NOVARTIS

Clinical Development

Dabrafenib (DRB436)

Protocol BRF116013 / NCT01677741

Phase I/IIa, 2-part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects with Advanced BRAF V600-Mutation Positive Solid Tumors

Document type	Amended Protocol Version (Clean)
EUDRACT number	2012-001499-12
Version number	11
Development phase	I/IIa
Document status	Final
Release date	21-Aug-2020
Novartis internal reference number	CDRB436A2102

Amendment 11 (21-Aug-2020)

Amendment Rationale

As of 17-Jul-2020, 85 patients have received study treatment in 8 countries; Part 1 dose escalation has enrolled 27 patients and is closed to enrollment. Part 2 has enrolled 58 pediatric patients, and is closed to enrollment. These 58 patients include: 28 patients with High Grade Glioma (HGG), 17 patients with Low Grade Glioma (LGG), 11 patients with Langerhans Cell Histiocytosis (LCH) and 2 patients with other (miscellaneous) solid tumors. 52 patients in Part 1 or Part 2 have completed or discontinued study treatment.

The purpose of this amendment is to change the target patient enrollment number for the miscellaneous tumor cohort. The clinical trial has achieved its major aims of identifying suitable doses to reach target exposure across various ages, demonstrated acceptable toxicity, and importantly, identified several disease cohorts where dabrafenib demonstrated sufficient antitumor activity to merit further clinical investigation. These aims have been previously aligned with EU and US regulatory agencies.

Note that the trial has enrolled only four patients with miscellaneous tumor types (those that are BRAFV600 mutant but are not HGG, LGG, or LCH); two in the dose finding portion, two in the dedicated miscellaneous cohort, over the more than 5 years of enrollment. The miscellaneous cohort is not required for regulatory obligations, and is not required to meet the aims of the clinical trial. Hence, the proposed enrollment target for the miscellaneous cohort is modified from ‘at least 10 patients’ to ‘up to ten patients.’

The protocol is also being amended 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.

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:

- List of Abbreviations Table: updated to include PIP and RANO.
- Removal of named contact details and integrated signature pages in alignment with current Novartis template and standards.
- Section 3.1.2: Amended to match the clinical measures in the current approved PIP.

- Appendix 15.2: 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.

Amendment 10 (04-Apr-2019)

Amendment Rationale

As of 06-Feb-2019, 85 patients have received study treatment in 8 countries; Part 1 dose escalation has enrolled 27 patients and is closed to enrollment. Based on the data from these 27 subjects, no maximum tolerated dose was established in this pediatric population and the recommended Phase 2 doses (RP2Ds) for dabrafenib monotherapy were determined based on exposure target as 5.25 mg/kg/day for patients < 12 years old and 4.5 mg/kg/day for patients ≥ 12 years old, divided into two equal daily doses, and not to exceed adult dose.

Part 2 has enrolled 58 pediatric patients, and is closed to enrollment. These 58 patients include: 28 patients with High Grade Glioma (HGG), 17 patients with Low Grade Glioma (LGG), 11 patients with Langerhans Cell Histiocytosis (LCH) and 2 patients with other solid tumors. 52 patients in Part 1 or Part 2 have completed or discontinued study treatment.

The purpose of this amendment is to add additional interim analyses of data to support health authority 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 5.3.2: Updated to include additional interim analyses to support health authority requests.
- Section 7.1.1: 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 8.2: Table 12 updated to remove oxcarbazepine from list of prohibited medications during study treatment. Based on the 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 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.

Amendment 9 (17-Sep-2018)

Amendment rationale

84 subjects have received study treatment in 7 countries; Part 1 dose escalation has enrolled 27 subjects and is closed to enrollment. Based on the data from these 27 subjects, no maximum tolerated dose was established in this pediatric population and the recommended Phase 2 doses (RP2Ds) for dabrafenib monotherapy were determined based on exposure target as 5.25

mg/kg/day for subjects < 12 years old and 4.5 mg/kg/day for subjects ≥ 12 years old, divided into two equal daily doses, and not to exceed adult dose.

Part 2 has enrolled 57 pediatric patients (27 patients with High Grade Glioma (HGG), 17 patients with Low Grade Glioma (LGG), 11 patients with Langerhans Cell Histiocytosis (LCH) and 2 patients with other solid tumors). Currently only the HGG and other solid tumor cohorts are open for enrollment in Part 2. 47 subjects in Part 1 or 2 have completed or discontinued study treatment.

The purpose of this amendment is:

i) Addition of a new pediatric formulation dosage form of dabrafenib 10mg as dispersible tablets.

ii) Update the withdrawal of consent language to align with the new Global Data Protection Requirements.

Changes to 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:

- Sponsor Signatory Page: update to current team member
- Section 1.1.4: Addition of PK data of Dabrafenib dispersible tablet formulation
- Section 3.2, 3.6, 10.3, 10.4: Addition of Dabrafenib dispersible tablet language
- Section 9.3: Withdrawal of consent wording added to align with new Global Data Protection Requirements.
- Section 4.2, 7.1: Updated program standard language regarding contraceptive methods

IRBs/IECs

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

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

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

Amendment 8 (19-May-2017)

Amendment rationale

As of 04-May-2017

78 subjects have received study treatment in 7 countries; Part 1 dose escalation has enrolled 27 subjects and is closed to enrollment. Based on the data from these 27 subjects, no maximum tolerated dose was established in this pediatric population and the recommended Phase 2 doses (RP2Ds) for dabrafenib monotherapy were determined based on exposure target as 5.25

mg/kg/day for subjects < 12 years old and 4.5 mg/kg/day for subjects ≥ 12 years old, divided into two equal daily doses, and not to exceed adult dose.

Part 2 has enrolled 51 subjects (21 pediatric High Grade Glioma (HGG), 17 pediatric Low Grade Glioma (LGG), 11 Langerhans Cell Histiocytosis (LCH) and 2 other solid tumor subjects). Currently only the HGG and other solid tumor cohorts are open for enrollment in Part 2. ***40*** subjects in Part 1 or 2 have completed or discontinued study treatment.

An interim analysis was performed in 2016 after all subjects with LGG had enrolled in Part 2 and completed at least 6 months of treatment or had discontinued treatment earlier. The interim analysis showed preliminary efficacy in overall response rate for subjects with HGG and LGG sufficient for further investigation.

The main objective of this protocol amendment 8 is

- To allow the enrollment of additional subjects in the HGG cohort of Part 2 of the study. This cohort was originally planned to include approximately 10 subjects and has enrolled 21 subjects in Part 2 to date. In view of the promising efficacy in this otherwise very poor prognosis disease, enrollment will remain open until another pediatric HGG study is open for enrollment of this population across all age groups in the same countries (expected by the end of 2018 and no later than mid 2019). Enrollment into the LGG and LCH cohorts have not been extended as subjects may be able to enroll into another pediatric study (MEK116540).

