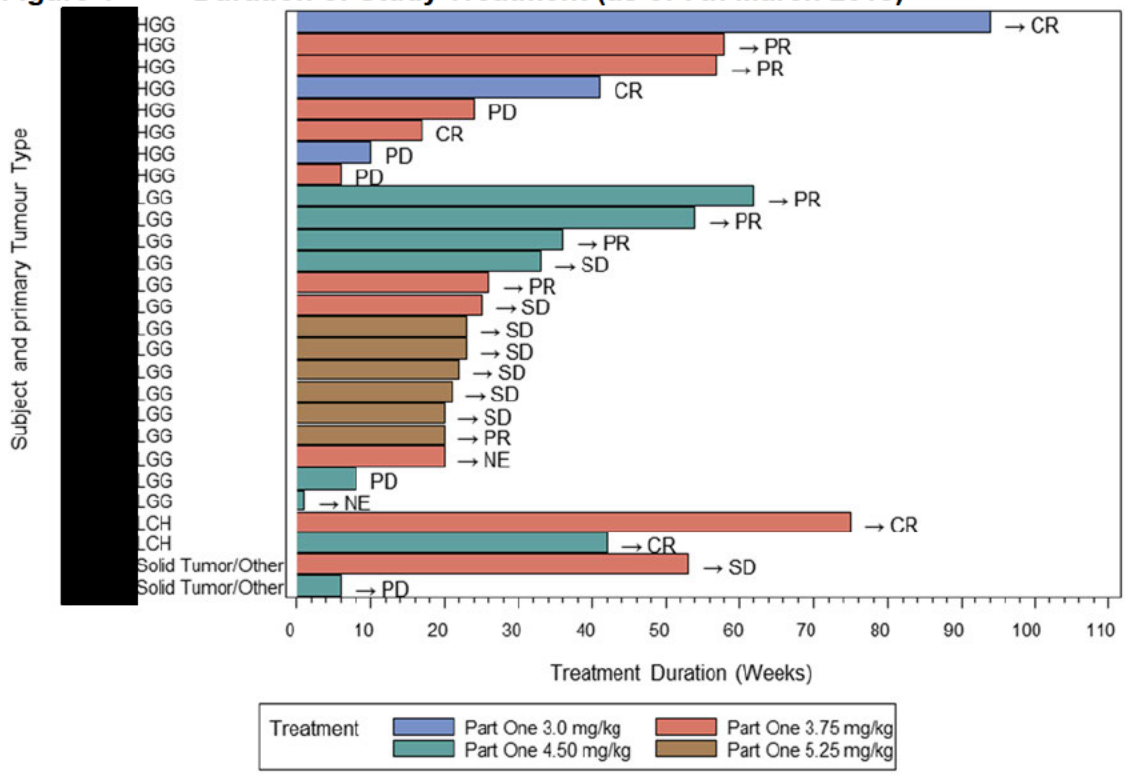
An interim data cut from this ongoing study was made 7 March 2015, and resultant tables and listing prepared for the 27 patients enrolled into part 1. Twenty-one of these 27 patients were continuing to receive dabrafenib at the time of the data cut off.

Table 1 Patient Numbers Enrolled at Each Dose: Extent of exposure

Dose	Numbers enrolled
[redacted]	

3 mg/kg	3
3.75 mg/kg	10
4.5 mg/kg	8
5.25 mg/kg	6
Total	27

Figure 1 Duration of Study Treatment (as of 7th March 2015)



→Indicate ongoing subjects.

Treatment duration counts time difference between first dosing date and dosing end date without accounting for dose interruptions.

Solid Tumor/Other : [redacted] - Thyroid; [redacted] - Neuroblastoma:

Confirmed Best Response: CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease,

NE = Not Evaluable, NA = Not Applicable.

HGG = High Grade Glioma , LGG = Low Grade Glioma ,LCH = Langerhans cell histiocytosis.

gullapv :/projects/gsk207418/stats/primary/prog/figures/f_study_drug.SAS 30APR2014 16:44:11.

Efficacy Results

HGG

Eight pediatric patients with relapsed, refractory or progressive HGG with BRAFV600 mutations were enrolled into the dose finding portion of BRF116013. Of these eight

[redacted]

patients, 3 had CRs, 2 had PRs and 4 of the eight patients were on study treatment for 9 months or more. This is shown graphically in Figure 1 above.

These results compare very favorably to the historical data where paediatric patients with relapsed, refractory or progressive HGG are expected to have a less than 10% RR and a median survival of 5 months, using conventional therapy.

LGG

Fifteen pediatric patients with relapsed, refractory or progressive LGG with BRAFV600 mutations were enrolled into the dose finding portion of BRF116013. Of these 15 patients, 5 had partial responses (33%), 7 had stable disease (47%), one had progressive disease and two were not yet evaluable for response.

LCH

Two pediatric patients with previously treated severe LCH and BRAFV600 mutations were enrolled into BRF116013. Both achieved complete responses as assessed by the investigator.

Other

Two patients with other solid tumors and BRAFV600 mutations were enrolled; neither had a response to dabrafenib therapy.

Safety Results

Adverse events

All subjects reported at least one AE. The most common (>30%) AEs were pyrexia, fatigue, vomiting, headache, and nausea. There were nine subjects (33%) with AEs of maximal grade 3, and 2 subjects with maximal grade 4 (intracranial hemorrhage, hypotension). No grade 3 event occurred in >2 subjects. The most common body system impacted by AEs was skin (93% all grades, including 7% G2 and 7% G3 with multiple terms for rash most common), general disorders (81% all grades, including 33% G2, with pyrexia and fatigue most common), and metabolic (74% all grades, including 15% G2 and 11% G3, various electrolyte abnormalities).

Serious Adverse Events

Nine subjects (33%) reported 22 SAEs during this time period, all resolved. Three subjects had related SAEs, one with rash, one with arthralgia, and one with pyrexia followed by DIC, hypotension, and increased INR. All three remain on study as of July, 2015.

Dose limiting toxicity

[redacted]

There was one subject with low grade glioma ([redacted] years old at 4.5 mg/kg/d dose) who experienced a DLT of Grade 3 maculopapular rash with onset on day 1 of dosing. After protocol specified dose interruption, the subject was able to resume treatment at 3.75 mg/kg/day and continues on treatment beyond one year, with tolerable skin toxicity of grade <=2.

Dose modifications

Eleven of the 27 subjects had at least one dose interruption while on study, mostly for rash and/or pyrexia, and followed protocol guidelines. Two subjects required dose reductions for toxicity, per protocol.

Discontinuations for toxicity

There were no subjects prematurely withdrawn from study for toxicity in part 1. However, through 7 March 2015, one subject in part 2 of the study was withdrawn for painful rash related to study drug, noted in the first week of study start, with recurrence upon re-challenge. The patient was aged [redacted] years, with a primary diagnosis of grade I Pilocytic Astrocytoma. An AE of grade 2 Erythema Nodosum resulted in study withdrawal.

Deaths

There were no deaths on study treatment.

Laboratory data

Review of laboratory data reveals no apparent safety signals. In most cases, it was possible to grade the laboratory data in this interim data analysis using local normal ranges. There were two events of G3 elevated hemoglobin and one event of G3 hypokalemia during viral upper respiratory tract infection. There was one patient with G2 hypokalemia and all other graded laboratory values were G1 or less.

Safety Conclusions

Based on preliminary data, the toxicity profile observed in these initial 27 paediatric subjects is generally similar to that observed in the adult subject experience. Both populations experienced frequent rash, pyrexia, fatigue, arthralgia and headache (m2.7.4 Section 2.1.1, common adverse events). The frequency of rash and similar adverse events may be higher in this paediatric population than in adults. There were two subjects (7%) with grade 3 Rash in the paediatric population while there is less than 1% rate in adults. Rash management guidelines suggested in the protocol were followed for subjects with rash as they remained on therapy. In contrast, there were no cases of cutaneous SCC observed in these paediatric subjects and fewer paediatric subjects have discontinued

[redacted]

treatment due to toxicity (0 of 27 in part 1) than adult subjects. The most common AEs were in the Skin body system. There was one dose limiting toxicity, a G3 Rash, although higher doses were later shown to be tolerable in this age group. There were no discontinuations due to toxicity. Adequate exposures were obtained without reaching a maximally tolerated dose.

Overall Conclusion

Overall, these results suggest that dabrafenib monotherapy represents a potentially favorable benefit risk to pediatric patients < 18 years old with BRAFV600 mutant relapsed refractory or progressive gliomas including HGG.

1.4 Combination of Trametinib and Dabrafenib

PREVIOUS TEXT

Please refer to the most current version of the GSK1120212+GSK2118436 Investigator Brochure for the most current safety information and additional details [GlaxoSmithKline Document Number 2011N126811/01].

As of 31 May 2012, 365 subjects with BRAF V600 mutation positive melanoma had received various doses of trametinib and dabrafenib in combination therapy, with over 200 of these subjects receiving the recommended concomitant monotherapy doses of dabrafenib 150 mg twice daily and trametinib 2 mg once daily.

In terms of drug-drug interaction, following repeat dosing (Day 21), administration of dabrafenib 150 mg BID in combination with trametinib had little impact on dabrafenib Cmax and AUC(0-τ) with least squares (LS) mean ratios (90% confidence interval [CI]) of dabrafenib and trametinib in combination relative to dabrafenib alone of 1.16 (0.80, 1.68) and 1.23 (0.89, 1.69), respectively. Trametinib PK parameters were similar regardless of whether trametinib was administered with dabrafenib 75 mg BID or 150 mg BID.

The 55 subjects who received dabrafenib 150 mg BID and trametinib 2 mg once daily in Study BRF113220 (Part C 150/2 group) represent the population with the longest exposure (mean of approximately 11 months). All subjects in this group had at least 1 AE and at least 1 drug-related AE, with the most commonly reported AEs (≥40%) being pyrexia, chills, fatigue, nausea, and vomiting. These AEs all occurred at frequencies that were higher than observed with either dabrafenib or trametinib monotherapy. The safety profile of the combination therapy was primarily impacted by the emergence of a higher rate of pyrexia. While fatigue and nausea occurred at a higher frequency relative to dabrafenib monotherapy, lower incidences of hyperkeratosis, alopecia, and skin papilloma were 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.

The incidence of SAEs, including drug-related SAEs, was up to 3-fold higher in the Part C 150/2 group (SAE: 62%) compared with either trametinib monotherapy (22%) or dabrafenib monotherapy (30%). The primary reason for this imbalance was due to the higher incidence of reported pyrexia. The percentage of subjects with AEs leading to permanent

[redacted]

discontinuation of study treatment was similar between the Part C 150/2 group (9%) and trametinib monotherapy (10%), but higher than dabrafenib monotherapy (3%).

As reported in Flaherty, 2012b, progression free survival was significantly improved in subject receiving the combination of dabrafenib 150 mg twice daily plus trametinib 2 mg daily compared to dabrafenib monotherapy (9.4 months vs 5.8 months P <0.001).

REVISED TEXT

Please refer to the most current version of the ~~GSK1120212+~~GSK2118436 Investigator Brochure for the most current safety information and additional details [GlaxoSmithKline Document Number 2011N126811/01].

~~As of 31 May 2012, 365 subjects with BRAF V600 mutation positive melanoma had received various doses of trametinib and dabrafenib in combination therapy, with over 200 of these subjects receiving the recommended concomitant monotherapy doses of dabrafenib 150 mg twice daily and trametinib 2 mg once daily.~~

~~In terms of drug-drug interaction, following repeat dosing (Day 21), administration of~~ **Data summarizing the clinical safety profile for** dabrafenib 150 mg BID in combination with ~~trametinib had little impact on dabrafenib Cmax and AUC(0-τ) with least squares (LS) mean ratios (90% confidence interval [CI]) of dabrafenib and trametinib in combination relative to dabrafenib alone of 1.16 (0.80, 1.68) and 1.23 (0.89, 1.69), respectively. Trametinib PK parameters were similar regardless of whether trametinib was administered with dabrafenib 75 mg~~ BID **2 mg QD in adult patients with BRAF V600 mutation-positive unresectable** ~~or 150 mg BID~~ **metastatic melanoma were pooled from two large randomized Phase III studies (N=559).** The ~~55 subjects who received dabrafenib 150 mg BID and trametinib 2 mg once daily in~~ **Phase III data are supported by data from the Phase II** Study BRF113220 Part C (150/2 **combination therapy** group ~~represent the population with the longest exposure (mean of approximately 11 months). All subjects in this group had at least 1 AE and at least 1 drug-related AE, with the most commonly reported AEs (≥40%) being pyrexia, chills, fatigue, nausea, and vomiting. These AEs all occurred at frequencies that were higher than observed with either dabrafenib or trametinib monotherapy.~~ **n=55) (m5.3.5.3 ISS Section 2.2), providing a total of over 600 subjects on randomized combination treatment.** The safety profile of the combination ~~therapy was primarily impacted by the emergence of a higher rate of pyrexia. While fatigue and nausea occurred at a higher frequency relative to dabrafenib monotherapy, lower incidences of hyperkeratosis, alopecia, and skin papilloma were 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.~~

of dabrafenib and trametinib generally reflect AEs of the individual agents. The ~~incidence of SAEs~~ **AE profile for combination therapy in both Phase III studies**, including ~~drug-related SAEs, was up to 3-fold higher in the Part C 150/2 group (SAE: 62%) compared with either trametinib monotherapy (22%) or dabrafenib monotherapy (30%). The primary reason for this imbalance was due to the higher incidence of reported pyrexia. The percentage of subjects with~~ **SAEs and** AEs leading to ~~permanent discontinuation of study treatment was similar between the Part C 150/2 group (9%) and trametinib monotherapy (10%), but higher than dabrafenib monotherapy (3%).~~ **dose modifications, were similar, indicating that the pooled data is a reliable representation of the combination therapy safety profile. The**

[redacted]

incidence of discontinuations and temporary dose modifications to manage AEs was higher for subjects on the combination therapy (discontinuations, 12%; dose reductions, 31%; dose interruptions, 55%) compared to dabrafenib monotherapy (discontinuations, 7%; dose reductions, 14%; dose interruptions, 37%) but similar to vemurafenib (discontinuations, 12%; dose reductions, 39%; dose interruptions, 56%). The intended dosing in subjects receiving combination therapy was not compromised.

~~As~~ **The most common SAE** reported ~~in, 2012b, progression free survival~~ **for combination therapy** was ~~significantly improved~~ **pyrexia, followed by ejection fraction decrease and chills. Discontinuations due to pyrexia and ejection fraction decrease each occurred in 3% of subjects** in ~~subject receiving~~ the combination ~~of dabrafenib 150 mg twice daily plus trametinib 2 mg daily~~ **therapy group.**

There were 8 fatal AEs reported for combination therapy; 6 of the 8 fatal SAEs were intracranial hemorrhages. The presence of various confounding factors in 5 of the 6 subjects with intracranial hemorrhage makes the evaluation of causality difficult; contribution of the combination therapy cannot be ruled out.