Additional changes were made as follow:

- The safety monitoring and management sections were revised to distinguish the procedures that are recommended or mandatory and updated to align with the program standard language. The management of renal insufficiency section was clarified to account for the young age population studied and their normal range.
- The monitoring process of dermatologic lesions was modified to allow local assessment during non-clinic visits or dermatologic assessment only visits to accommodate subjects who have to travel from afar.
- Collection of imaging scans from the most recent prior chemotherapy for subjects with LGG was added to explore the comparison of retrospective data with data collected while on treatment. Tumor shrinkage at a six month time-point of treatment has been utilized as a surrogate for treatment effect in LGG, where durable stability or shrinkage is considered clinical benefit. Performing a similar comparison in subjects with HGG would be more difficult due to the aggressive nature of the disease and the need to review the entire prior clinical course.
- The table of time and events schedule was modified to align the assessments to decrease the frequency of visits after one year of treatment.
- The data analysis and statistical consideration was updated to align the analysis populations with the statistical analysis plan.
- Two interim analyses were added to explain a past unplanned interim analysis and a future interim analysis for decision making of development options.
- Independent review of HGG tumor histology was clarified in the protocol. It has been shown that LGG can be misdiagnosed for HGG, so the independent review will ensure

consistent application of the WHO glioma classification scale to allow for more reliable comparison to historical studies. As a sensitivity analysis, the efficacy data will be analyzed including only subjects with centrally confirmed HGG.

- Due to the possible harm to the fetus from dabrafenib exposure, male contraception requirement was added.
- The permitted and prohibited concomitant medication section was modified to permit immunization and to remove the need to be cautious with medicinal products that increase gastric pH due to the low drug-drug interaction risk. Co-administration of dabrafenib with the pH elevating agent rabeprazole (proton pump inhibitor) did not result in clinically meaningful changes to dabrafenib PK (study CDRB436A2103).
- Editorial changes and text corrections were made for clarification, where required, and to align with Novartis terminology procedures and format.

Changes to 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 2: Clarified anti-tumor activity objectives between investigator assessed and independent assessed response
- Section 3.1, Section 3.1.2, Section 4.1, Section 5.2.1.2, Section 5.2.2: Amended to increase the sample size
- Section 3.3: Clarified DLT evaluable population definition
- Section 3.7.4.1, Section 3.7.4.2, Section 3.7.4.4: These sections and tables were updated to provide clarity on the recommended or mandatory safety monitoring and management procedures. The adverse event management guidelines remain largely the same as protocol amendment 7.
- Section 3.7.4.2: Added clarification on management of renal insufficiency in this young studied population
- Section 3.7.4.3, Section 3.8, Section 6.3: Added and modified dermatologic monitoring and assessment.
- Section 3.7.5: Added dose modification guidance for uveitis
- Section 3.8: Updated table to provide clarity on assessments and to decrease frequency of assessments after 48 weeks of treatment
- Section 3.8, Section 6.1: Added collection of imaging scans from the most recent prior chemotherapy for subjects with LGG
- Section 5.3: Clarified analysis population definition and aligned with Novartis terminologies.
- Section 5.3.2: Added 2 interim analyses (one past unplanned interim analysis and a future interim analysis)
- Section 5.3.3.1, Section 5.3.3.1.3, Section 5.3.3.1.4, Section 5.3.3.3: Clarified analysis plan
- Section 6.2.1: Clarified BRAF mutation testing procedure
- Section 6.2.3: Clearly described the independent review of HGG tumor histology

- Section 6.3: Removed ANC testing requirement. Percentage is acceptable. Clarified laboratory testing requirement needed for LCH scoring.
- Section 7.1.2: Added male contraception requirement
- Section 8.1: Added immunization to the permitted medication and non-drug therapies section.
- Section 8.3: removed a risk from 'Medications to be Used with Caution' as studies have shown it is not considered a risk.
- Section 11.1, Section 11.7: Clarified adverse event definition and SAE reporting requirement
- Section 13.7: Amended timing of study result posting
- Section 14: Added one reference

IRBs/IECs

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

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

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

Amendment 7

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound ***GSK2118436*** by Novartis, the purpose of this protocol Amendment ***7*** 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 ***19-Aug-2016***:

- ***68*** patients have received study treatment in ***6*** countries;
- ***28*** 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 6

Amendment rationale and summary of changes for previous amendments 1 to 6 are provided below in the Revision Chronology section and also in Appendix 07 as tracked changes.

Revision Chronology:

2012N131371_00	2012-JUL-24	Original
2012N131371_01	2012-OCT-19	Amendment No. 01 corrected Inclusion Criteria #6 to ensure consistency with the contraception requirements as outlined in Section 7.1.1; the requirement for male contraception was deleted since the risk of embryofetal developmental toxicity as a consequence of exposure to female pregnant partners is very low. In addition, the dose escalation procedure table provided in Appendix 1 was changed to ensure that escalation of dose when 6 subjects are enrolled occurs only if there are ≤1 subject with a DLT and no subject data pending, and to fix the reference and formatting.
2012N131371_02	2012-DEC-13	Amendment No. 02 is a country-specific amendment for France which prohibits children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules from inclusion in the study in France (pending availability of an oral suspension formulation); changes the QTc stopping criteria to 500 msec for French subjects (as compared to 530 msec); adds cardiac monitoring by echocardiogram (ECHO) at Week 4; and highlights that ECHOs are to be performed by the same operator throughout the study, where possible.
2012N131371_03	2013-MAR-28	Amendment No.: 03: To take into account potential renal effects, Amendment 03 changed the lower age limit of inclusion criterion #2 from subjects 1 month old to ≥12 months old, adjusted criteria for adequate renal function in inclusion criterion #7, added guidelines for renal insufficiency and additional laboratory testing. Information on the new suspension formulation was incorporated. The section on dose modification was re-organized for consistency. The Time and Events Table was adjusted to include assessments on Day 22, Week 4 was clarified to be Day 29, and increased chemistry and urinalysis evaluations were added. The timing and volume of PK samples for subjects <25 kg and ≥10 kg was corrected
2012N131371_04	2013-JUN-19	Amendment No. 04 expanded eligibility to subjects with refractory disease, and allows for BID dosing on Day 1. Clarifications made to glioma scan requirements and BRAF mutation testing timing. Pyrexia management guidelines updated and Prohibited and Cautionary medication section updated.