The rate of permanent discontinuation due to AEs for combination therapy was 12%. Dose reductions due to AEs were required in approximately one-third of subjects receiving combination therapy (31%). Dose interruptions due to AEs were required in more than one-half of subjects receiving combination therapy (55%). The most frequently occurring AEs requiring dose modifications were those where management guidance was provided in the protocols. AEs of special interest were identified based on the clinical significance, frequency and the potential association with the mode of action of BRAF and MEK inhibitors.

Pyrexia occurred at increased frequency and severity for combination therapy subjects as compared to dabrafenib **either** monotherapy. **Approximately 60% of the dose interruptions and 50% of the dose reductions in the combination therapy group were due to AEs of pyrexia. With appropriate management and dose modifications, most patients were able to continue on treatment.**

Bleeding events occurred at a similar frequency on combination therapy compared to dabrafenib monotherapy, and at a higher frequency compared to vemurafenib monotherapy. The majority of bleeding events for all treatments were Grade 1, and resolved without dose modification. There were 6 fatal intracranial hemorrhages for combination treatment. Bleeding in other critical sites (e.g., gastrointestinal, pulmonary, genitourinary) have also occurred, none of which were fatal.

Ejection fraction decreased occurred in 7% of subjects for combination therapy and the majority of the LVEF decreases that met interruption criteria were asymptomatic and resolved. Most subjects who were re-challenged were able to continue on treatment without further dose modification. These findings suggest that by regular, longitudinal monitoring with appropriate dose modification, more severe sequelae may be prevented.

Hyperproliferative skin lesions, including keratoacanthoma and cuSCC, occurred at a reduced frequency and with a prolonged latency in subjects receiving this combination regimen as compared to BRAF inhibitors as

[redacted]

monotherapy; substantiating the non-clinical hypothesis that addition of trametinib abrogates an important safety concern resulting from the paradoxical activation of the MAP kinase pathway exerted by BRAF-inhibitors.

Other treatment-emergent malignancies (for example pancreatic and colorectal) were reported at rates of 1% for combination treatment, which is not higher than what would be expected in the population, and comparable to that observed with monotherapy.

Other adverse events of special interest such as renal insufficiency and pancreatitis for dabrafenib, and skin-related toxicities, ocular events, pneumonitis, and diarrhea for trametinib, appeared at a frequency and/or severity consistent with the known AE profiles of either dabrafenib or trametinib monotherapy.

The safety profile for dabrafenib + trametinib combination therapy in adult subjects with unresectable/metastatic melanoma has been established and is well-characterized with consistent results across two randomized Phase III studies, with 33% of subjects receiving >12 months ~~vs 5.8~~ **of combination treatment. There were no new or unexpected safety concerns compared to those observed in the Study BRF113220 Part C combination group. In addition, no new or unexpected safety concerns have been identified for subjects on combination treatment in studies with prolonged additional follow-up (an additional 17 months for MEK115306; an additional 20 months for BRF113220 Part C [m5.3.5.3 ISS Section 2.2]). The safety profile of the combination generally reflects the safety profiles of the individual agents.**

The combination regimen of dabrafenib at the recommended dose of 150 mg BID and trametinib at the recommended dose of 2 mg QD has an acceptable safety profile in adult patients with unresectable or metastatic BRAF V600 mutation positive melanoma, with toxicities that are manageable with appropriate intervention. Administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib relative to administration of either compound alone.

There is no pediatric experience with the combination of dabrafenib and trametinib. In adults, data from phase I/II and phase III studies of the combination of these two agents demonstrates that both agents can be delivered together at their full recommended monotherapy doses, and that generally the observed AE profile represents the profiles of each individual agent. Some events were higher in the combination arms than in dabrafenib alone arms, including pyrexia, diarrhea, chills, vomiting and hypertension. Some events were lower in the combination arms than in the dabrafenib arms, including cuSCC alopecia, hyperkeratosis, PPES and skin papilloma. Bleeding events overall were similar in dabrafenib monotherapy and combination arms, although there were 6 fatal intracranial hemorrhage events out of 559 adult subjects treated in the combination therapy arms versus none in the 211 adult subjects on dabrafenib monotherapy. These events of intracranial hemorrhage were generally confounded and were considered not related to treatment by the treating physicians but were more frequent in the combination therapy arms.

[redacted]

The combination therapy in the pediatric population may result in a higher frequency and severity of pyrexia as compared to dabrafenib monotherapy, including pyrexia requiring dose interruption and the use of antipyretics, as well as increased rates of chills, diarrhea, vomiting, and edema peripheral. The combination may result in a lower rate of hyperkeratosis, skin papilloma, alopecia, palmar plantar erythrodysesthesia syndrome, and palmoplantar keratoderma as compared to dabrafenib monotherapy.

The efficacy of the combination of dabrafenib plus trametinib in the treatment of adults with BRAFV600 mutant advanced melanoma has been shown to be superior to that of dabrafenib alone. Similarly, the combination of dabrafenib and trametinib appears superior to that of dabrafenib alone in the treatment of adult subjects with BRAFV600 mutant NSCLC. Current clinical trial data on dabrafenib monotherapy in the treatment of pediatric subjects with BRAFV600 mutant solid tumors suggests clinically relevant efficacy that compares favorably with the current standard of care available for the various diseases that have been studied. Nonetheless, there may be an opportunity for further improvement in efficacy with combination therapy, perhaps manifest as higher response rates, and/or responses of longer duration.

1.5 Rationale for BRAF and MEK inhibitors in Pediatric Cancers

PREVIOUS TEXT

Given the central role of MAPK signaling in cell proliferation, growth, and adhesion, and available evidence of enhanced MAPK activity in many human cancers, it is hypothesized that the MEK inhibitor trametinib may confer beneficial effects against the pediatric cancers including:

Relapsed or refractory neuroblastoma

Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion

Neurofibromatosis (NF)-related PNs.

BRAF V600 mutant tumors

The safety and activity of the combination of dabrafenib with trametinib in adults with BRAF V600 mutation positive melanoma has been demonstrated. Once the doses of dabrafenib and trametinib monotherapy are determined in children and adolescents, a treatment arm to evaluate the safety of dabrafenib in combination with trametinib in children and adolescents will be opened.

REVISED TEXT

Given the central role of MAPK signaling in cell proliferation, growth, and adhesion, and available evidence of enhanced MAPK activity in many human cancers, it is hypothesized that the MEK inhibitor trametinib may confer beneficial effects against the pediatric cancers including:

Relapsed or refractory neuroblastoma

Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion

[redacted]

Neurofibromatosis (NF)-related PNs.

BRAF V600 mutant tumors

Langerhans cell histiocytosis with MAP2K1 mutation

The safety and activity of the combination of dabrafenib with trametinib in adults with BRAF V600 mutation positive melanoma has been demonstrated. Once the doses of dabrafenib and trametinib monotherapy are determined in children and adolescents, a treatment arm to evaluate the safety of dabrafenib in combination with trametinib in children and adolescents will be opened.

1.7.2 Predicted Toxicities for Combination of Trametinib and Dabrafenib PREVIOUS TEXT

The assessment of the risk for the combination of trametinib and dabrafenib, and suggestions for management of risk, are based on clinical data from the concluded and ongoing combination studies in adults. Additional information may be found in the IB for trametinib and dabrafenib [GlaxoSmithKline Document Number 2011N126811/01].

Pyrexia: Pyrexia was reported in clinical trials with dabrafenib monotherapy and in combination with trametinib. In dabrafenib monotherapy clinical studies, pyrexia was one of the most frequently occurring AEs in up to 27% of subjects across all dabrafenib studies. Most of the pyrexia events (64%) were considered to be related to study treatment. The incidence and severity of pyrexia are increased when dabrafenib is used in combination with trametinib. In patients who received the combination dose of dabrafenib 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About half of the patients who experienced pyrexia had a single event. Pyrexia may be accompanied by severe rigors, dehydration and hypotension which in some cases can lead to acute renal insufficiency.

Guidelines for the management of pyrexia will be provided in the amendment to open Part C of the study.

Dermatological Effects

Cutaneous Squamous cell carcinoma (cuSCC): In vitro experiments have demonstrated a paradoxical activation of MAP-kinase signaling in keratinocytes and potentially other cells harboring a wild-type BRAF kinase but a mutated RAS kinase upon exposure to a BRAF inhibitor. This paradoxical MAP-kinase pathway activation is potentially associated with a higher risk for the development of squamous cell carcinoma induction.

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with dabrafenib in combination with trametinib. In patients who received the combination dose of dabrafenib in combination with trametinib, cutaneous SCC (including keratoacanthoma [KA]) occurred in a lower percentage of subjects and events occurred later than with dabrafenib monotherapy, with the median time to onset of 22 weeks. All patients on combination therapy who developed cuSCC continued on dabrafenib treatment without dose modification. Skin examination should be performed prior to initiation of dabrafenib and during treatment with dabrafenib, every 2 months throughout therapy. An additional examination should be

considered 2 months after discontinuation of dabrafenib. Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new skin lesions develop.

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

Rash: Skin-related toxicities, primarily rash (maculopapular type rash with dabrafenib and acneiform-type rash with trametinib) have been reported with both trametinib and dabrafenib monotherapies. The incidence of skin-related events reported with the combination regimen appears to be lower than what has been observed following trametinib monotherapy. Rash management guidelines are provided in Section 3.13.1.

Hemorrhage: Major hemorrhagic events can occur in patients receiving dabrafenib in combination with trametinib. Monitor for signs and symptoms of bleeding.

Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving dabrafenib in combination with trametinib.

Interstitial lung disease (ILD)/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 if clinically indicated.

Pancreatitis – Pancreatitis has been observed in subjects receiving dabrafenib. Subjects will be monitored for abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis.

Hyperglycemia: Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Serum glucose levels will be monitored as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia.

Hepatic Events:

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib.

Ocular effects: Both trametinib and dabrafenib have been associated with ocular toxicities which appear to be class effects, including papilledema, RPED, and RVO, uveitis and iritis associated with trametinib and dabrafenib. Please refer to Section 1.7.1 and Section 3.13.3.

Decreased LVEF: Left ventricular dysfunction was reported with trametinib as well as with other MEK inhibitors in clinical development. Please refer to Section 1.7.1 and Section 3.11.3.1.

Non-cutaneous secondary/recurrent malignancy: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling in BRAF wild type cells with RAS mutations which are exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have

[redacted]

been seen with BRAF inhibitors including dabrafenib, and with dabrafenib/trametinib combination therapy. Patients should be monitored as clinically appropriate.

Reproductive Effects: Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals given dabrafenib. In repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Male subjects should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. In combined female fertility, early embryonic and embryofetal development studies in rats, numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects were seen at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC). There are no adequate and well-controlled studies of dabrafenib in pregnant women.

REVISED TEXT

The assessment of the risk for the combination of trametinib and dabrafenib, and suggestions for management of risk, are based on clinical data from the concluded and ongoing combination studies in adults. Additional information may be found in the IB for trametinib and dabrafenib [GlaxoSmithKline Document Number 2011N126811/01].

Pyrexia: Pyrexia was reported in clinical trials with dabrafenib monotherapy and in combination with trametinib. In dabrafenib monotherapy clinical studies, pyrexia was one of the most frequently occurring AEs in up to 27% of subjects across all dabrafenib studies. Most of the pyrexia events (64%) were considered to be related to study treatment. The incidence and severity of pyrexia are increased when dabrafenib is used in combination with trametinib. In patients who received the combination dose of dabrafenib 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About ~~half~~ **one-third** of the patients **receiving combination therapy** who experienced pyrexia had ~~a single event~~ **3 or more events**. Pyrexia may be accompanied by severe rigors, dehydration and hypotension which in some cases can lead to acute renal insufficiency.

~~Guidelines for the management of pyrexia will be provided in the amendment to open Part C of the study~~. **Serious non-infectious febrile events have been observed.These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials. Subjects should be evaluated for signs and symptoms of infection and work up considered as clinically indicated. Dabrafenib must be held for fever of 38.5C or higher, and blood samples for an absolute neutrophil count (ANC) and serum creatinine must be drawn in the setting of fever. Trametinib can be continued in subjects receiving combination therapy.**

Dermatological Effects

Cutaneous Squamous cell carcinoma (cuSCC): In vitro experiments have demonstrated a paradoxical activation of MAP-kinase signaling in keratinocytes and potentially other cells harboring a wild-type BRAF kinase but a mutated RAS kinase upon exposure to a BRAF

[redacted]

inhibitor. This paradoxical MAP-kinase pathway activation is potentially associated with a higher risk for the development of squamous cell carcinoma induction.

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with dabrafenib in combination with trametinib. In patients who received the combination dose of dabrafenib in combination with trametinib, cutaneous SCC (including keratoacanthoma [KA]) occurred in a lower percentage of subjects and events occurred later than with dabrafenib monotherapy, with the median time to onset of ~~22 weeks. All~~ **the first occurrence of 20 to 32 weeks as compared to approximately 8 weeks with dabrafenib monotherapy. Most** patients on combination therapy who developed cuSCC continued on dabrafenib treatment without dose modification. Skin examination should be performed prior to initiation of dabrafenib and during treatment with dabrafenib, every 2 months throughout therapy. An additional examination should be considered 2 **to 3** months after discontinuation of dabrafenib **or until initiation of another anti-neoplastic therapy**. Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new skin lesions develop.

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

Rash: Skin-related toxicities, primarily rash (maculopapular type rash with dabrafenib and acneiform-type rash with trametinib) have been reported with both trametinib and dabrafenib monotherapies. The incidence of skin-related events reported with the combination regimen appears to be lower than what has been observed following trametinib monotherapy. Rash management guidelines are provided in Section 3.13.1.

Hemorrhage: Major hemorrhagic events **including fatal events** can occur in patients receiving dabrafenib in combination with trametinib. Monitor for signs and symptoms of bleeding.

Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving dabrafenib in combination with trametinib.

Interstitial lung disease (ILD)/Pneumonitis:

Pneumonitis has been observed in subjects receiving trametinib **and trametinib in combination with dabrafenib.** To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests if clinically indicated. **No modification of dabrafenib is required when taken in combination with trametinib.**

Pancreatitis – Pancreatitis has been observed in subjects receiving dabrafenib **and dabrafenib in combination with trametinib**. Subjects will be monitored for abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis.

Hyperglycemia: Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Serum glucose levels will be monitored as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia.

[redacted]

Hepatic Events:

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib.

Ocular effects: Both trametinib and dabrafenib have been associated with ocular toxicities which appear to be class effects, including papilledema, RPED, and RVO **associated with trametinib**, uveitis and iritis associated with ~~trametinib and~~ dabrafenib. Please refer to Section 1.7.1 and Section 3.13.3.

Decreased LVEF: Left ventricular dysfunction was reported with trametinib as well as with other MEK inhibitors in clinical development. Please refer to Section 1.7.1 and Section 3.11.3.1.