2012N131371_05	2013-JUL-25	Amendment No.: 05 was made to allow an administrative change (i.e. additional abbreviation added); to clarify the dose escalation rules to allow selection of the appropriate dose by age group in the absence of MTD; to include 2 additional dose levels: To clarify that at least 5 subjects less than 6 years old will be enrolled to be consistent with the binding elements of the PIP to permit intra-subject dose escalation during Part 1; intra-subject dose escalation determined on case by case basis after evaluation of PK and safety; subjects who are allowed to dose escalate will be required to have additional PK samples collected 15 days after starting the higher dose level; to include the recommendation for an additional dermatological examination 2 months after discontinuation of dabrafenib; to clarify the general dose modification guidelines; to incorporate instructions for due diligence in contacting subjects who may be lost to follow up; to clarify the DLT evaluable population and PK population; to update the T&E table to specify that ECHOs will be collected for all subjects; to correct Appendix 1.
2012N131371_06	2013-AUG-20	Re-Publishing to include a component of the binding elements; to include some details that were missed in the previous version.
2012N131371_07	2014-JUL-30	Amendment No.: 06 Title changed to specify children and adolescents instead of specific years. Lower age range increased to ≥12 months from >1 month. Study rationale updated to specify refractory disease. Clarification of the dose escalation rules for selection of the appropriate dose by age group in the absence of MTD. Correction of units for exposure criterion. Update of dose modification guidelines in accordance with the most recent information available for dabrafenib. Addition of LCH assessments to the time and events schedule, and addition of the LCH scoring system. Addition of follow-up skin assessments to the time and events schedule and safety assessments, including French country specific guidelines. Clarification of timing for final study visit in the time and events schedule. [redacted]. Removal of the restriction on foods that may inhibit cytochrome (CYP) 3A4 activity. Clarification that children that are breastfeeding may continue to breast feed on demand, but that if child is breast fed during collection of PK samples the time of breastfeeding should be recorded. Overdose section updated in accordance with the most recent information available for dabrafenib. SAE definition of protocol-specific SAEs updated for clarity and modified based on additional understanding of the compound.
2012N131371_08	2016-Sep-15	Amendment No.: 07 References to GSK or its staff were deleted and replaced with those of Novartis/Novartis and its authorized agents. Administrative changes to align with Novartis processes and procedures were made

Sponsor Information Page

Clinical Study Identifier: BRF116013

Sponsor Contact Addresses

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 contact information and further details.

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

- Regulatory Agency Identifying Number(s):
- IND No.: 117,898
- EudraCT Number: 2012-001499-12

Table of contents

List of tables

List of figures

ABBREVIATIONS

ACCIS	Automated Childhood Cancer Information System
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-HCG	Beta-Human Chorionic Gonadotropin
BID	Twice daily
BUN	Blood urea nitrogen
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
CNS	Central nervous system
C_τ	Pre-dose (trough) concentration at the end of the dosing interval
CPK	Creatine phosphokinase
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form
CRP	C-Reactive protein
CRO	Contract Research Organization
CT	Computed tomography
cuSCC	Cutaneous squamous cell carcinomas
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ED50	One-half the maximal effect
eGFR	Calculated Glomerular Filtration Rate
ERK	Extra-cellular signal related kinase
EU	Europe
FDA	Food and Drug Administration
FDG-PET	Fludeoxyglucose positron emission tomography
FTIH	First time in humans
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GCPH	Global Clinical Program Head
GGT	Gamma glutamyltransferase
GI	Gastrointestinal

GSK	GlaxoSmithKline
hCG	Human chorionic gonadotropin
HFSR	Hand foot skin reactions
HGG	High grade gliomas
HIV	Human Immunodeficiency Virus
HPMC	Hydroxylpropyl methylcellulose
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ka	Absorption rate
KA	Keratoacanthomas
Kg	Kilogram
L	Liter
LCH	Langerhans cell histiocytosis
LGG	Low-grade gliomas
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
µg	Microgram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Milliseconds
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PD	Progression of disease
pERK	Phosphorylated ERK
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PP	Polypropylene
PPES	Palmar Plantar erythrodysaethesia Syndrome
PR	Partial response
PTC	Papillary Thyroid Carcinoma
QTc	QT duration corrected for heart rate
QTcB	QT duration corrected for heart rate by Bazett's formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	Red blood cells
RR	Response rate
RSD	Rolling six design
SAE	Serious adverse event(s)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software

SCC	Squamous cell carcinoma
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
SNIFS	Serious non-infectious febrile syndrome
SPM	Study Procedures Manual
t½	Terminal phase half-life
TID	Three times a day
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
UPC	Urine Protein:Creatinine Ratio
US	United States
V/F	Volume of distribution
WBC	White blood cells

1 INTRODUCTION

1.1 Background

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 biomarker (phosphorylated extracellular signal-related kinase [pERK]) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutation-positive tumor cell lines, achieved proximal biomarker suppression and tumor regression in BRAF mutant xenograft models, and has demonstrated significant anti-tumor efficacy in BRAF V600-mutation positive tumors, including melanoma, papillary thyroid cancer, and non-small cell lung cancer. Dabrafenib is currently approved in many jurisdictions for adult subjects with BRAF V600 mutation-positive advanced or metastatic melanoma, and is being studied in subjects with other BRAF V600 mutation-positive tumor types.

As of May, 2012, there were 4 completed Phase I studies including the First-Time-in-Human (FTIH) study (BRF112680), a food effect/particle size evaluation study (BRF113468) with 2 different capsule shells (gelatin and hydroxylpropylmethyl cellulose [HPMC]), a human mass balance study (BRF113463), and a microdose absolute bioavailability study (BRF113479), and 1 ongoing clinical pharmacology study, a repeat dose, drug-drug interaction study (BRF113771). There were ongoing Phase II studies (BRF113710 in subjects with metastatic melanoma, BRF113928 in subjects with non-small cell lung cancer [NSCLC] and BRF113929 in subjects with metastatic melanoma to the brain), and one ongoing Phase III study (BRF113683) in advanced or metastatic melanoma. Three pediatric subjects were given dabrafenib on a compassionate use basis. There is an ongoing Phase I/II combination study with trametinib (GSK1120212), a MEK inhibitor (BRF113220). A separate rollover protocol is available for subjects still benefitting from treatment at the end of the Phase I, II or III studies.

Complete safety, clinical activity and pharmacokinetic (PK) data for clinical and non-clinical studies conducted with dabrafenib are provided in the Investigator Brochure (IB). A summary of safety, clinical activity and PK data are also provided below. Please refer to the current Investigator's Brochure for the most up to date safety and efficacy data.