Non-cutaneous secondary/recurrent malignancy: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling in BRAF wild type cells with RAS mutations which are exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have been seen with BRAF inhibitors including dabrafenib, and with dabrafenib/trametinib combination therapy. Patients should be monitored as clinically appropriate.

Reproductive Effects: Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals given dabrafenib. In repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Male subjects should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. In combined female fertility, early embryonic and embryofetal development studies in rats, numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects were seen at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC). There are no adequate and well-controlled studies of dabrafenib in pregnant women.

[redacted]

2 OBJECTIVE(S), ENDPOINT(S) AND HYPOTHESIS(ES)

PREVIOUS TEXT

Objective	Endpoint	Hypothesis(es)
Primary		
To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (Cτ) to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib	Infants, children and adolescents will tolerate doses of trametinib that achieve steady state trough concentrations associated with clinical benefit in adults
Secondary		
To characterize the pharmacokinetics of trametinib	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and t½ of trametinib, as appropriate.	
To characterize the safety and tolerability of trametinib	AEs; ECG; changes in laboratory values and vital signs	
To assess any preliminary anti-tumor activity of trametinib	Tumor response as defined in Appendix 3 through Appendix 7	
To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach	CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates	
To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and t½ of trametinib and dabrafenib when administered in combination	
To determine the acceptability and palatability of trametinib in pediatric subjects		

[redacted]

[redacted]

REVISED TEXT

Objective	Endpoint	Hypothesis(es)
Primary		
To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (Cτ) to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib	Infants, children and adolescents will tolerate doses of trametinib that achieve steady state trough concentrations associated with clinical benefit in adults
Secondary		
To characterize the pharmacokinetics of trametinib	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and t½ of trametinib, as appropriate.	
To characterize the safety and tolerability of trametinib	AEs; ECG; changes in laboratory values and vital signs	
To assess any preliminary anti-tumor activity of trametinib	Tumor response as defined in Appendix 3 through Appendix 7	
To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach	CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates	
To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and t½ of trametinib and dabrafenib when administered in combination	
To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination	**Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs.**	
To determine the ~~acceptability~~**safe** and ~~palatability of~~ **tolerable dabrafenib dose(s) when**	**Adverse Events (AEs); ECG; ECHO; changes in laboratory**	

[redacted]

Objective	Endpoint	Hypothesis(es)
administered in combination with the recommended trametinib **dose for chronic continuous daily dosing** in pediatric subjects **(infants, children, and adolescents) that achieves similar exposures (trough concentration [C□]) to the recommended adult dose**	**values and vital signs. Steady state Cτ of trametinib**	
To determine the acceptability and palatability of trametinib in pediatric subjects	**Palatability questionnaire data**	
[redacted]		

3.1 Discussion of Study Design

PREVIOUS TEXT

This is a 3-part (Part A, Part B, Part C), Phase I/IIa, multi-center, open label study in pediatric subjects with refractory or recurrent tumors likely to have pathway activation and thus more likely to benefit from therapy. The overall goal of this trial is to efficiently establish safe, pharmacologically relevant dose of trametinib in infants, children and adolescents and determine preliminary activity of trametinib monotherapy in selected recurrent, refractory or unresectable childhood tumors. In addition, Part C of the study is designed to establish the safety, tolerability and activity of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAFV600E mutated tumors.

Part A will be a pharmacokinetically driven limited dose escalation in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18

[redacted]

subjects to the age expansion phase (subjects less than 2 years of age will not be included in the initial dose escalation until the age specific cohorts are opened).

Part B will be an expansion study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of Ras/MAPK activation in childhood solid tumors. Forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts.

- B1: Refractory or relapsed neuroblastoma
- B2: Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion
- B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant.
- B4: BRAF V600 mutant tumors.

Part C is a limited dose escalation of the combination of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study, with a planned enrollment of up to 18 subjects, will not open until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib monotherapy is established in Part A and all available PK and safety data is reviewed. Part C will require an amendment prior to enrollment to include updated safety data and dabrafenib dosing in children. Part B and C may be open to accrual simultaneously.

Subjects may not enroll in more than one part of the study.

All parts of the study will use currently available trametinib tablet strengths (0.125, 0.5, and 2 mg tablets) for children who are able to reliably swallow tablets. In addition, an oral solution formulation (0.05 mg/mL) is available. Doses will be calculated using body weight in kilograms and prescribed using a dosing nomogram (See Appendix 2).

For Part C of the study dabrafenib capsules (10, 25, 50, 75 mg) or suspension (10 mg/ml) will be used.

General outline of study conduct:

The screening visit will be completed within 14 days prior to enrollment.

Safety and PK assessments will be performed at regular intervals as outlined in the Time and Events Tables (Section 7.1).

[redacted]

Overall response will be assessed at regular intervals as outlined in the Time and Events Tables according to the appropriate guidelines as determined by the disease(s) under study (see Appendix 3 through Appendix 6).

Additional details for the conduct of each part of the study are provided in Section 3.2 (Part A) Section 3.3 (Part B), and Section 3.4 (Part C).

[redacted]

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential.

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

REVISED TEXT

This is a 3-part (Part A, Part B, Part C), Phase I/IIa, multi-center, open label study in pediatric subjects with refractory or recurrent tumors likely to have pathway activation and thus more likely to benefit from therapy. The overall goal of this trial is to efficiently establish safe, pharmacologically relevant dose of trametinib in infants, children and adolescents and determine preliminary activity of trametinib monotherapy in selected recurrent, refractory or unresectable childhood tumors. In addition, Part C of the study is designed to establish the safety, tolerability and activity of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAFV600E mutated tumors.

Part A will be a pharmacokinetically driven limited dose escalation in subjects with an expansion for safety, tolerability, and PK in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase (subjects less than 2 years of age will not be included in the initial dose escalation until the age specific cohorts are opened).

Part B will be an expansion study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations. Disease cohorts are selected based on current data of Ras/MAPK activation in childhood solid tumors. Forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts. **Part B will use the dose determined in Part A.**

- B1: Refractory or relapsed neuroblastoma
- B2: Recurrent or unresectable low grade gliomas with BRAF tandem duplication with fusion
- B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant.
- B4: BRAF V600 mutant tumors.

Part C is a limited dose escalation of the combination of trametinib in combination with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study, with a planned enrollment of up to 18 subjects **with up to 6 adolescent subjects with BRAF V600 mutant metastatic melanoma**, will not open until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib monotherapy is established in Part A and all available PK and safety data is reviewed. ~~Part C will require an amendment prior to enrollment to~~

[redacted]

include **Amendment 3 provides the** updated safety data and dabrafenib dosing in children **to allow enrollment into Part C**. Part B and C may be open to accrual simultaneously.

Subjects may not enroll in more than one part of the study.

All parts of the study will use currently available trametinib tablet strengths (0.125, 0.5, and 2 mg tablets) for children who are able to reliably swallow tablets. In addition, an oral solution formulation (0.05 mg/mL) is available. Doses will be calculated using body weight in kilograms and prescribed using a dosing nomogram (See Appendix 2).

For Part C of the study dabrafenib capsules (~~10, 25,~~ 50, 75 mg) or suspension (10 mg/ml) will be used.

General outline of study conduct:

The screening visit will be completed within 14 days prior to enrollment.

Safety and PK assessments will be performed at regular intervals as outlined in the Time and Events Tables (Section 7.1).

[redacted]

Overall response will be assessed at regular intervals as outlined in the Time and Events Tables according to the appropriate guidelines as determined by the disease(s) under study (see Appendix 3 through Appendix 6).

Additional details for the conduct of each part of the study are provided in Section 3.2 (Part A) Section 3.3 (Part B), and Section 3.4 (Part C).

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential.

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

3.4 Part C: Trametinib in Combination with Dabrafenib

PREVIOUS TEXT

Part C will determine the safety, tolerability and preliminary activity of the RP2D of trametinib in combination with a limited dose escalation of dabrafenib (50% of pediatric RP2D and 100% RP2D). Part C will enroll up to 18 subjects aged 1 to <18 years with recurrent or refractory malignant solid tumors harboring a V600 mutation.

Part C of this study will not be open to enrolment until the pediatric Phase 1 study of dabrafenib (BRF116013) has established the recommended dabrafenib dose in children and Part A of this study has been completed. Starting dose of the combination and dose escalation schema will be provided in an amendment to the protocol. The amendment and supporting data will be submitted to relevant regulatory authorities prior to implementation.

PK samples will be collected on Day1, Day 15, and Day 22.

[redacted]

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Study treatment will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

REVISED TEXT

Part C will **be a 3+3 study design to** determine the safety, tolerability and preliminary activity of the RP2D of trametinib in combination with a limited dose escalation of dabrafenib (50% of pediatric RP2D and 100% RP2D). Part C will enroll up to 18 subjects aged 1 to <18 years with recurrent or refractory malignant solid tumors harboring a V600 mutation.

~~Part C of this study will not be open to enrolment until~~ **Amendment 3 provides information from** the pediatric Phase 1 study of dabrafenib (BRF116013)**, which** has established the recommended dabrafenib dose in children and **provides relevant safety information for dabrafenib monotherapy in children and dabrafenib/trametinib combination therapy in adults. Once** Part A of this study has been completed~~. Starting dose~~ **for at least one** of the ~~combination and dose escalation~~ schema **three age specific cohorts, enrollment into Part C will commence. Enrollment for Part C** will ~~be provided in an amendment to~~ **close upon enrollment of 12 non melanoma pediatric patients and up to 6 BRAF V600 mutant melanoma patients or 36 months from** the ~~protocol. The amendment and supporting data will be submitted to relevant regulatory authorities prior to implementation.~~ **time Part C was opened for enrollment, whichever should come first.**

PK samples will be collected on Day1, Day 15, and Day 22.

Blood samples for clinical laboratory tests will be collected throughout the study, and safety, tolerability and clinical activity assessments will be conducted according to the Time and Events Tables (Section 7.1).

Study treatment will be continued until disease progression, until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent, begin a new anti-cancer therapy, or the Sponsor terminates the study. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 6.2.

3.5 Criteria for Continuing in the Study

PREVIOUS TEXT

For subjects enrolled on Part A, Part B and Part C, the following criteria must be met to advance beyond the first 28 days:

Subjects have not met discontinuation of treatment criteria (Section 6.3)

No evidence of progressive disease (See Section 7.6) defined as no clinical evidence of progression for assessments that do not require imaging/disease assessment or no evidence of radiographic or histologic/morphologic progression if disease assessment included imaging (solid tumor)

[redacted]

Toxicity resolved to baseline or grade ≤ 2 with specific exception of:

Specific criteria for Ejection Fraction Results (Section 3.11.3).

For subjects in Part B who are not evaluable for hematological toxicity due to marginal bone marrow function from disease infiltration or prior therapy, the following hematologic criteria must be met:

- Absolute neutrophil count > 500 cell/μL,
- Platelet count > 25,000/μL (without transfusion in ≥ 7 days),
- No life threatening consequences of anemia (no grade 4 anemia per NCI-CTCAE v4.03) [NCI, 2009].

REVISED TEXT

For subjects enrolled on Part A, Part B and Part C, the following criteria must be met to advance beyond the first 28 days:

Subjects have not met discontinuation of treatment criteria (Section 6.3)

No evidence of progressive disease (See Section 7.6) defined as no clinical evidence of progression for assessments that do not require imaging/disease assessment or no evidence of radiographic or histologic/morphologic progression if disease assessment included imaging (solid tumor)

Patients will be permitted to continue study treatment beyond initial Investigator-assessed disease progression, as long as they meet the following criteria:

Investigator assessed clear evidence of clinical benefit

Tolerance of study drug

Continuation of study treatment is in the best interest of the patient as determined by the Investigator. For this determination, the investigator should consider all relevant data, such as:

Absence of symptoms and signs of progressive disease

No decline in performance status

Absence of rapid progression of disease or of progressive tumor at critical anatomic sites (e.g., cord compression) that would require urgent medical intervention.

Patient/guardian is willing to continue on the study

If the Investigator determines that all above criteria are met, the patient may continue study treatment and follow all study related procedures, including tumor assessments, as scheduled in the appropriate Time and Events Tables (Section 7.1 table.

After each tumor assessment, the investigator must confirm if the patient is still benefitting from study treatment, and document this in patient medical records.

Toxicity resolved to baseline or grade ≤ 2 with specific exception of:

[redacted]

Specific criteria for Ejection Fraction Results (Section 3.11.3).

For subjects in Part B who are not evaluable for hematological toxicity due to marginal bone marrow function from disease infiltration or prior therapy, the following hematologic criteria must be met:

- Absolute neutrophil count > 500 cell/μL,
- Platelet count > 25,000/μL (without transfusion in ≥ 7 days),
- No life threatening consequences of anemia (no grade 4 anemia per NCI-CTCAE v4.03) [NCI, 2009].

3.6.2 Part B Intra-subject Dose Escalation

PREVIOUS TEXT

Not permitted.

REVISED TEXT

~~Not permitted.~~

Subjects may be allowed to re-escalate following dose reduction for AE upon resolution of AE. Please follow guidelines in Section 3.13 and Section 3.14.

3.6.3 Part C Intra-subject Dose Escalation

PREVIOUS TEXT

~~Not permitted.~~

REVISED TEXT

~~Not permitted.~~

Subjects may be allowed to re-escalate following dose reduction for AE upon resolution of AE. Please follow guidelines in Section 3.13 and Section 3.14.

3.8.3.2 Starting dose for Part C, Trametinib in Combination with Dabrafenib

PREVIOUS TEXT

In adults the recommended dose of trametinib in combination with dabrafenib is the full adult monotherapy dose of each: trametinib 2 mg PO daily and dabrafenib 150 mg PO twice daily. In the context of this clinical trial, the trametinib dose administered in Part C will be the trametinib monotherapy RP2D from Part A. The monotherapy RP2D of dabrafenib in children will be established on a separate trial (BRF116013). For the evaluation of combination therapy on this trial, the starting dose of dabrafenib will be 50% of the monotherapy dabrafenib dose from BRF116013. If tolerated a single dose escalation to the dabrafenib RP2D will be evaluated. Actual doses will be added to this protocol by a protocol amendment prior to enrolment to Part C.