1.1.1 Summary of Safety Data (All Studies) and Available Clinical Activity Data (BRF112680 and BRF113710)

1.1.1.1 BRF112680 (FTIH)

As of 20 February, 2012, a total of 184 subjects received at least one dose of dabrafenib. As of 19 March 2012 all subjects were discontinued from the study. One hundred and eighty-two (99%) subjects experienced an adverse event (AE) of any grade. The most common (>20% of all subjects) AEs of any grade across all dosing cohorts in Part 1 and Part 2 were fatigue (42%), pyrexia (37%), headache (35%), nausea (34%), hyperkeratosis (33%), diarrhoea (27%), arthralgia (25%), pain in extremity (25%), decreased appetite (24%), alopecia (23%) and rash (23%). Serious adverse events (SAEs) were reported in 39% of subjects. SAEs occurring in 3% or more subjects were squamous cell carcinoma (SCC) (12%), pyrexia (7%), and urinary tract infection (3%). Sixty four subjects are reported to have had study drug interrupted due to

the occurrence of AEs. Pyrexia was the most common AE leading to a dose interruption. Fifteen subjects reported a dose reduction due to the occurrence of 23 AEs. There were no instances of discontinuation of study treatment due to AEs and no fatal AEs reported in the study among subjects who received at least one dose of dabrafenib.

PK, pharmacodynamic and clinical activity results supported 1) the conclusion that the recommended clinical dose of dabrafenib in adult subjects is 150 mg twice daily (BID) and 2) the conclusion that dabrafenib has demonstrated significant efficacy in subjects with BRAF V600E or V600K mutant-positive advanced melanoma.

An investigator-assessed best unconfirmed response rate of 67% was observed in subjects with BRAF V600E/K mutation-positive melanoma receiving the recommended dose of 150 mg BID (n=45).

In addition, data from a small number of adult subjects with BRAF V600 mutation-positive solid tumors other than melanoma, who were enrolled in an expansion cohort in the FTIH study, suggested that dabrafenib may have beneficial effects in these subjects as well [BRF112680]. There were 7 subjects enrolled with colorectal cancer (CRC), 10 subjects with thyroid cancer, 1 subject with NSCLC and 1 subject with ovarian cancer. A summary of investigator-assessed unconfirmed response for CRC and thyroid cancer are summarized in Table 1 and Table 2, respectively. The NSCLC subject was enrolled in Part 2 (150 mg BID) and reported an unconfirmed partial response (PR) at 6 weeks followed by disease progression at 12 weeks. The ovarian cancer subject was enrolled in Part 1 (100 mg BID) and reported stable disease before progressing at approximately 36 weeks.

Table 1-1 Investigator–Assessed Response for V600 Mutation-Positive CRC from Part 1 and Part 2 of Study BRF112680

	Part 1 (N=1)	**Part 2 (N=6)**	**Total (N=7)**
Best Response, n (%)			
Complete Response (CR)	0	0	0
Partial Response (PR)	0	1 (17%)	1 (14%)
Stable Disease	0	5 (83%)	5 (71%)
Progressive Disease (PD)	0	0	0
Unknown	1 (100%)	0	1 (14%)
Response Rate, n (%)			
CR+PR	0	1 (17%)	1 (14%)
95% Confidence Interval		(0.4%, 64.1%)	(0.4%, 57.9%)

Table 1-2 Investigator-Assessed Response for V600 Mutation Positive Papillary Thyroid Cancer from Part 1 and Part 2 in Study BRF112680

	Part 1 (N=2)	**Part 2 (N=8)**	**Total (N=10)**
Best Response, n (%)			
Complete Response (CR)	0	0	0
Partial Response (PR)	1 (50%)	1 (13%)	2 (20%)
Stable Disease	0	6 (75%)	6 (60%)

Progressive Disease (PD)	1 (50%)	0	1 (10%)
Unknown	0	1 (13%)	1 (10%)
Response Rate, n (%)			
CR+PR	1 (50%)	1 (13%)	2 (20%)
95% Confidence Interval	(1.3%, 98.7%)	(0.3%, 52.7%)	(2.5%, 55.6%)

1.1.1.2 BRF113710 (Phase II in Metastatic Melanoma)

As of 20 February 2012, 92 subjects were enrolled in BRF113710 and 87 (95%) of subjects experienced at least one AE of any grade. The majority of all AEs were Grade 1 or 2. The most commonly reported AEs (>20% of subjects) were arthralgia (33%), hyperkeratosis (28%), pyrexia (27%), fatigue (23%), headache (23%) and nausea (21%). SAEs were reported in 29 (32%) subjects. SAEs occurring in 3% or more subjects were cutaneous SCC (9%), basal cell carcinoma (4%), anemia (3%), pyrexia (3%) and vomiting (3%). Twenty-nine subjects (32%) had study drug interrupted and 16 (17%) subjects required dose reduction due to the occurrence of AEs. One adverse event (pancytopenia, unrelated to dabrafenib) resulted in permanent discontinuation of study drug. No fatal Grade 5 SAEs were reported in the study.

The primary objective of this study was achieved with an overall investigator-assessed confirmed response rate in the BRAF V600E Population of 59% (95% CI: 48.2-70.3%), including a 7% complete response rate. Additionally, 16% of subjects in the BRAF V600E Population experienced stable disease for a minimum of 12 weeks. Two subjects (13%) in the BRAF V600K Population had a confirmed response (95% CI: 0-28.7%). Seven subjects (44%) in the BRAF V600K Population had SD for a minimum of 12 weeks and 5 subjects (31%) had PD as a best response.

1.1.1.3 BRF113683 (Phase III in Advanced or Metastatic Melanoma)

As of 19 December 2011, 187 (75%) subjects randomized to dabrafenib and 59 (25%) subjects randomized to dacarbazine (DTIC) and received at least one dose of study treatment. The majority of subjects in both treatment arms (99% in the dabrafenib arm and 92% in the DTIC arm) experienced at least 1 AE. Grade 3 AEs were reported at a similar frequency in both arms (dabrafenib: 29%; DTIC: 27%) and Grade 4 AEs were more frequently experienced by 14% of subjects in the DTIC arm compared to the 4% of subjects in the dabrafenib arm. The most common (≥20% of subjects) AEs of any grade reported in the dabrafenib arm were hyperkeratosis (37%), headache (32%), pyrexia (28%), arthralgia (27%), skin papilloma (24%), alopecia (22%) and palmar-plantar erythrodysaethesia (PPE) syndrome (20%). Each of these events was reported in a greater proportion of subjects in the dabrafenib arm than in the DTIC arm. AEs typically expected with cytotoxic chemotherapy including gastrointestinal (GI) symptoms (nausea, vomiting, abdominal pain) and cytopenias (including neutropenia, anemia and thrombocytopenia) were more common in the DTIC arm than in the dabrafenib arm. Fatigue and asthenia were common (≥15%) in both arms of the study.

A similar proportion of subjects experienced SAEs in both treatment groups (dabrafenib: 43 [23%] subjects; DTIC 13 [22%] subjects). SAEs reported in more than 1% of the dabrafenib arm were cutaneous SCC (5%); reported under the preferred terms of squamous cell carcinoma [4%] and squamous cell carcinoma of the skin [2%]), pyrexia (4%) and malignant melanoma (2%).

The same proportion of subjects (27%) experienced AEs resulting in dose interruptions/delays in the 2 treatment arms. The AEs resulting in dose delays/interruptions in ≥ 2% of subjects in the dabrafenib arm were pyrexia (11%), PPE syndrome (3%), chills (3%), alanine aminotransferase increased (2%), hyperkeratosis (2%) and in the DTIC arm the events were the known events for this compound. During the randomized phase, AEs resulting in discontinuation of study treatment occurred in 3% of subjects in both treatment groups. In the dabrafenib arm the following AEs caused a discontinuation: hepatic pain, constipation, mitral and tricuspid valve disease, muscular weakness and myocardial infarction.

A similar proportion of subjects experienced AEs resulting in dose reductions (dabrafenib: 18%; DTIC: 17%). The AEs resulting in dose reductions in ≥2% of the subjects in the dabrafenib arm were pyrexia (9%), PPE syndrome (3%), chills (3%), fatigue (2%), and headache (2%).

Twenty-one (11%) subjects in the dabrafenib arm and 9 (15%) subjects in the DTIC arm have died. All but 1 death (elective euthanasia, dabrafenib arm) was attributed to the disease under study.

Preliminary efficacy data from this study have now been published (Hauschild, 2012).

1.1.1.4 BRF113929 (Phase II, Metastatic Melanoma to the Brain)

As of 28 November 2011, 172 subjects were enrolled into BRF113929 with 89 subjects in Cohort A (subjects with no prior local therapy for brain metastasis) and 83 subjects in Cohort B (subjects who received prior local therapy for brain metastasis). Most subjects (92%) experienced at least one AE. Most AEs experienced by subjects in the study were of Grade 1 or 2 in intensity. The most common AEs (experienced by ≥20% subjects) in both cohorts were headache (28%), hyperkeratosis (26%), nausea (26%), pyrexia (26%), fatigue (25%) and vomiting (20%).

A total of 51 (30%) subjects experienced SAEs. Grade 3 or 4 AEs occurred in 68 (40%) subjects. Headache, PPE syndrome, SCC, hypokalemia and hyponatremia were the most frequent Grade 3 AEs (3% each), while neutropenia at 2% was the most frequent Grade 4 AE.

Fifty-five (32%) subjects had an AE leading to dose interruption. Pyrexia was the most common AE leading to dose interruptions in the study (10%). Other AEs that led to dose interruptions in at least 2 subjects in the study were vomiting, chills, hypotension, decreased appetite, and fatigue.

Twenty-four (14%) subjects experienced AEs leading to dose reductions in the study; pyrexia (4%) and hypophosphatemia (2%) were the 2 most common AEs leading to dose reductions.

Few subjects (2%) discontinued study treatment due to AEs. Two subjects in Cohort A and 1 in Cohort B died as a result of cerebral hemorrhage unrelated to study treatment; according to the investigator, the primary cause of death for all 3 cases was disease under study.

Preliminary efficacy data from this study have now been published (Hauschild, 2012).

1.1.1.5 Compassionate Use in Pediatric Subjects

Four subjects <18 years of age with melanoma have received dabrafenib on a compassionate use basis. Two subjects were in the UK (2 [redacted] aged [redacted] and [redacted] years at time of first administration of dabrafenib), one subject was in Italy (a [redacted] aged [redacted] years at the time of first administration of dabrafenib) and one subject was in Australia (a [redacted] aged [redacted] years at the time of first administration of dabrafenib). The [redacted] year old [redacted] received 150 mg BID of dabrafenib for approximately 4.5 months before disease progression (from [redacted] until [redacted]). The [redacted] year old [redacted] subject began treatment with 150 mg BID of dabrafenib on/around [redacted] 1 and was continuing treatment as of [redacted]. The [redacted] year old [redacted] received 150 mg BID of dabrafenib for approximately 1 month before disease progression; this [redacted] subject subsequently died due to melanoma. The [redacted] year old [redacted] began treatment with 150 mg BID of dabrafenib on/around [redacted] and was continuing treatment as of [redacted]. No SAEs were reported for any of these subjects. Subjects received dabrafenib as a gelatin capsule until September 2011, at which point all subjects still on treatment were switched to dabrafenib as the HPMC capsule.

1.1.2 Pharmacokinetics

Following oral administration of dabrafenib HPMC capsules, plasma concentrations of parent drug peaked approximately 2 hours post-dose and decreased thereafter following a bi-exponential decline. Terminal half-lives is 8.4 hours due to a prolonged terminal phase after oral administration. Terminal half-life following IV microdose is 2.6 hours. Increases in maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) were generally dose-proportional with single doses and less than dose-proportional after repeat BID dosing. Following administration of 150 mg BID, AUC on Day 18 was 27% lower than on Day 1. Following administration of 150 mg BID (HPMC capsules), geometric mean Cmax, AUC(0-τ) and predose concentration (Cτ) were 1478 ng/mL, 4341 ng*hr/mL and 26.1 ng/mL, respectively. Intersubject variability was 37-38% for Cmax and AUC(0-τ) and 119% for Cτ.

Results of a population pharmacokinetic analysis indicated that body weight is a significant predictor of oral clearance and apparent volume of distribution for dabrafenib, with higher weight being associated with higher clearance and lower plasma concentrations; however this does not appear to have a clinically relevant effect on exposure. The range of body weights of subjects included in the population PK analysis was 36 to 150 kg. Dabrafenib apparent oral clearance and apparent volume of distribution were predicted in a typical adult subject with low (50 kg) or high (140 kg) body weight and were shown to be within 20% of the value of a typical 80 kg subject. This difference was not considered clinically relevant.