REVISED TEXT

In adults the recommended dose of trametinib in combination with dabrafenib is the full adult monotherapy dose of each: trametinib 2 mg PO daily and dabrafenib 150 mg PO twice daily. In the context of this clinical trial, the trametinib dose administered in Part C will be the trametinib monotherapy RP2D from Part A. The monotherapy RP2D of dabrafenib in

[redacted]

children ~~will be~~ **was** established on a separate trial (BRF116013). **The following RP2D doses were determined for dabrafenib:**

- **< 12 years old subjects: 5.25 mg/kg/day dabrafenib administered orally, divided into two equal doses**
- **≥ 12 years old subjects: 4.5 mg/kg/day dabrafenib administered orally, divided into two equal doses**

For the evaluation of combination therapy on this trial, the starting dose of dabrafenib **(Dose Level 1)** will be 50% of the ~~monotherapy dabrafenib dose from BRF116013.~~ **RP2D, divided into two equal doses.** If tolerated a single dose escalation to the **full** dabrafenib RP2D **(Dose Level 2)** will be evaluated. ~~Actual doses will be added to this protocol by a protocol amendment prior to enrolment to Part C.~~ **If dose levels proposed are not well tolerated, intermediate dose levels of dabrafenib and/or trametinib may be evaluated if warranted.**

Table 4 Recommended dabrafenib dose levels

	Dabrafenib		Trametinib
Dose Level	**< 12 years**	**≥ 12 years**	**All ages**
1 (Starting dose)	**2.63 mg/kg/d**	**2.25 mg/kg/d**	**RP2D**
2	**5.25 mg/kg/d**	**4.5 mg/kg/d**	**RP2D**

3.8.4 Rationale for Endpoints

PREVIOUS TEXT

This study will be the first administration of trametinib to pediatric subjects. Safety parameters will be carefully and systematically monitored.

Part A: The expectation is that a PK endpoint will help define a dose that will provide an efficacious exposure in pediatric subjects without the need to reach maximum toxicity levels. In the absence of DLT in this pediatric study, a PK target endpoint will be used as the primary endpoint for dose determination. In adults, there is minimal intersubject variability in the steady state Cτ (CV 19%, 95%CI=10.86-13.4), and responses were observed at exposures as low as Cτ = 7 ng/mL in subjects with melanoma, while efficacy has been clearly identified at known plasma levels of study drug (≥10 ng/mL trough) which were well tolerated. However, safety will be carefully reviewed and DLT definitions are incorporated in the protocol should safety in pediatric subjects differ from those in adult subjects following treatment with trametinib.

Part B: The RP2D established in Part A and verified by age cohorts (1 month to <2 years, 2 years to ≤12 years and >12 years) will be administered in Part B. The primary objective in Part B will be objective response measured by specific disease appropriate measures.

Part C: Subjects will be monitored for DLT and toxicity. Safety, tolerability and preliminary activity are the primary endpoints of this part of the study. In the absence of DLT, dose escalation will not exceed the trametinib monotherapy RP2D in combination with the dabrafenib monotherapy RP2D.

[redacted]

REVISED TEXT

This study will be the first administration of trametinib to pediatric subjects. Safety parameters will be carefully and systematically monitored.

Part A: The expectation is that a PK endpoint will help define a dose that will provide an efficacious exposure in pediatric subjects without the need to reach maximum toxicity levels. In the absence of DLT in this pediatric study, a PK target endpoint will be used as the primary endpoint for dose determination. In adults, there is minimal intersubject variability in the steady state $C\tau$ (CV 19%, 95%CI=10.86-13.4), and responses were observed at exposures as low as $C\tau$ = 7 ng/mL in subjects with melanoma, while efficacy has been clearly identified at known plasma levels of study drug (≥10 ng/mL trough) which were well tolerated. However, safety will be carefully reviewed and DLT definitions are incorporated in the protocol should safety in pediatric subjects differ from those in adult subjects following treatment with trametinib.

Part B: The RP2D established in Part A and verified by age cohorts (1 month to <2 years, 2 years to ≤12 years and >12 years) will be administered in Part B. The primary objective in Part B will be objective response measured by specific disease appropriate measures.

Part C: Subjects will be monitored for DLT and toxicity **using the same DLT criteria as Part A.** Safety, tolerability and preliminary activity are the primary endpoints of this part of the study. In the absence of DLT, dose escalation will not exceed the trametinib monotherapy RP2D in combination with the dabrafenib monotherapy RP2D.

3.10.1 Trametinib

PREVIOUS TEXT

Trametinib is administered orally once daily under fasting conditions, either 1 hr before or 2 hr after a meal. Subjects should be encouraged to take trametinib approximately 24 hours apart at the same time each day. Dose levels are provided in Section 3.2.1.

For trametinib tablets, it is recommended that subjects drink approximately 4 to 6 mL of water/kg body weight with each dose.

Trametinib pediatric oral solution formulation will be administered with a graduated syringe. It is recommended that subjects drink 4 to 6 mL of water/kg body weight following dosing.

A dosing nomogram (see Appendix 2) based on weight and dose level will be used to prescribe trametinib to minimize inter-subject dosing variability. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose. If a subject misses a dose, subject should not double the next regularly scheduled dose. However, subject can take the missed dose immediately if the next scheduled dose is at least 12 hr later. Subject should take the next dose at its usual time.

Refer to Section 3.12 and Section 3.13 for dose modifications for toxicity.

REVISED TEXT

Please note that study drug dispensed to subjects in the original container should not be repackaged without explicit permission from the Sponsor. Trametinib is administered orally once daily under fasting conditions, either 1 hr before or 2 hr after a meal. Subjects should be encouraged to take trametinib approximately 24 hours apart at the same time each day. Dose levels are provided in Section 3.2.1.

[redacted]

Ideally, patients will take the trametinib study drug in the morning up through the PK day. After the PK day, the patient may change to evening dosing, if they prefer. If the patient is on an evening dosing regimen as they enter the PK testing period, the evening dose prior to the PK day SHOULD BE taken by the patient. In all cases, the timing of the dose prior to the PK sampling must be maintained and recorded accurately.

For trametinib tablets, it is recommended that subjects drink approximately 4 to 6 mL of water/kg body weight with each dose.

Trametinib pediatric oral solution formulation will be administered with a graduated syringe. It is recommended that subjects drink 4 to 6 mL of water/kg body weight following dosing.

A dosing nomogram (see Appendix 2) based on weight and dose level will be used to prescribe trametinib to minimize inter-subject dosing variability. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose. If a subject misses a dose, subject should not double the next regularly scheduled dose. However, subject can take the missed dose immediately if the next scheduled dose is at least 12 hr later. Subject should take the next dose at its usual time.

Refer to Section 3.12 and Section 3.13 for dose modifications for toxicity.

3.10.2 Dabrafenib

PREVIOUS TEXT

Dose levels, dose modifications for events of special interest, and a dosing nomogram will be added in a future amendment to open Part C once the RP2D of dabrafenib and trametinib monotherapy is established in children.

REVISED TEXT

~~Dose levels, dose modifications for events of special interest, and a dosing nomogram will be added in a future amendment to open Part C once the RP2D of dabrafenib and trametinib monotherapy is established in children.~~ **Please note that study drug dispensed to subjects in the original container and should not be repackaged without explicit permission from the Sponsor.**

Capsules: Dabrafenib capsules will be supplied by GSK (for subjects able to reliably and consistently swallow capsules).

Suspension: Dabrafenib will be supplied as a powder for oral suspension contained in single-use foil laminated stickpacks. The powder will be constituted with a specified volume of water at the time of use to form an oral suspension of 10 mg/mL dabrafenib. Administration will be performed using appropriate-sized oral syringes (1 mL, 5 mL, or 20 mL) to enable adjustments in dosing volume for individualized doses. The constituted suspension is intended for immediate consumption and the unused portion of the suspension will be discarded. Supplies for constitution will be supplied by GSK. Detailed instructions for constitution and dosing will be provided in the SPM.

Dabrafenib (either formulation) will be administered orally, twice daily based on weight at the appropriate study dose level. A dosing nomogram (Appendix 2) based on weight and dose level will be used to prescribe dabrafenib to minimize inter-subject dosing variability. For capsule administration, only 50 mg and 75 mg dose strengths are available. Therefore, the dose recommendations by weight range are within 20% of the

[redacted]

ideal dose. The same dosing recommendation was applied to the suspension nomograms, at the same weight ranges that overlap with the capsule nomograms.

Dabrafenib capsules will be taken with approximately 1 ounce (30 mLs) of water for every 10 pounds of body weight, twice a day. Subjects should be encouraged to take their doses at approximate 12 hour intervals and at similar times every day.

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

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

Children younger than 6 years and subjects, regardless of age, with a risk of choking when swallowing capsules will be required to use the suspension formulation.

3.11.2 QTc Stopping Criteria

PREVIOUS TEXT

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥500 msec	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline • Restart at current dose level[b] • If event recurs, permanently discontinue study treatment

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

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

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

Every attempt should be made to obtain a blood sample to test serum potassium, calcium, phosphorus and magnesium levels. If any of these are below the lower limits of normal, correct with supplements to within normal limits.

A review of concomitant medication usage for any medications that may prolong QTc should also be performed.

[redacted]

REVISED TEXT

QTc-Prolongation[a]	Action and Dose Modification
~~QTcB ≥500~~ **QTc ≥501** msec	Interrupt **all** study ~~treatment~~ **treatments (trametinib and dabrafenib)** until ~~QTcB~~ **QTc** prolongation resolves to grade 1 or baseline ~~Restart~~ **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** ~~treatment~~ **treatments. Consider evaluation with cardiologist.**

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

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

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

Every attempt should be made to obtain a blood sample to test serum potassium, calcium, phosphorus and magnesium levels. If any of these are below the lower limits of normal, correct with supplements to within normal limits.

A review of concomitant medication usage for any medications that may prolong QTc should also be performed.

3.11.3.1 LVEF Stopping Criteria

Note the Table numbers have changed

PREVIOUS TEXT

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 (Section 7.1). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 3.

[redacted]

ECHO should be performed at baseline and at follow up visit(s). Electronic copies of all ECHO scans will be collected by GSK for review. Instructions for submission of ECHO scans are provided in the Study Procedures Manual (SPM).

[redacted]

Table 28 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinical Observation	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Grade 2: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	Interrupt trametinib and dabrafenib and repeat ECHO within 2 weeks[a] If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) Consult with the GSK medical monitor and request approval for restart Restart treatment with trametinib reduced by one dose level Restart dabrafenib at previous dose level[b] Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter If LVEF **does not recover** within 4 weeks • Consult with cardiologist • **Permanently discontinue trametinib** • Report as an SAE • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution • Consult with GSK medical monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	**Permanently discontinue trametinib.** **Discontinue dabrafenib** **Report as SAE** **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[e]

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

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

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

If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult medical monitor.

Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.

[redacted]

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

[redacted]

REVISED TEXT

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 (Section 7.1). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table ~~3~~5.

ECHO should be performed at baseline and at follow up visit(s). Electronic copies of all ECHO scans will be collected by GSK for review. Instructions for submission of ECHO scans are provided in the Study Procedures Manual (SPM).

Table 5 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinical Observation	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Grade 2: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	Interrupt trametinib ~~and dabrafenib~~ and repeat ECHO within 2 weeks[a] If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) Consult with the GSK medical monitor and request approval for restart Restart treatment with trametinib reduced by one dose level Restart dabrafenib at previous dose level[b] Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter If LVEF **does not recover** within 4 weeks • Consult with cardiologist • **Permanently discontinue trametinib** • Report as an SAE • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution • Consult with GSK medical monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	**Permanently discontinue trametinib.** **Discontinue dabrafenib[d]**

[redacted]

Clinical Observation	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
	Grade 4: resting LVEF <20%	**Report as SAE** **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[e]

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

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

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

If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult medical monitor.

Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with GSK medical monitor.

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

3.12 Dose Delay and Modification for Events Considered Related to Trametinib

PREVIOUS TEXT

A maximum of one trametinib dose reduction is allowed. If a second dose level reduction is required, treatment will be permanently discontinued.

Trametinib dose modification guidelines are outlined in Table 4 for clinically significant toxicities that are deemed related to trametinib (i.e. peripheral and periorbital edema) with exception for following events of special interest:

rash (Section 3.13.1)

diarrhea (Section 3.13.2),

ejection fraction changes (Section 3.11.3.1),

hypertension (Section 3.13.3)

prolonged QTc (Section 3.11.2)

pneumonitis (Section 3.13.4),

visual changes (Section 3.13.3),

liver chemistry elevation (Section 3.11.1)

For these refer to the relevant sections for dose modification guidelines for adverse events of special interest as stated above.

[redacted]

Table 29 Dose Delay and Modification for Events Considered Related to Trametinib

CTCAE Grade	Action and Dose Modification
Grade 1 and tolerable Grade 2	Continue trametinib at current dose level Monitor closely Provide supportive care according to institutional standards
Intolerable Grade 2 and Grade 3	Interrupt trametinib Monitor closely Provide supportive care according to institutional standards When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by one dose level** If the intolerable Grade 2 or Grade 3 toxicity recurs, permanently discontinue trametinib
Grade 4	Interrupt trametinib Monitor closely Provide supportive care according to institutional standards If event resolves to Grade 1 or baseline discuss potential continuation of trametinib with GSK Medical Monitor; if continuation of treatment agreed then restart trametinib at dose **reduced by one dose level** **If event does not resolve permanently discontinue trametinib**

Abbreviation: GSK = GlaxoSmithKline

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

REVISED TEXT

A maximum of one trametinib dose reduction is allowed. If a second dose level reduction is required, treatment will be permanently discontinued.

Trametinib dose modification guidelines are outlined in Table 6 for clinically significant toxicities that are deemed related to trametinib (i.e. peripheral and periorbital edema) with exception for following events of special interest:

rash (Section 3.13.1)

diarrhea (Section 3.13.2),

ejection fraction changes (Section 3.11.3.1),

hypertension (Section 3.13.3)

prolonged QTc (Section 3.11.2)

pneumonitis (Section 3.13.4),

visual changes (Section 3.13.3),

[redacted]

liver chemistry elevation (Section 3.11.1)

For these refer to the relevant sections for dose modification guidelines for adverse events of special interest as stated above.

If treatment related toxicities occur when dabrafenib is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions described below.

Table 6 Dose Delay and Modification for Events Considered Related to Trametinib and/or Dabrafenib

CTCAE Grade	Action and Dose Modification
Grade 1 and tolerable Grade 2	Continue ~~trametinib~~ **study drug(s)** at current dose level Monitor closely Provide supportive care according to institutional standards
Intolerable Grade 2 and Grade 3	Interrupt ~~trametinib~~ **study drug(s)** Monitor closely Provide supportive care according to institutional standards When toxicity resolves to Grade 1 or baseline, restart ~~trametinib~~ **study drug(s) reduced by one dose level** ~~If the intolerable Grade 2 or Grade 3 toxicity recurs, permanently discontinue trametinib~~
Grade 4	Interrupt ~~trametinib~~ **study drug** Monitor closely Provide supportive care according to institutional standards If event resolves to Grade 1 or baseline discuss potential continuation of ~~trametinib~~ **study drug(s)** with ~~GSK~~ Medical Monitor; **permanently discontinue or**, if continuation of treatment agreed then restart ~~trametinib~~ **study drug(s)** at dose **reduced by one dose level** **If event does not resolve permanently discontinue ~~trametinib~~ study drug(s)**

Abbreviation: GSK = GlaxoSmithKline

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

3.13.1 Management of Rash

PREVIOUS TEXT

Rash is a frequent AE observed in subjects receiving trametinib (see the Investigator's Brochure for more information) A proactive approach is recommended. Encourage subjects to avoid unnecessary exposure to sunlight and encourage use of sunscreens and sunblock (see Section 3.13.1.1). If subjects develop rash, verify treatment intervention and consider recommended steps outlined under Section 3.13.1.2 and Table 5.