Studies demonstrated that the oxidative metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4. Dabrafenib is metabolized sequentially to three known metabolites: hydroxy-dabrafenib (GSK2285403, M7), carboxy-dabrafenib (GSK2298683, M4), and desmethyl-dabrafenib (GSK2167542, M8). Plasma concentrations of hydroxy-dabrafenib peak at about 4 hours post-dose, and exposure of the metabolite is similar to that of parent with a metabolite:parent AUC ratio of 0.9, with a similar half-life (9.7 hrs). Carboxy- and desmethyl-dabrafenib accumulates with repeat dosing due to their long half-life (21-22 hrs). Metabolite to parent AUC ratios after repeat-dose administration of dabrafenib 150 mg BID are 11.2 and 0.7 for carboxy-, and desmethyl-dabrafenib, respectively. The preclinical activities of

dabrafenib 3 metabolites have been characterized in multiple studies and compared to dabrafenib. Based on the pre-clinical activity and systemic exposure of the metabolites relative to dabrafenib, hydroxy- and desmethyl-dabrafenib are thought to be likely to contribute to clinical activity while the carboxy-metabolite is predicted to be inactive.

1.1.3 Pharmacodynamics

Analyses of the relationship between dabrafenib exposure and efficacy endpoints were conducted with combined data from the FTIH (BRF112680), the Phase II (BRF113710), and Phase III (BRF113683) studies. Different measures of exposure were evaluated including average dose, predicted average concentration of dabrafenib (Cavg), and predose concentrations of hydroxy-, carboxy- and desmethyl-dabrafenib to assess contribution of metabolite(s) to the activity of dabrafenib. Predose concentrations of dabrafenib (observed or predicted) were also evaluated. Predicted concentrations were based on the population PK model.

Objective response rate at first assessment (dabrafenib doses of 35 mg BID to 300 mg BID) or confirmed response (dabrafenib doses of 50 mg BID to 300 mg BID) from different studies were evaluated in the analysis. The probability (P) that the response was CR/PR, stable disease or PD was modeled using an ordered categorical logistic regression model. Across studies, higher exposure was associated with greater response rate, until the response rate reached a maximum value at dabrafenib Cavg of approximately 300 ng/mL. Response rate data were related to dabrafenib Cavg using an Emax model with estimated EC50 (95% CI) values of 68.9 (14.9, 159) and 77.4 (21.4, 176) ng/mL, for first assessment and confirmed response, respectively.

A model of tumor growth kinetics was developed based on the sum of longest diameter over time to demonstrate the effect of dabrafenib on tumor growth. A total of 392 subjects who received dabrafenib and 58 subjects who received dacarbazine (DTIC) were included in the analysis. The tumor size model was able to characterize baseline tumor size (BSL), tumor growth dynamics with exponential growth (K_L), dabrafenib drug effect on tumor growth (K_D) and drug resistance/disease progression (λ). Consistent with the analysis of objective response, dabrafenib Cavg was a significant predictor of changes in tumor size. Drug effect was significant on the parameter describing disease progression/resistance (λ) using a linear model, with subjects with higher dabrafenib Cavg having longer duration of response (lower value of λ) than those with lower exposures.

Administration of dabrafenib 150 mg BID (gelatin) resulted in inhibition (>80%) of tumor phosphorylated extracellular signal-related kinase (pERK), a downstream biomarker of the RAS/RAF/MEK/ERK pathway that has been shown to be associated with clinical response in BRAF mutant tumor models (Bollag, 2010).

1.1.4 Relative Bioavailability of Dabrafenib Administered as HPMC versus Suspension and dispersible tablet

Dabrafenib was administered as a suspension to 4 subjects with BRAF mutation positive tumors in a Phase I study (Study BRF113463) to characterize the absorption, distribution, metabolism, and excretion of dabrafenib. Administration of dabrafenib as a suspension resulted in faster

absorption (tmax 1 hr), higher Cmax, but similar overall exposure relative to administration of HPMC capsules. Based on cross-study comparisons, the bioavailability of dabrafenib as the suspension is approximately 85% relative to administration as HPMC capsules.

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.

1.1.5 Dabrafenib in Pediatric Cancers

When present, the BRAF V600 mutation appears to result in constitutive activation of the BRAF enzyme in cancer cells regardless of tumor context, and as such, BRAF V600 mutations may be relevant drivers of cancer in other settings, including childhood cancers. Reports citing the frequencies of BRAF mutations in childhood cancers are currently limited in the scientific literature, however, to date, BRAF V600E mutations have been positively identified in 50% of pediatric patients with malignant melanoma (Daniotti, 2009), 57% of patients with Langerhans cell histiocytosis (LCH) (Badalian-Very, 2010), and >10% of patients with certain types of gliomas (both low- and high-grade tumors) (Dougherty, 2010; MacConaill, 2009; Schiffman, 2010). As more childhood tumors are analyzed for the presence of relevant DNA mutations, other tumor types with BRAF mutations are likely to be identified. Given that non-melanoma BRAF V600 mutant tumors have been shown to be responsive to treatment with dabrafenib, strong rationale exists for exploring the activity of dabrafenib in BRAF V600 mutant pediatric tumors. A brief overview of pediatric tumors with known BRAF V600 activating mutations is provided below.

1.1.5.1 Malignant Melanoma

Cutaneous melanoma is the most aggressive form of all skin cancers. In Europe, 67,400 incident melanoma cases occur each year, which accounts for approximately 2.7% of all cancers (Ferlay, 2010). The overwhelming majority of these cases occur in adult patients.

Malignant melanoma is extremely rare in children <12 years of age, but does occur among adolescents aged 12-18 years, with approximately 271 new melanoma cases were expected to occur during 2010 in the European Union (EU), with the most cases in United Kingdom (UK) (n=62), Germany (n=54) and France (n=47) (WEUKBRE5092, 2010) based on an estimation made using the incidence rates from the Automated Childhood Cancer Information System (ACCIS) (deVries, 2006) applied to age-specific 2010 mid-year population projections (United Nations, 2010) using an incidence rates across Europe range from 0.04-0.14 per 100,000 for children (0-14 years) and 0.63-1.87 per 100,000 for adolescents (15-19 years) (deVries, 2006). In the United States (US), the numbers of incident cases were 206 for Stage I, 22 for Stage II, 35 for Stage III and 5 for Stage IV, based on the Surveillance Epidemiology and End Results (SEER) stage distribution for 0-19 year olds (SEER, 2010).

Histopathologically, adult and pediatric melanomas appear to be similar. According to the scientific literature, approximately 50% of cases of pediatric melanoma may involve BRAF V600E mutations, which is a proportion similar to that observed in adults (Daniotti, 2009).

1.1.5.2 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 (National Cancer Institute (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).

1.1.5.3 Low-Grade and High-Grade Gliomas

As compared to adults, where primary brain tumors represent only 1-2% of new cases of cancer in adult, central nervous system (CNS) tumors comprise approximately 25% of all pediatric cancers, and are second only to leukemia in terms of incidence. Among children in the US, the overall incidence rate for 2004-2006 for malignant primary brain and CNS tumors was 3.2 cases per 100,000 person-years for children 0-19 years of age (CBTRUS, 2010). Approximately 50% of all CNS tumors are astrocytomas, most of which are low-grade (Qaddoumi, 2009; Dougherty, 2010). Specific low-grade tumor types include ganglioglioma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, pilomyxoid astrocytoma, and pilocytic astrocytoma. Glioma accounts for 71% of malignant CNS tumors among those aged 0-14 years and accounts for 74% among those aged 15-19 years (CBTRUS, 2010), resulting in an incidence of approximately 2.3 cases per 100,000 person-years. The annual incidence of low-grade gliomas (LGGs) in general is approximately 1 case per 100,000 children. Of all the low-grade tumor types, pilocytic astrocytomas are the most frequently occurring, accounting for approximately 20% of all pediatric brain tumors (Dougherty, 2010). The incidence of pilocytic astrocytoma in children is over 10 times that in adults (0.5 per million in adults versus 8.3 per million in children). Conversely, high-grade gliomas (HGGs) are less common in children than adults,

comprising <10% of all pediatric CNS tumors. Similar rates have been reported for UK and Great Britain (Cancer Research UK, 2010). Examples of HGGs are glioblastoma multiforme and anaplastic astrocytoma.

BRAF V600E point mutations have been reported to occur in several low- and high-grade tumor types in pediatric patients, including 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). While there is only limited evidence, it appears that the frequency of BRAF activating mutations may be more common in pediatric astrocytomas than in adult tumors (Knobbe, 2004). This is consistent with observations that while grade 3 to 4 pediatric astrocytomas share histopathologic similarities with their corresponding adult counterparts, the pattern of genetic alterations seen in adult astrocytomas is distinct from that seen in pediatric astrocytomas (Schiffman, 2010).

1.1.5.4 Papillary Thyroid Carcinoma (PTC)

Thyroid nodules are rare in childhood and adolescence, with a general prevalence of less than 2%; however, they are more frequently malignant than in adults (approximately 20% of cases) (Corrias, 2010). Thyroid carcinomas have an average incidence of approximately 5 per million in patients under the age of 20 years (NCI, 2012). Incidence typically increases with age in this time-frame, such that the majority of cases are observed in adolescents 15 to 19 years old (approximately 15 per million) (NCI, 2012). PTC currently comprises approximately 70% of all diagnoses (NCI, 2012).

Pediatric PTC usually presents at an advanced stage, but still has excellent prognosis, with a 5-year survival rate of >99% (NCI, 2012). 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). Conditions known to increase risk of childhood PTC are elevated plasma thyroid stimulating hormone (TSH) concentration, Hashimoto's disease, exposure to radiation, and mutations in RET-oncogene.

BRAF V600E mutations are common in adult PTC, reported at a rate of approximately 50% (Nikiforova, 2009; Melck, 2010). In pediatric PTC, the proportion of BRAF V600E-positive tumors appears to be slightly lower. In recent publications, BRAF V600E mutations were identified in approximately 20% of cases in patients aged <20 years (Rosenbaum, 2005; Kumagai, 2004).

1.2 Rationale

1.2.1 Study Rationale

The proposed study is a Phase I/IIa, open-label study to determine the safety, tolerability, and pharmacokinetics of oral dabrafenib in pediatric and adolescent subjects aged ≥12 months to less than 18 years of age with advanced BRAF V600 mutation positive advanced solid tumors. As noted above, dabrafenib has demonstrated promising efficacy in adults with BRAF V600 mutation-positive advanced or metastatic melanoma as well as other tumors types with BRAF V600 mutations. For patients with refractory, recurrent gliomas, LCH, melanoma, or PTC, the 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. Recent data identifying BRAF V600 activating mutations in pediatric melanoma, gliomas, LCH, and PTC coupled with the recent development of specific BRAF inhibitors may allow for the development of a new therapeutic opportunity for children, and is the primary rationale for this study.

In addition, BRAF inhibitors such as dabrafenib have a substantially different safety profile than cytotoxic chemotherapeutics and radiation therapy, both of which are employed in standard of care regimens for advanced pediatric solid tumors. Moreover, radiation and cytotoxic therapies can have significant long-term effects on the health and development (both physical and cognitive) of children. The Childhood Cancer Survivors Study, a large cohort study conducted in the United States, found that greater than 40% of survivors of pediatric cancers are burdened with long-term adverse health effects (Hudson, 2002). Specifically, the individual components of current therapy for solid tumors lead to both short and long term morbidities. Surgical resection can lead to loss of function or disfigurement, or in the case of CNS tumors, long term neurologic and cognitive sequelae. Cytotoxic chemotherapeutics, especially when administered in dose- or time-intensive manners, can lead to neutropenia and increased risk of infection, sepsis, and death, cardiac dysfunction (doxorubicin), infertility (cyclophosphamide), renal injury and hearing loss (cisplatin). In addition, many of these cytotoxic agents, in particular, DNA alkylating agents and epipodophyllotoxins, have long been known to predispose patients to treatment-associated leukemias (Hawkins, 1992). Radiotherapy can also have profound effects on skeletal growth and, for patients with CNS tumors, on endocrine function, cognition, vasculopathy and risk of second tumors. New targeted therapeutics such as dabrafenib may offer a way of reducing the need for cytotoxics, or may offer a means by which to reduce dose or exposure, thereby reducing the likelihood of treatment-associated morbidity and mortality.

Given the similarity between adult and pediatric melanoma, data from this study will be used to support a bridging approach to demonstrate that the PK, and (where available) pharmacodynamic and efficacy data in adolescent subjects are similar to that of adults, using a modelling and simulation approach.

In summary, it is thought that dabrafenib has the potential to provide therapeutic benefit to those pediatric patients with advanced solid tumors with BRAF V600 activating mutations. Due to the scarcity of BRAF mutation positive tumors in children, and the anticipated favourable safety profile of dabrafenib in children (based on adult data), enrolment of different pediatric age groups will not be staggered.

1.2.2 Dose Rationale

A maximum tolerated dose (MTD) was not established in adults for dabrafenib in Study BRF112680. However, relationships between the total daily dabrafenib dose and markers of clinical benefit (reduction in FDG-PET uptake and tumor shrinkage) were determined and the PK, safety, pharmacodynamic and efficacy data were used to identify a recommended Phase II dose of 150mg BID. As such, in this pediatric study, dabrafenib dose escalation will proceed to the target geometric mean steady-state plasma exposure observed in adults given the efficacious Phase III dose of dabrafenib 150 mg BID as HPMC capsules. It is not anticipated

that a true MTD will be identified given the low incidence of dose-limiting toxicities (DLTs) seen in the adult clinical development of dabrafenib.