[redacted]

REVISED TEXT

Rash is a frequent AE observed in subjects receiving trametinib **and dabrafenib** (see the Investigator's Brochure for more information) A proactive approach is recommended. Encourage subjects to avoid unnecessary exposure to sunlight and encourage use of sunscreens and sunblock (see Section 3.13.1.1). If subjects develop rash, verify treatment intervention and consider recommended steps outlined under Section 3.13.1.2 and Table ~~5~~**7.**

3.13.1.2 Reactive Management

PREVIOUS TEXT

It is strongly recommended that subjects who develop rash/skin toxicities receive evaluations for management of the specific side effect.

For **pruritic lesions**, the use of cool compresses and oral antihistamine agents may be helpful.

For **fissuring**, the use of Monsel's solution, silver nitrate or zinc oxide cream is advised.

For **desquamation**, thick emollients and mild soap are recommended.

For **paronychia**, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended, and if no improvement is seen, a dermatology or surgery consultation is recommended.

For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

Table 30 Management of Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	Initiate prophylactic and symptomatic treatment measures[a] Use moderate strength topical steroid[b] Reassess after 2 weeks;	Continue trametinib If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level** (Appendix 2).
Grade 2	Initiate prophylactic and symptomatic treatment measures[a] Use moderate strength topical steroid[b] Reassess after 2 weeks.	**Reduce trametinib by one dose level** (Appendix 2). Reassess after 2 weeks: 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 trametinib until recovery to ≤grade 1, restart trametinib at reduced dose level
Grade ≥3	Use moderate strength topical steroids[b] (PLUS methylprednisolone dose pack. Consult dermatologist	Interrupt trametinib until rash recovers to Grade ≤1 **Restart[c] with trametinib reduced by one dose level[d]** (Appendix 2)

[redacted]

CTCAE Grade	Adverse Event Management	Action and Dose Modification
		If no recovery to grade ≤2 within 4 weeks, **permanently discontinue trametinib.**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of GSK medical monitor is required to re-start study treatment after >4 weeks of interruption
d. Escalation of trametinib to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

REVISED TEXT

It is strongly recommended that subjects who develop rash/skin toxicities receive evaluations for management of the specific side effect.

For **pruritic lesions**, the use of cool compresses and oral antihistamine agents may be helpful.

For **fissuring**, the use of Monsel's solution, silver nitrate or zinc oxide cream is advised.

For **desquamation**, thick emollients and mild soap are recommended.

For **paronychia**, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended, and if no improvement is seen, a dermatology or surgery consultation is recommended.

For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

[redacted]

Table ~~5~~ 7 Management of Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	Initiate prophylactic and symptomatic treatment measures[a] Use moderate strength topical ~~steroid~~[b] **steroids**[b] Reassess after 2 weeks;	Continue ~~trametinib~~ **study drug(s)** If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce** ~~trametinib~~ **study drug (s) by one dose level** (Appendix 2).
Grade 2	Initiate prophylactic and symptomatic treatment measures[a] Use moderate strength topical steroid[b] Reassess after 2 weeks.	**Reduce** ~~trametinib~~ **study drug (s) by one dose level** (Appendix 2). Reassess after 2 weeks: 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 ~~trametinib~~ **study drug(s)** until recovery to ≤grade 1, restart ~~trametinib~~ **study drug (s)** at reduced dose level
Grade ≥3	Use moderate strength topical steroids[b] (PLUS **consider a brief period of oral high dose steroid such as** methylprednisolone~~ dose pack.~~ Consult dermatologist	Interrupt ~~trametinib~~ **study drug(s)** until rash recovers to Grade ≤1 **Restart[c] with** ~~trametinib~~ **study drug(s) reduced by one dose level[d]** (Appendix 2) If no recovery to grade ≤2 within 4 weeks, **permanently discontinue** ~~trametinib~~ **study drug(s).**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of ~~GSK~~ medical monitor is required to re-start study treatment after >4 weeks of interruption
d. Escalation of ~~trametinib~~ **study drug (s)** to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

3.13.3 Hypertension

PREVIOUS TEXT

The algorithm in Figure 4 will be used to grade and manage trametinib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine,) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 3.11.3.2

[redacted]

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section.3.13.3.1.

See requirements for Baseline blood pressure measurements in Section 7.3.4.

REVISED TEXT

The algorithm in Figure will be used to grade and manage trametinib **and dabrafenib** related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine,) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 3.11.3.2

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section 3.13.3.1.

See requirements for Baseline blood pressure measurements in Section 7.3.4.

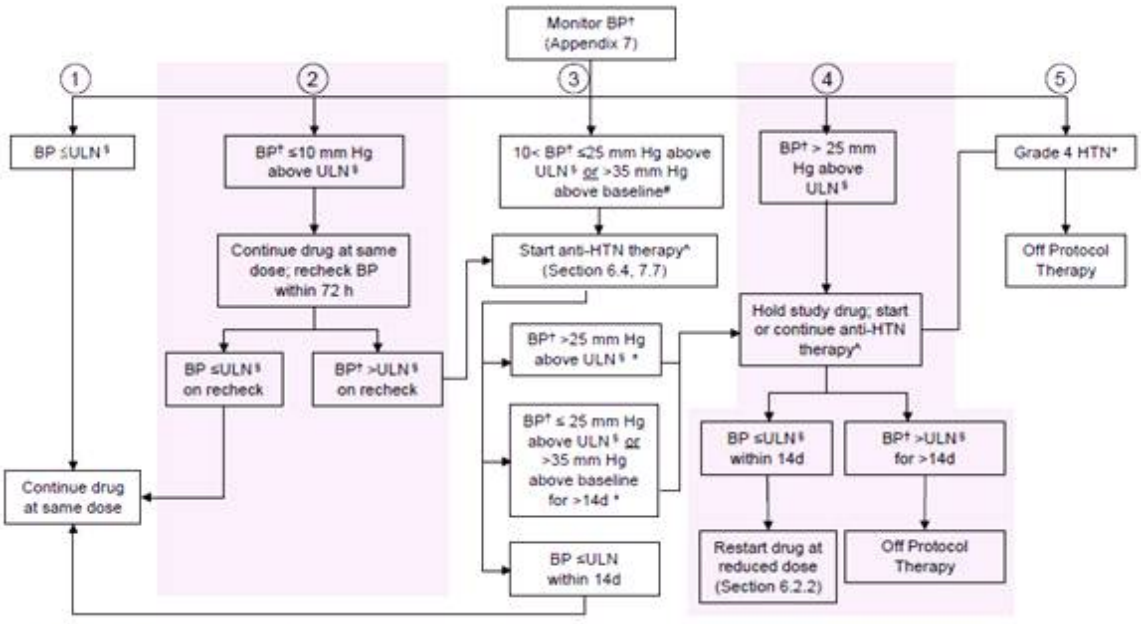
3.13.3.1 Management of Hypertension

PREVIOUS TEXT

- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. (Appendix 7)
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with an elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage trametinib related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

[redacted]

Figure 4 Algorithm For Management of Trametinib-Related Hypertension



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix 7)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 3.13.3.1.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95%ile for age, height, and gender: continue trametinib at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue trametinib at the same dose and recheck the BP within 72 hours.
    - If the BP is ≤ ULN on recheck, continue trametinib at the same dose.
    - If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start/adjust anti-hypertensive therapy and continue trametinib at the same dose. Monitor BP at least twice weekly.
    - If the BP returns to ≤ ULN within 14 days, continue trametinib at the same dose and continue anti-hypertensive therapy.

[redacted]

- If the BP remains elevated ≥ 25 mm Hg above the ULN or > 35 mm Hg above baseline for more than 14 days after the institution/adjustment of anti-hypertensive therapy, **hold trametinib**, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that trametinib is held. The anti-hypertensive therapy should be continued until the BP is less than the ULN.

- If the BP returns to ≤ ULN within 14 days, restart trametinib at a reduced dose.
- If the BP remains > ULN for more than 14 days, patient must be removed from protocol therapy.

  - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, hold trametinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that trametinib is held.
- If the BP is ≤ULN within 14 days, trametinib may be restarted at a reduced dose
- If the BP is > ULN for > 14 days, the patient must be removed from protocol therapy (Section 6.3)

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN **hold trametinib**, monitor BP, and administer/adjust anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, trametinib may be restarted at a reduced dose.
  - If the BP is > ULN for >14 days, the patient must be removed from protocol therapy (Section 6.3).

Arm 5 of algorithm:

If the participant develops Grade 4 hypertension, discontinue trametinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 6.3).

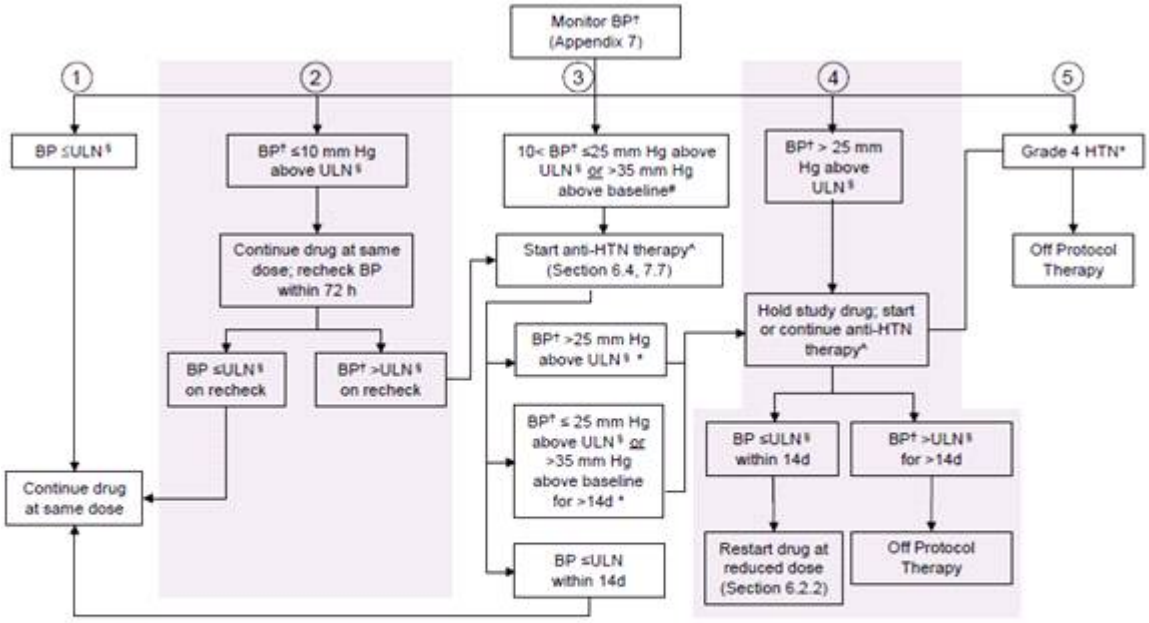
REVISED TEXT

- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. (Appendix 7)
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with an elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage trametinib **study drug(s)** related hypertension.

[redacted]

- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

Figure 5 Algorithm For Management of ~~Trametinib~~ Study Drug(s)-Related Hypertension



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix 7)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 3.13.3.1.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95%ile for age, height, and gender: continue ~~trametinib~~ **study drug(s)** at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue ~~trametinib~~ **study drug(s)** at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue ~~trametinib~~ **study drug(s)** at the same dose.
  - If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

[redacted]

- If BP is 11 to 25 mm Hg above the ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start/adjust anti-hypertensive therapy and continue ~~trametinib~~ **study drug(s)** at the same dose. Monitor BP at least twice weekly.
    - If the BP returns to ≤ ULN within 14 days, continue ~~trametinib~~ **study drug(s)** at the same dose and continue anti-hypertensive therapy.
    - If the BP remains elevated ≥ 25 mm Hg above the ULN or > 35 mm Hg above baseline for more than 14 days after the institution/adjustment of anti-hypertensive therapy, **hold** ~~trametinib,~~ **study drug(s)**, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that trametinib is held. The anti-hypertensive therapy should be continued until the BP is less than the ULN.
- If the BP returns to ≤ ULN within 14 days, restart ~~trametinib~~ **sudy drug (s)** at a reduced dose.
- If the BP remains > ULN for more than 14 days, patient must be removed from protocol therapy.

    - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, hold ~~trametinib,~~ **study drug(s),** but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that ~~trametinib~~ **study drug(s)** is held.
- If the BP is ≤ULN within 14 days, ~~trametinib~~ **study drug (s)** may be restarted at a reduced dose
- If the BP is > ULN for > 14 days, the patient must be removed from protocol therapy (Section 6.3)

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN **hold** ~~trametinib,~~ **study drug (s)**, monitor BP, and administer/adjust anti-hypertensive therapy as clinically indicated.
    - If the BP returns to ≤ ULN within 14 days, ~~trametinib~~ **study drug(s)** may be restarted at a reduced dose.
    - If the BP is > ULN for >14 days, the patient must be removed from protocol therapy (Section 6.3).

Arm 5 of algorithm:

[redacted]

If the participant develops Grade 4 hypertension, discontinue ~~trametinib,~~ **study drug(s),** monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 6.3).

Section 3.14 has been retitled.

PREVIOUS TEXT

3.14 Guidelines and Dose Modifications for Dabrafenib Events of Special Interest

Guidelines for dose modifications and interruptions for management of common toxicities associated with the combination of trametinib and dabrafenib will be provided along with dosing instructions for dabrafenib in the amendment to open Part C.

REVISED TEXT

- **3.14 Dose Delay and Modification for Events Considered Related to Dabrafenib**

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and for which specific guidelines do not apply are provided in Table 6. These guidelines are intended primarily for toxicities not easily managed with routine supportive care. For example, alopecia is not an indication for dose modification, nor is grade 2 nausea and vomiting that can be easily managed with anti-emetics.

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

PPES – Measures for PPES should include:

- **Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles**
- **Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40 % cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.**

Dose modification may also be required.

[redacted]

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

Uveitis - Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy.

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

Investigators should always err on the side of caution in these settings if treatment-related toxicity is a possibility.

Please refer to Table 6 for general dose modification guidelines for trametinib and dabrafenib.

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

New Section added 3.15

3.15 Guidelines for Dose Modifications and Toxicity Management for Combination Therapy

If treatment related toxicities occur when dabrafenib is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exception shown below:

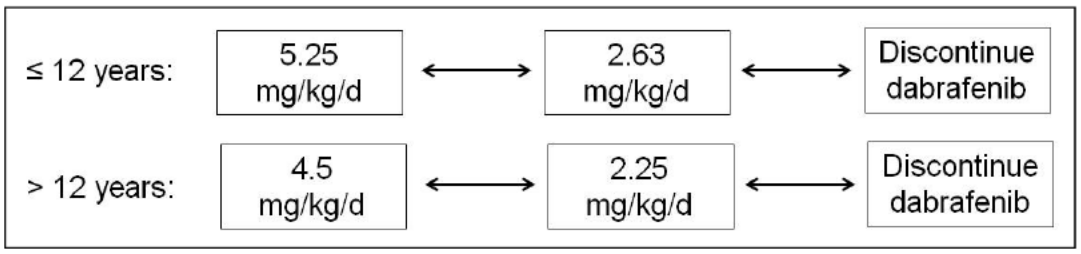
- **Dose modification is necessary for only dabrafenib**
    - **Mild to moderate pyrexia (Section 3.15.1)**
    - **Uveitis**
- **Dose modifications are necessary for only trametinib:**
    - **Retinal vein occlusions (RVO) and retinal pigment epithelial detachment (RPED) (Section 3.13.4)**
    - **Left ventricular ejection fraction (LVEF) reduction**
    - **Pneumonitis and interstitial lung disease (ILD)**

[redacted]

The severity of adverse events (AEs) will be graded utilizing the NCI-CTCAE v4.03 [NCI, 2009]. Guidelines for dose modifications and interruptions for management of common toxicities associated with dabrafenib are provided in this section.

If a patient in Part C and treated at Dose Level 1 requries a dose reduction of dabrafenib, then debrafenib should be discontinued. Dose modification scheme for dabrafenib is shown in Figure 6.

Figure 6 Dose modification scheme for dabrafenib



3.15.1 Pyrexia

Pyrexia has been observed in adult subjects receiving dabrafenib. In a minority of cases pyrexia was accompanied by symptoms such as severe chills/rigors, dehydration, and hypotension, which in some cases can lead to acute renal insufficiency. Serious non-infectious febrile events have been observed and typically occurred within the first month of therapy.

Subjects should be instructed on the importance of immediately reporting febrile episodes. Therapy with dabrafenib should be interrupted if the patient's temperature is ≥38.5ºC or 101.3° Fahrenheit. In the event of a fever, the subject should be instructed to take anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol as appropriate to control fever). The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

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

[redacted]

Table 12 Management and Dose Modification Guidelines for Pyrexia[a, b]

Occurrence	Action and Dose Modification
Any	Clinical evaluation for infection and hypersensitivity[c] Laboratory work-up[c] Hydration as required[d]
1st Event[b]:	Administer anti-pyretic treatment as clinically indicated[f] Interrupt dabrafenib Interrupt trametinib for fever higher than 40°C (104°F) Once pyrexia resolves to baseline (<38.5°C (101.3°F)) , restart dabrafenib at the same dose level (for pyrexia of 38.5°C (101.3°F) to 40°C (104°F)) or at the lower dose level (for pyrexia > 40°C (104°F)) and restart trametinib (if applicable) If fever was associated with dehydration, hypotension, rigors or chills, or renal failure, interrupt dabrafenib and trametinib[g]
2nd Event [e]	Same as for 1st event, and Consider oral corticosteroids (i.e. prednisone 10mg) for at least 5 days or as clinically indicated[g]
Subsequent Events:	Interrupt dabrafenib Once pyrexia resolves to baseline, restart dabrafenib (consider dose reduction by one dose level)[h]. Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f] If corticosteroids have been tapered and pyrexia recurs, restart steroids If corticosteroids cannot be tapered or escalating doses are required, consult medical monitor

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

c. Pyrexia is defined as a body temperature equal to or above 38.5○ Celsius or 101.3○ Fahrenheit.

For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended.

Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work up should include full blood count, electrolytes, creatinine, BUN, CRP, and liver function tests, blood culture and urine culture.

Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.

Anti-pyretic treatment may include acetaminophen (paracetamol), 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

In subjects 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.

Dabrafenib should be reduced by one dose level at discretion of the investigator if pyrexia is accompanied by severe rigors which cannot be managed by best supportive care, including increasing doses of oral steroids. Re-escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

[redacted]

3.15.2 Renal insufficiency

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

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

For the purposes of this guideline, increases from baseline should have *at least* the following *absolute* increase to qualify for the noted *percent* increase in this guideline. The normal serum creatinine values anticipated for young patients on this protocol are near the reporting limits of the laboratory analysis, and are thus subject to variability in reported results and high calculated percent changes. The absolute increase values are intended to alleviate dosing changes due to spuriously high calculations for percentage change.

For a 25% increase – that must also be at least a 0.10mg/dL absolute increase

For a 50% increase – that must also be at least a 0.20 mg/dL absolute increase

For a 100% increase – that must also be at least a 0.40 mg/dL absolute increase

[redacted]

Table 13 Renal Insufficiency Guidelines

For subjects with creatinine rise ≥50% from baseline :	

1 st occurrence	• If patient has fever: treat pyrexia as per Table 12 (please note NSAIDs can induce renal insufficiency, especially in patients with dehydration); consider IV hydration
	• Pediatric nephrology consult is recommended
	• Re-check within 24 hours
	  • If creatinine rise is < 25% from baseline:
	  • Continue dabrafenib and trametinib at current dose
	  • Monitor creatinine weekly for 4 weeks to ensure levels remain within 25% of baseline
	  • If creatinine rise is ≥ 25% but < 50% from baseline:
	  • Continue dabrafenib and trametinib at current dose
	  • Monitor creatinine at least twice weekly, can decrease frequency if creatinine rise < 25% from baseline
	  • Avoid nephrotoxic agents
	  • If creatinine rise is ≥ 50% but < 100% from baseline:
	  • Interrupt dabrafenib and trametinib
	  • Monitor creatinine at least twice weekly
	  • Avoid nephrotoxic agents
	  • May restart dabrafenib at reduced dose and trametinib at reduced dose if creatinine rise returns to < 25% from baseline
	  • If creatinine rise is ≥ 100% from baseline:
	  Permanently discontinue dabrafenib and trametinib

2nd occurrence	Permanently discontinue dabrafenib and continue trametinibdabrafenib

3.15.3 Malignancies

Cutaneous Squamous Cell Carcinomas (CuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been observed in subjects treated with dabrafenib. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however cuSCC should be reports as an SAE. In addition, a

biopsy of the lesion should be taken, where possible, and a summary of the results submitted to the Sponsor.

Patients should be instructed to immediately inform their physician if new lesions develop. Skin examination should be performed prior to initiation of dabrafenib and during treatment with dabrafenib, every 2 months throughout therapy. Monitoring of the skin should continue every 2 to 3 months for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

New Primary Melanoma

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

Non-Cutaneous Malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. Patients should be monitored as clinically appropriate.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

New non-cutaneous malignancies should be reported as a SAE. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses with the results provided to GSK. Testing of these biopsies may include analysis of genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens, and would analyze the biological pathways known to be associated with, and relevant to, BRAF-mutant tumor activation. For any new non-cutaneous maligancy every effort should be made to identify the RAS mutation status and submit the results to GSK.

Refer to Appendix 6 for French country **specific dermatological follow up.**

3.15.4 Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in Section 3.11.2.

4.1.1 Trametinib

PREVIOUS TEXT

Table 31 Investigational Product

REVISED TEXT

Table 14 Investigational Product - Trametinib

4.1.2 Dabrafenib

PREVIOUS TEXT

[redacted]

This information will be provided in the amendment to open Part C.

REVISED TEXT

Dabrafenib

~~This information will be provided in the amendment to open Part C.~~

Table 15 Investigational Product - Dabrafenib

Formulation description:	**Dabrafenib capsules**	**Dabrafenib powder for oral suspension**
Dosage form:	Capsule	Powder for oral suspension
Unit dose strengths:	50 mg and 75 mg	150 mg (in stickpack) 10 mg/mL (as oral suspension)
Route/ Frequency:	Oral / BID	Oral / BID
Physical description:	50 mg: opaque capsules composed of a dark red body and cap, each printed with one thick black line and one thin black line 75 mg: opaque capsules composed of pink body and cap, each printed with one thick black line and one thin black line	Supplied to clinical sites as a powder for oral suspension contained in white foil laminated stickpacks.
Manufacturer/ source of procurement:	GSK	GSK
Method for individualizing dosage:	Unit dose capsules	Administered using oral syringes

4.2.2 Dabrafenib

PREVIOUS TEXT

This information will be provided in the amendment to open Part C.

[redacted]

REVISED TEXT

~~This information will be provided in the amendment to open Part C.~~

Preparation

No special preparation of study treatment is required for dabrafenib HPMC capsules.

Dabrafenib powder for oral suspension requires constitution with water at the time of use. Instructions for preparation of the dabrafenib suspension are provided in the SPM. Supplies for constitution and dosing will be supplied by GSK.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may prepare and supply [administration will be performed by caretakers] study treatment.

Handling

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or study manager.

Storage

All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff.

Dabrafenib capsules are to be stored at room temperature up to 30°C. Maintenance of a temperature log (manual or automated) is required.

Dabrafenib powder for oral suspension is to be stored at up to 30°C. Maintenance of a temperature log (manual or automated) is required.

5.1 Number of Subjects

PREVIOUS TEXT

Approximately 94 subjects will be enrolled in the study (approximately 36 subjects in Part A, 40 subjects in Part B, and 18 subjects in Part C) In Part A during the age expansion cohort, every attempt will be made to enroll 4-6 subjects in each age group. In Part B a minimum of 10 subjects will be enrolled in each group with at least 4 in each cohort under the age of 6. In Part C, no specific age expansion is planned but every attempt will be made to enroll at least 4 children under the age of 12.

REVISED TEXT

Approximately 94 subjects will be enrolled in the study (approximately 36 subjects in Part A, **at least** 40 subjects in Part B, and 18 subjects in Part C) In Part A during the age expansion cohort, every attempt will be made to enroll 4-6 subjects in each age group. In Part B a

[redacted]

minimum of 10 subjects will be enrolled in each group with at least 4 in each cohort under the age of 6. In Part C, no specific age expansion is planned but every attempt will be made to enroll at least 4 children under the age of 12.

5.2.1.1 General Eligibility Criteria (All Parts)

PREVIOUS TEXT

6. Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 10.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to start of study drugs, throughout treatment period and for 4 months after last dose of study drug.

REVISED TEXT

6. Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 10.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to start of study drugs, throughout treatment period and for 4 months after last dose of study **drugs**.

5.2.1.3 Specific Eligibility Criteria, Part B

PREVIOUS TEXT

3. **BRAF Fusion Cohort (B2) Specific Criteria**:

- Relapsed or refractory gliomas or other primary brain tumors with BRAF fusion/duplication documented in Clinical Laboratory Improvement Amendments (CLIA) certified laboratory at diagnosis or relapse.
- Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) ≥1000/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
  - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

REVISED TEXT

3. **BRAF Fusion Cohort (B2) Specific Criteria**:

- Relapsed or refractory gliomas or other primary brain tumors with BRAF fusion/duplication (documented in Clinical Laboratory Improvement Amendments (CLIA) certified laboratory ~~at diagnosis~~) or ~~relapse~~ **NF1 subjects with gliomas who are not suitable for the NF1 with PN cohort**.
- Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) ≥1000/μL;
  - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)

[redacted]

- Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

PREVIOUS TEXT

4. **NF-1 Plexiform Neurofibroma Cohort (B3) Specific Criteria**

- Subjects with NF-1 must have a PN(s) that are progressive OR are cause of significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Subjects with paraspinal PN will be eligible for this trial. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected.
- A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with connection between the levels or extending laterally along the nerve.
- For subjects enrolled for tumor progression, progression is defined as:
  - Presence of new PN on MRI or CT (documented by comparison with prior MRI or CT), OR
  - A measurable increase in PN size (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) documented by comparison of two scans (MRI or CT) in the time period of approximately one year or less prior to evaluation for this study.
- For subjects enrolled for a "major deformity" or "significantly disfiguring" tumor, eligible tumors will be limited to tumors of the head & neck or those on other areas of the body that are unable to be concealed by standard garments.
- All subjects must have either the clinical diagnosis of NF-1 using the National Institutes of Health (NIH) Consensus Conference criteria or have a constitutional NF-1 mutation documented in a CLIA/College of American Pathologist (CAP) certified lab.
- Subjects must have measurable PN(s) amenable to volumetric MRI analysis. For the purpose of this study, the target lesion must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest. Tumors must be at least 3 mL in volume (most PNs 3 cm in longest diameter will meet this criteria). If the tumor is <3 cm in longest diameter, the subject may still be eligible. Central

[redacted]

review of the MRI of the target PN is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis. After consenting, please follow instructions in Appendix 6 or the SPM for central review of MRI. Central review will take 3-7 days (please plan accordingly).

- Adequate hematologic function defined as:

  Absolute neutrophil count (ANC) ≥1000/μL;

  Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)

  Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)

- Subjects with NF-1 will only be eligible if complete tumor resection is not feasible, or if a subject with a surgical option refuses surgery.
  - Since there is no standard effective chemotherapy for subjects with NF-1 and PN, subjects may be treated on this trial without having received prior medical therapy directed at their PN.
  - Must not have received myelosuppressive chemotherapy within prior 4 weeks.
  - Must be at least 2 weeks since undergoing major surgery and must be recovered from effects of surgery.
  - Subjects who have received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorefenib, imatinib or vascular endothelial growth factor receptor (VEGFR) or MEK inhibitors are eligible for enrolment if general eligibility criteria are met.
  - Subjects who have received therapy for PN that included other MAPK/MEK /RAS inhibitors are eligible for this study.

REVISED TEXT

4. **NF-1 Plexiform Neurofibroma Cohort (B3) Specific Criteria**

- Subjects with NF-1 must have a PN(s) that are progressive OR are cause of significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Subjects with paraspinal PN will be eligible for this trial. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected.

[redacted]

- A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with connection between the levels or extending laterally along the nerve.
- For subjects enrolled for tumor progression, progression is defined as:
    - Presence of new PN on MRI ~~or CT (~~documented by comparison with prior MRI ~~or CT~~), OR
    - A measurable increase in PN size (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) documented by comparison of two scans (MRI ~~or CT~~) in the time period of approximately one year or less prior to evaluation for this study.
- For subjects enrolled for a "major deformity" or "significantly disfiguring" tumor, eligible tumors will be limited to tumors of the head & neck or those on other areas of the body that are unable to be concealed by standard garments.
- All subjects must have either the clinical diagnosis of NF-1 using the National Institutes of Health (NIH) Consensus Conference criteria or have a constitutional NF-1 mutation documented in a CLIA/College of American Pathologist (CAP) certified lab.
- Subjects must have measurable PN(s) amenable to volumetric MRI analysis. For the purpose of this study, the target lesion must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest. Tumors must be at least 3 mL in volume (most PNs 3 cm in longest diameter will meet this criteria). If the tumor is <3 cm in longest diameter, the subject may still be eligible. Central review of the MRI of the target PN is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis. After consenting, please follow instructions in Appendix 6 or the SPM for central review of MRI. Central review will take 3-7 days (please plan accordingly).
- Adequate hematologic function defined as:
    - Absolute neutrophil count (ANC) ≥1000/μL;
    - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
    - Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
- Subjects with NF-1 **and PN** will only be eligible if complete tumor resection is not feasible, or if a subject with a surgical option refuses surgery.

[redacted]

- Since there is no standard effective chemotherapy for subjects with NF-1 and PN, subjects may be treated on this trial without having received prior medical therapy directed at their PN.
- Must not have received myelosuppressive chemotherapy within prior 4 weeks.
- Must be at least 2 weeks since undergoing major surgery and must be recovered from effects of surgery.
- Subjects who have received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorefenib, imatinib or vascular endothelial growth factor receptor (VEGFR) or MEK inhibitors are eligible for enrolment if general eligibility criteria are met.
- Subjects who have received therapy for PN that included other MAPK/MEK /RAS inhibitors are eligible for this study.

5.2.2 Exclusion Criteria (All Parts)

PREVIOUS TEXT

6. Subjects with NF-1 and only PN lesions that cannot be evaluated by volumetric analysis.
10. Part B and Part C only: Previous treatment with dabrafenib (cohort B4), trametinib or another MEK inhibitor (exception: prior treatment with sorafenib is permitted)
19. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.

REVISED TEXT

6. Subjects with NF-1 and only PN lesions that cannot be evaluated by volumetric analysis **(only applicable to Part B).**
10. Part B and Part C only: Previous treatment with dabrafenib ~~(cohort B4),~~ **or any RAF inhibitor,** trametinib or another MEK inhibitor**, or an ERK inhibitor** (exception: prior treatment with sorafenib is permitted). **Patients who have received prior dabrafenib or another BRAF inhibitor may enrol into Part B4. Patients who have had prior dabrafenib or BRAF inhibitor therapy may enroll in part C if they have had prior benefit to dabrafenib or BRAF inhibitor monotherapy, as determined by the investigator.**

[redacted]

19. A history of known ~~Human Immunodeficiency Virus (HIV),~~ Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection may be enrolled.

[redacted]

7.1 Time and Events Tables

PREVIOUS TEXT

Table 32 Time and Events, Treatment Phase: Screening through Day 28

Clinical Activity [redacted]		SCREEN					
Target and non-target lesion assessment	Must be identified at time of screening scan.	X					
Brain MRI (**glioma subjects ONLY)**	May use brain MRI obtained within 35 days of the first dose. CT with contrast allowed only if brain MRI is contraindicated.	X					
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X	X	X	X
MRI with volumetric assessment for **Plexiform Neurofibromas**	NF-1 PN Cohort Only. May be performed up to 4 weeks prior to enrollment, and requires central review (see Section 5.2.1.3)	X					
Tumor biopsy	Optional fresh biopsy		X		X		
[redacted]							

REVISED TEXT

Table 16 Time and Events, Treatment Phase: Screening through Day 28

Clinical Activity [redacted]		SCREEN					
Target and non-target lesion assessment	Must be identified at time of screening scan.	X					
Brain MRI (**glioma subjects ONLY)**	May use brain MRI obtained within 35 days of the first dose. CT with contrast allowed only if brain MRI is contraindicated.	X					
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X	X	X	X
MRI with volumetric assessment for **Plexiform Neurofibromas**	NF-1 PN Cohort Only. May be performed up to 4 weeks prior to enrollment, and requires central review (see Section 5.2.1.3)	X **(Part B)**					
Tumor biopsy	Optional fresh biopsy		X		X		
[redacted]							

[redacted]

PREVIOUS TEXT

Table 33 Time and Events, Treatment Phase, Week 9 to Final Visit

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Safety Assessments									
Brief Physical examination	Will include height and weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated]	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Dermatologic skin assessment	Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam for the duration of the study to ensure consistency between evaluations. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits.	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Plain radiograph of wrist and tibial growth plate	Only in subjects with open growth plates at screening	X				X	Every 24 weeks (6 months)	Every 52 weeks (12 months)	X
Tanner Stage						X	Every 24 weeks (6 months)	Every 24 weeks	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Urine Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Ophthalmologic examination	Performed by ophthalmologist. See Section 7.3.2 for details.			X		X	Every 12 weeks	Every 12 weeks	
ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by personnel with experience in this study population	X		X		X	Every 12 weeks	Every 12 weeks	X
Echocardiogram (ECHO)	Copies of all ECHOs will be collected and sent to the study sponsor during the study. An ECHO does not need to be performed at study discontinuation unless one was not performed within the previous 8 weeks.			X		X	Every 12 weeks	Every 12 weeks	X
Concomitant medications	See Protocol Section 9 for list of prohibited and cautionary medications.	X	X	X	X	X	X	X	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	X	X
Blood Sampling									
Chemistry	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4weeks	Every 12 weeks	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Clinical Activity [redacted] ***Assessments***									
Part A and Part C only; for Part B please see Table 15									
Target and non-target lesion assessment	Target and non-target lesions identified at time of screening scan must be re-assessed at each restaging scan. If the last radiographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation	X		X		X	Every 12 weeks	Every 12 weeks (or more frequently per local standard of care)	X
Response	Complete response/partial response confirmation assessments may take place at Week 13 if initial response was seen at the Week 9 scan. Initial response (complete response/partial response) that is observed at Week 17 or after should be confirmed not less than 4 and not more than 8 weeks after the initial response. LCH assessment : ONLY required at Week 13 and Week 25, then every 12 weeks	X	X (LCH only)	X		X +LCH	Every 12 weeks	Every 12 weeks	X
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X		X	Every 12 weeks	Every 12 weeks	X
Tumor Biopsy	Optional fresh biopsy	Upon disease progression							

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE	TREATMENT WEEK 9+							
Visit	Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)	±3	±7	±7	±7	±7	±7	±7	
[redacted]								

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Study Medication									
Dispense oral study medication and assess compliance	Dispense a 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	Every 4 weeks	Every 4 weeks	
Post Treatment Follow-up – See Section 6.6									

MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram

[redacted]

REVISED TEXT

Table 19 Time and Events, Treatment Phase, Week 9 to Final Visit

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Safety Assessments									
Brief Physical examination	Will include height and weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated]	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Dermatologic skin assessment	Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam for the duration of the study to ensure consistency between evaluations. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits.	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Plain radiograph of wrist and tibial growth plate	Only in subjects with open growth plates at screening	X				X	Every 24 weeks (6 months)	Every 52 weeks (12 months)	X
Tanner Stage						X	Every 24 weeks (6 months)	Every 24 weeks	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Urine Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Ophthalmologic examination	Performed by ophthalmologist. See Section 7.3.2 for details.			X		X	Every 12 weeks	Every 12 weeks	
ECG	Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary. ECG data should be reviewed by personnel with experience in this study population	X		X		X	Every 12 weeks	Every 12 weeks	X
Echocardiogram (ECHO)	Copies of all ECHOs will be collected and sent to the study sponsor during the study. An ECHO does not need to be performed at study discontinuation unless one was not performed within the previous 8 weeks.			X		X	Every 12 weeks	Every 12 weeks	X
Concomitant medications	See Protocol Section 9 for list of prohibited and cautionary medications.	X	X	X	X	X	X	X	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	X	X
Urinalysis	**Routine Urinalysis (See Table 21)**	**X**	**X**	**X**	**X**	**X**	**Every 4 weeks**	**Every 12 weeks**	**X**

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Blood Sampling									
Chemistry	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4 weeks	Every 12 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	Every 4weeks	Every 12 weeks	X

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Clinical Activity [redacted] ***Assessments***									
Part A and Part C only; for Part B please see Table 20									
Target and non-target lesion assessment	Target and non-target lesions identified at time of screening scan must be re-assessed at each restaging scan. If the last radiographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation	X		X		X	Every 12 weeks	Every 12 weeks (or more frequently per local standard of care)	X
Response	Complete response/partial response confirmation assessments may take place at Week 13 if initial response was seen at the Week 9 scan. Initial response (complete response/partial response) that is observed at Week 17 or after should be confirmed not less than 4 and not more than 8 weeks after the initial response. LCH assessment : ONLY required at Week 13 and Week 25, then every 12 weeks	X	X (LCH only)	X		X **(LCH only)**	Every 12 weeks	Every 12 weeks	X
Performance status (Karnofsky/Lansky)	See Appendix 1	X	X	X		X	Every 12 weeks	Every 12 weeks	X
Tumor Biopsy	Optional fresh biopsy	Upon disease progression							

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE	TREATMENT WEEK 9+							
Visit	Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)	±3	±7	±7	±7	±7	±7	±7	
[redacted]								

[redacted]

All subjects unless specified) week 9- final visit: STUDY PHASE		TREATMENT WEEK 9+							
Visit		Week 9	Week 13	Week 17	Week 21	Week 25	Weeks 25+ (after 6 months)	Weeks 53+ (after 1 year)	Final Visit
VISIT WINDOW (±days)		±3	±7	±7	±7	±7	±7	±7	
Study Medication									
Dispense oral study medication and assess compliance	Dispense a 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	Every 4 weeks	Every 4 weeks	
Post Treatment Follow-up – See Section 6.6									

MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram

[redacted]

7.3.2 Ophthalmology Examination

PREVIOUS TEXT

An age-appropriate ophthalmologic examination should be performed by an ophthalmologist at screening and at the timepoints specified in the Time and Events Tables (Section 7.1).

During the study, ophthalmologic exams may be repeated as clinically warranted. If any changes are noted during the required age-appropriate exam, or otherwise clinically indicated, a detailed ophthalmologic exam is mandatory (with sedation if necessary).

For subjects with clinical suspicion of RVO or RPED, fundus photography, fluorescein angiography, and/or optical coherence tomography are highly recommended.

REVISED TEXT

An age-appropriate ophthalmologic examination should be performed by an ophthalmologist at screening and at the timepoints specified in the Time and Events Tables (Section 7.1).

During the study, ophthalmologic exams may be repeated as clinically warranted. If any changes are noted during the required age-appropriate exam, or otherwise clinically indicated, a detailed ophthalmologic exam is mandatory (with sedation if necessary).

~~For subjects with clinical suspicion of RVO or RPED, fundus photography, fluorescein angiography, and/or optical coherence tomography are highly recommended.~~

[redacted]

7.3.7 Laboratory Assessments

PREVIOUS TEXT

Table 34 List of Clinical Laboratory Tests

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
Red blood cell (RBC) Count		MCV	Neutrophils
White blood cell (WBC) Count (absolute)		MCH	Lymphocytes
Hemoglobin		MCHC	Monocytes
Hematocrit			Eosinophils
HbA1c			Basophils
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin (Bilirubin fractionation recommended if total bilirubin is >2x the upper limit of normal)
Creatinine	Chloride	Alanine aminotransferase (ALT)	Total Protein
Glucose (recheck fasting if >160 mg/dL)	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	**Albumin**
Sodium	Calcium	Alkaline phosphatase (ALP)	
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Urine Protein Creatinine – Part C only			
Other screening tests			
Serum pregnancy test			
HVA/VMA in random or 24 hr urine for subjects with neuroblastoma			
In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.			

RBC = Red Blood Cell; WBC = White Blood Cell; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin: MCHC = Mean Corpuscular Hemoglobin Concentration; HVA/VMA = Homovanillic Acid / Vanillylmandelic Acid (ratio); CSF = Cerebrospinal fluid.

[redacted]

REVISED TEXT

Table 21 List of Clinical Laboratory Tests

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
Red blood cell (RBC) Count		MCV	Neutrophils
White blood cell (WBC) Count (absolute)		MCH	Lymphocytes
Hemoglobin		MCHC	Monocytes
Hematocrit			Eosinophils
HbA1c			Basophils
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin (Bilirubin fractionation recommended if total bilirubin is >2x the upper limit of normal)
Creatinine	Chloride	Alanine aminotransferase (ALT)	Total Protein
Glucose (recheck fasting if >160 mg/dL)	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	**Albumin**
Sodium	Calcium	Alkaline phosphatase (ALP)	
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
~~Urine Protein Creatinine – Part C only~~			
Other screening tests			
Serum pregnancy test			
HVA/VMA in random or 24 hr urine for subjects with neuroblastoma			
In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.			

RBC = Red Blood Cell; WBC = White Blood Cell; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin: MCHC = Mean Corpuscular Hemoglobin Concentration; HVA/VMA = Homovanillic Acid / Vanillylmandelic Acid (ratio); CSF = Cerebrospinal fluid.

[redacted]

7.4.1 Blood Sample Collection for Pharmacokinetics

PREVIOUS TEXT

Parts A and B:

Blood samples for PK analysis of trametinib will be collected at the time points indicated in the Time and Events Table, Section 7.1. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered to ensure thorough PK monitoring (but the total number of samples and total blood volume collected will not change).

Part C:

Blood samples for PK analysis of dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib (GSK2285403, GSK2298683 and GSK2167542, respectively), will be collected at the time points indicated in Time and Events Table, Section 7.1. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered to ensure thorough PK monitoring (but the total number of samples and total blood volume collected will not change). Plasma concentrations of dabrafenib and its metabolites GSK2285403, GSK2298683 and GSK2167542 will be determined from the 2 mL blood samples collected. Plasma concentrations of dabrafenib and its metabolites GSK2285403, and GSK2167542 will be determined from the 1 mL blood samples collected.

REVISED TEXT

Parts A and B:

Blood samples for PK analysis of trametinib will be collected at the time points indicated in the Time and Events Table, Section 7.1. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered to ensure thorough PK monitoring (but the total number of samples and total blood volume collected will not change).

Part C:

Blood samples for PK analysis of **trametinib,** dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib (GSK2285403, GSK2298683 and GSK2167542, respectively), will be collected at the time points indicated in Time and Events Table, Section 7.1. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered to ensure thorough PK monitoring (but the total number of samples and total blood volume collected will not change). ~~Plasma concentrations of dabrafenib and its metabolites GSK2285403, GSK2298683 and GSK2167542 will be determined from the 2 mL blood samples collected. Plasma concentrations of dabrafenib and its metabolites GSK2285403, and GSK2167542 will be determined from the 1 mL blood samples collected.~~

7.4.2 Pharmacokinetic Sample Analysis

PREVIOUS TEXT

Parts A, B, and C:

Plasma analysis will be performed under the management of [redacted]

[redacted]. Concentrations of trametinib as well as dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored in the GSK Archives. Once the plasma has been analyzed for trametinib, dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol. Raw data will be stored in the Good Laboratory Practice (GLP) GSK Archives.

Details on PK blood sample collection, processing, storage and shipping procedures are provided in the SPM.

REVISED TEXT

Parts A, B, and C:

Plasma analysis will be performed under the management of [redacted]. Concentrations of trametinib as well as dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored in the GSK Archives. Once the plasma has been analyzed for trametinib, dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol. Raw data will be stored in the Good Laboratory Practice (GLP) GSK Archives.

Details on PK blood sample collection, processing, storage and shipping procedures are provided in the SPM.

8.2 Definition of a SAE

PREVIOUS TEXT

An SAE is any untoward medical occurrence that, at any dose:

Results in death

Is life-threatening

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

Requires hospitalization or prolongation of existing hospitalization

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

[redacted]

Results in disability/incapacity, or

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

Is a congenital anomaly/birth defect.

Medical or scientific 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.

Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (INR) >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

  NOTE: Bilirubin fractionation is performed if testing is available. If testing is not available, 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 ≥2 times ULN, then the event is still reported as a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.
- Any new primary malignancy with a histology different from the primary tumor.
- LVEF that meets stopping criteria.
- RPED or RVO.
- Pyrexia accompanied by ≥ Grade 3 hypotension or hypotension that is clinically significant in the judgement of the investigator, or dehydration requiring IV fluids for greater than 72 hours, or severe rigors/chills.

REVISED TEXT

An SAE is any untoward medical occurrence that, at any dose:
Results in death

Is life-threatening

[redacted]

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

Requires hospitalization or prolongation of existing hospitalization

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

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

Results in disability/incapacity, or

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

Is a congenital anomaly/birth defect.

Medical or scientific 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.

Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (INR) >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

  NOTE: Bilirubin fractionation is performed if testing is available. If testing is not available, 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 ≥2 times ULN, then the event is still reported as a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

[redacted]

- Any new primary malignancy with a histology different from the primary tumor.
- LVEF that meets stopping criteria.
- RPED or RVO.
- ~~Pyrexia accompanied by ≥ Grade 3 hypotension or hypotension that is clinically significant in the judgement of the investigator, or dehydration requiring IV fluids for greater than 72 hours, or severe rigors/chills.~~

8.2.1 Sentinel Events

PREVIOUS TEXT

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

REVISED TEXT

Section 8.2.1 has been removed completely.

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

PREVIOUS TEXT

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

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

[redacted]

Any new primary cancer must be reported as a 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.

REVISED TEXT

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

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

~~Any new primary cancer must be reported as a 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.

12.2.2 Part B: Expansion Cohort

PREVIOUS TEXT

The sample size for Part B is s based on feasibility, practicality, and what would be sufficient for the characterization of the safety of trametinib and the plasma PK for the populations enrolled. Each of the 4 expansion cohorts will enroll at least 10 evaluable subjects, 5 subjects in each cohort will be under the age of 6 years. Therefore, an estimated 40 subjects will be enrolled into Part B.

If less than 1 response is observed after 10 subjects complete the study, the treatment could be considered to have insufficient clinical activity in that cohort. The estimated sample size (n=10) for the Part 2 expansion cohorts was further evaluated using exact binominal distribution probabilities, and the details are provided in Table 22. For example, if zero responses are observed among 10 subjects in a cohort [if the response rate (RR)=5%], the chance of declaring the cohort as having insufficient clinical activity after 10 subjects is 60%. If the true RR=15% for GSK1120212 in unresectable low grade gliomas subjects, the chance of declaring the cohort as having insufficient clinical activity after 10 subjects is approximately 20%.

REVISED TEXT

The sample size for Part B is s based on feasibility, practicality, and what would be sufficient for the characterization of the safety of trametinib and the plasma PK for the populations enrolled. Each of the 4 expansion cohorts will enroll at least 10 evaluable subjects, 5 subjects in each cohort will be under the age of 6 years. Therefore, ~~an~~ **it is** estimated **that at least** 40 subjects will be enrolled into Part B.

If less than 1 response is observed after 10 subjects complete the study, the treatment could be considered to have insufficient clinical activity in that cohort. The estimated sample size

[redacted]

(n=10) for the Part 2 expansion cohorts was further evaluated using exact binominal distribution probabilities, and the details are provided in Table 27. For example, if zero responses are observed among 10 subjects in a cohort [if the response rate (RR)=5%], the chance of declaring the cohort as having insufficient clinical activity after 10 subjects is 60%. If the true RR=15% for GSK1120212 in unresectable low grade gliomas subjects, the chance of declaring the cohort as having insufficient clinical activity after 10 subjects is approximately 20%.

12.5.2.3 Clinical Laboratory Evaluations

PREVIOUS TEXT

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4.03 [NCI, 2009]. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE v4.03 criteria will be summarized using proportions. Further details will be provided in the RAP.

REVISED TEXT

Hematology ~~and~~, clinical chemistry **and urinalysis** data will be summarized using frequencies and proportions according to NCI-CTCAE v4.03 [NCI, 2009]. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE v4.03 criteria will be summarized using proportions. Further details will be provided in the RAP.

15.2 Appendix 2: Dosing Nomograms

PREVIOUS TEXT

	DOSE LEVEL:	**0.0125 mg/kg/dose**
	SUBJECT WEIGHT:	**≤ 19.4 kg**
	FORMULATION:	**TRAMETINIB 0.05 MG/ML ORAL SOLUTION**
	[The 0.05 mg/mL oral solution will be administered to all patients ≤19.4 kg]	

REVISED TEXT

Dosing nomogram - Trametinib

	DOSE LEVEL:	**0.0125 mg/kg/dose**
	SUBJECT WEIGHT:	**≤ 19.4 kg**
	FORMULATION:	**TRAMETINIB 0.05 MG/ML ORAL SOLUTION**
	~~[The~~**[At this dose level, the** 0.05 mg/mL oral solution will be administered to all patients ≤19.4 kg]	

PREVIOUS TEXT

	DOSE LEVEL:	**0.025 mg/kg/dose**
	SUBJECT WEIGHT:	**< 10 kg**
	FORMULATION:	**TRAMETINIB 0.05 MG/ML ORAL SOLUTION**
	[The 0.05 mg/mL oral solution will be administered to all patients ≤9.9 kg]	

[redacted]

REVISED TEXT

	DOSE LEVEL: **0.025 mg/kg/dose** **SUBJECT WEIGHT:** **< 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** ~~[The~~**[At this dose level, the** 0.05 mg/mL oral solution will be administered to all patients ≤9.9 kg]

[redacted]

PREVIOUS TEXT

	DOSE LEVEL: **0.04 mg/kg/dose** **SUBJECT WEIGHT:** **< 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** [The 0.05 mg/mL oral solution will be administered to all patients ≤9.9 kg]

REVISED TEXT

	DOSE LEVEL: **0.04 mg/kg/dose** **SUBJECT WEIGHT:** **< 10 kg** **FORMULATION:** **TRAMETINIB 0.05 MG/ML ORAL SOLUTION** ~~[The~~**[At this dose level, the** 0.05 mg/mL oral solution will be administered to all patients ≤9.9 kg]

Additional New Text in Section 15.2

Dosing Nomogram - Dabrafenib

Dabrafenib **Suspension** Dosing Nomogram

Dose Level 1									
< 12 year olds					≥ 12 year olds				
Daily dose: 2.63 mg/kg dabrafenib suspension					Daily dose: 2.25 mg/kg dabrafenib suspension				
Body weight (kg)	Unit dose (mg)	Dosing volume (mL)	Syringe size (mL)	No. of stickpacks	Body weight (kg)	Unit dose (mg)	Dosing volume (mL)	Syringe size (mL)	No. of stickpacks
10-11	14	1.4	5	1	**10-11**	12	1.2	5	1
12-13	16	1.6	5	1	**12-13**	14	1.4	5	1
14	18	1.8	5	1	**14-15**	16	1.6	5	1
15-16	20	2.0	5	1	**16**	18	1.8	5	1
17	22	2.2	5	1	**17-18**	20	2.0	5	1
18-19	24	2.4	5	1	**19-20**	22	2.2	5	1
20	26	2.6	5	1	**21-22**	24	2.4	5	1
21-22	28	2.8	5	1	**23**	26	2.6	5	1
23	30	3.0	5	1	**24-25**	28	2.8	5	1
24-25	32	3.2	5	1	**26-27**	30	3.0	5	1
26	34	3.4	5	1	**28-29**	32	3.2	5	1
27-28	36	3.6	5	1	**30-31**	34	3.4	5	1
29	38	3.8	5	1	**32**	36	3.6	5	1
30-31	40	4.0	5	1	**33-34**	38	3.8	5	1
32-47	50	5.0	5	1	**35-36**	40	4.0	5	1
48-71	75	7.5	20	1	**37-38**	42	4.2	5	1
72-94	100	10.0	20	1	**39-55**	50	5.0	5	1

[redacted]

Dose Level 1									
< 12 year olds					≥ 12 year olds				
Daily dose: 2.63 mg/kg dabrafenib suspension					Daily dose: 2.25 mg/kg dabrafenib suspension				
Body weight (kg)	Unit dose (mg)	Dosing volume (mL)	Syringe size (mL)	No. of stickpacks	Body weight (kg)	Unit dose (mg)	Dosing volume (mL)	Syringe size (mL)	No. of stickpacks
95-118	125	12.5	20	2	**56-83**	75	7.5	20	1
≥ 119	150	15.0	20	2	**84-111**	100	10	20	1
					112-138	125	12.5	20	2
					≥ 139	150	15.0	20	2

Dose Level 2									
< 12 year olds					≥ 12 year olds				
Daily dose: 5.25 mg/kg dabrafenib suspension					Daily dose: 4.5 mg/kg dabrafenib suspension				
Body weight (kg)	Unit dose (mg)	Dosing volume (mL)	Syringe size (mL)	No. of stickpack	Body weight (kg)	Unit dose (mg)	Dosing volume (mL)	Syringe size (mL)	No. of stickpack
10	26	2.6	5	1	**10**	22	2.2	5	1
11	28	2.8	5	1	**11**	24	2.4	5	1
12	32	3.2	5	1	**12**	28	2.8	5	1
13	34	3.4	5	1	**13**	30	3.0	5	1
14	36	3.6	5	1	**14**	32	3.2	5	1
15	40	4.0	5	1	**15**	34	3.4	5	1
16-23	50	5.0	5	1	**16**	36	3.6	5	1
24-33	75	7.5	20	1	**17**	38	3.8	5	1
34-42	100	10.0	20	1	**18**	40	4.0	5	1
43-52	125	12.5	20	2	**19-27**	50	5.0	5	1
≥ 53	150	15.0	20	2	**28-38**	75	7.5	20	1
					39-50	100	10.0	20	1
					51-61	125	12.5	20	2
					≥ 62	150	15.0	20	2

[redacted]

Dabrafenib **Capsule** Dosing Nomogram

Dose Level 1 (Starting dose)					
< 12 year olds			≥ 12 year olds		
Daily dose: 2.63 mg/kg dabrafenib capsule			Daily dose: 2.25 mg/kg dabrafenib capsule		
Body weight (kg)	Capsules/ dose	Total Daily (actual)	Body weight (kg)	Capsules/ dose	Total Daily (actual)
<32	See suspension nomogram		<38	See suspension nomogram	
32-47	50 mg	100 mg	38-55	50 mg	100 mg
48-71	75 mg	150 mg	56-83	75 mg	150 mg
72-94	100 mg	200 mg	84-111	100 mg	200 mg
95-118	125 mg	250 mg	112-138	125 mg	250 mg
≥ 119	150 mg	300 mg	≥ 139	150 mg	300 mg

Dose Level 2					
< 12 year olds			≥ 12 year olds		
Daily dose: 5.25 mg/kg dabrafenib capsule			Daily dose: 4.5 mg/kg dabrafenib capsule		
Body weight (kg)	Capsules/ dose	Total Daily (actual)	Body weight (kg)	Capsules/ dose	Total Daily (actual)
<16	See suspension nomogram		<19	See suspension nomogram	
16-23	50 mg	100 mg	19-27	50 mg	100 mg
24-33	75 mg	150 mg	28-38	75 mg	150 mg
34-42	100 mg	200 mg	39-50	100 mg	200 mg
43-52	125 mg	250 mg	51-61	125 mg	250 mg
≥ 53	150 mg	300 mg	≥ 62	150 mg	300 mg

Children younger than 6 years and subjects, regardless of age, with a risk of choking when swallowing capsules will be required to use the suspension formulation.

The investigator or responsible site personnel should instruct the patient and guardians to take the study drug as per protocol (promote compliance).

Amendment 4

Where the Amendment Applies

Amendment 4 applies to all sites and is submitted prior to initiation of the study.

Summary of Amendment Changes with Rationale:

Global Changes:

Section(s)	Change	Rationale
Sponsor signatory	Change of sponsor signatory	Change in study sponsor from GSK to Novartis

[redacted]

Section(s)	Change	Rationale
Multiple	Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents	To align with the change of sponsorship from GSK to Novartis.
Multiple	Replace references to Medical Monitor with Medical Lead	To align with the change of sponsorship from GSK to Novartis.
Multiple	Make administrative changes	To align with the change of sponsorship from GSK to Novartis.

Amendment Details:

Section: Title Page:

Text changed:

The title page replaced as per Novartis requirements.

Reason for change:

Change in study sponsorship.

Section: Sponsor Information Page

Text changed:

The GSK contact information has been replaced with Novartis details.

The term medical monitor has been replaced by Medical Lead and the email for Medical Lead provided.

Reason for change:

Change in study sponsorship.

Section: Pregnancy Testing and Reporting:

Text changed:

To ensure subject safety, each pregnancy must be reported to Novartis within ~~2 weeks~~**24 hours** of learning of its occurrence.

Reason for change:

Change in study sponsorship.

Section: Pharmacokinetic Sample Analysis:

Text changed:

Raw data will be stored in the ~~Good Laboratory Practice (GLP) GSK~~**Novartis** Archives.

Reason for change:

Change in study sponsorship.

Section: 8.4. Time Period and Frequency of Detecting AEs and SAEs:

Text changed:

From the time a subject consents to participate in and completes the study (See Section 6), all SAEs assessed as related to study participation (e.g., protocol-mandated

[redacted]

procedures, invasive tests, or change in existing therapy), will be reported promptly to Novartis, as indicated in.

~~SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hr, as indicated in Section 8.4.2.~~

Reason for change:

Change in study sponsorship.

Section: Prompt Reporting of SAEs and Other Events to GSK:

Text changed in Table 23:

Pregnancy	~~2 weeks~~ **24 hours**	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form

Reason for change:

Change in study sponsorship.

Section: Data Management:

Text changed:

For this study subject data will be entered into ~~GSK defined~~**the** eCRFs, transmitted electronically to ~~GSK~~**the sponsor** or designee and **be** combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable ~~GSK~~ standards and data cleaning procedures to ensure the integrity of the data, e.g., ~~removing~~ **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 validated medicationa~~ **custom drug** dictionary~~, GSKDrug. The eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy~~.

Reason for change:

Change in study sponsorship.

Section: Quality Control (Study Monitoring):

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

Novartis (or designated CRO) personnel will monitor the study~~Monitoring visits will be conducted in a manner~~ to ensure that the:

Text changed:

Reason for change:

Change in study sponsorship.

Section: Study and Site Closure:

[redacted]

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

Text changed:

Reason for change:

Change in study sponsorship.

Section: Records Retention:

~~GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.~~**Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless 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.**

Text changed:

Reason for change:

Change in study sponsorship.

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

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

Text changed:

Reason for change:

Change in study sponsorship.

[redacted]