The rationale for this pharmacokinetically-based dose-escalation approach is based on the likelihood that therapeutic benefit in children will be achieved by targeting the adult dabrafenib exposure, principally steady-state AUC(0-τ) following 150 mg BID dabrafenib as HPMC capsules. The geometric mean (95% CI) dabrafenib AUC(0-τ) after administration of 150 mg BID as the HPMC capsule in the Phase III study (BRF113683) was 4341 (3749, 5485) ng*h/mL. These Phase III data were consistent with the preliminary results from the monotherapy arm of study BRF113220 where geometric mean dabrafenib AUC(0-τ) after administration of 150 mg BID as the HPMC capsule was 4648 ng*h/mL. Therefore, the median population target AUC(0-τ) for pediatric subjects will be approximately 4500 ng*h/mL, with the goal of identifying, where possible, a dose for each age grouping (12-18, 6-12, 2-6, and less than 2 years of age) that results in a median dabrafenib AUC(0-τ) that is within the 95% CI for the geometric mean exposure measured in adults in the Phase III study (3749, 5485 ng*h/mL).

The dabrafenib dose selection will be weight-based according to regulatory guidances (European Medicines Agency, 2006; U.S. Food and Drug Administration, 2000). The recommended adult dose of dabrafenib is 150 mg BID. This dose corresponds to a 3.75 mg/kg total daily dose in an 80 kg adult. The starting dose in Part 1 will be 3 mg/kg total daily dose, approximately 80% of the adult dose adjusted for body weight. Dose escalation in Part 1 will occur in a stepwise manner until the median AUC(0-τ) is greater than approximately 4000 ng*h/mL and does not exceed approximately 5500 ng*h/mL. Dose escalation in Part 1 also will be influenced by the real-time analysis of the safety and other available data obtained during the study.

Based on clinical pharmacology considerations in the pediatric population, the selection of suitable dabrafenib doses for ages 2 to <18 years is not expected to be significantly complicated by developmental factors. However, given the rapidly changing absorption, distribution, metabolism, and excretion processes in children <2 years old, it is difficult to predict the impact of the physiology of infants on dabrafenib exposure. As noted above, since a MTD of dabrafenib was not established in adult subjects with cancer, it is expected that dose-limiting toxicities also will be rare in children. Therefore, a starting dose of 80% of the weight-based dose in adults will provide an adequate safety margin for infants. The total daily dose administered in this study will not exceed 300 mg (150 mg BID).

1.3 Summary of Risk Management

The assessment of the risk of dabrafenib, and suggestions for management of risk, is based on non-clinical data and clinical data from an integrated safety population of 578 adult subjects with melanoma receiving 150 mg dabrafenib BID.

Dermatological effects: Epidermal hyperplasia (acanthosis) and hyperkeratosis of the skin was seen in dogs and in rats. In clinical studies hyperkeratosis (29%), skin lesions including actinic keratosis (7%) and seborrhoeic keratosis (7%), palmar-plantar erythrodysesthesia (PPE) syndrome (13%), rash (18%) and cutaneous squamous cell carcinomas (cuSCC) including keratoacanthomas (KA) (9%) have been observed. Most events were Grade 1 with the exception of cutaneous squamous cell carcinomas, which were predominantly Grade 3.

Dermatological changes are being monitored in subjects through interim medical history, assessment of adverse events and physical examination including examination of the skin. Guidelines on management of hand foot skin reactions (HFSR)/ PPE syndrome and skin rashes have been provided, with stopping criteria for persistent National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAEv4.0 or higher) NCI-CTCAE Grade 2 or Grade 3 HFSR toxicity. Treatment of SCC, KA and keratotic lesions should occur based upon institutional practice. Dose interruptions or modifications are usually not required for SCC/KA.

Ophthalmology effects: Eye effects including blurred vision (2%), uveitis/iritis (<1%), eye pain (<1%), visual impairment (<1%) and reduced visual acuity (<1%) have been observed in clinical studies to date, with all events Grade 1 or 2. An ophthalmologic consult is required for subjects developing symptoms associated with uveitis including blurry vision, eye pain or erythema.

Pyrexia: In clinical studies, pyrexia was one of the most frequently occurring AEs (27%), most of which (64%) were considered to be related to study treatment. Events were primarily Grade 1 (55%) or Grade 2 (39%) in severity. The majority of events occurred early during study treatment, with a median time to onset of 1st occurrence of 3 weeks, and most cases (74% of first occurrences) were of short duration (≤5 days). The majority of subjects with pyrexia were managed without dose interruption or dose reduction. Across dabrafenib studies, all SAEs of pyrexia, influenza-like illness, cytokine release syndrome, and systemic inflammatory response syndrome underwent clinical review for the identification of serious non-infectious febrile events, with complications of severe rigors, hypotension, dehydration, or renal failure in the absence of another identifiable etiology (i.e., infection). 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. Subjects with fever should have a medical evaluation including measurement of blood pressure. Cases of fever with severe rigors or fever with hypotension should be reported as SAEs (regardless of whether or not hospitalization was required).

Acute Renal Failure: Acute renal failure/renal failure has been rarely reported (<1%) in subjects receiving dabrafenib, and a case of granulomatous interstitial nephritis has also been reported in a clinical trial. In some cases complicated pyrexia may be associated with renal insufficiency/renal failure, possibly secondary to dehydration or hypotension. Renal function should be monitored carefully, especially in subjects with pyrexia. Dabrafenib should be interrupted in subjects with significantly elevated serum creatinine (creatinine rise >0.5 mg/dL [44 µmol/L] above baseline or creatinine >2.0 mg/dL [177 µmol/L]).

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.

Pancreatitis: Pancreatitis (<1%) and/or increased lipase/amylase (2%) have been reported at a low frequency with dabrafenib, typically occurring within 14 days of starting therapy. For AEs of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples must be monitored locally.

Hypersensitivity: There has been a report of hypersensitivity (blisters), occurring on the same day as the first dose of study drug as well as upon rechallenge. Grade 1 AEs of blisters on limbs (4 subjects) and drug hypersensitivity (rash, 1 subject) have been reported in previous studies with dabrafenib. However, the precise etiology of these events is unclear.

Embryofetal Development and Reproductive Effects: In embryofetal development studies in rats, developmental toxicities including reduced fetal body weight, embryo-lethality, cardiac ventricular septal defect malformations, delayed skeletal development and variation in thymic shape have been observed. Dabrafenib must not be administrated to pregnant women or nursing mothers. Female subjects of childbearing potential are required to use effective methods of contraception from the time of a negative serum pregnancy test within 14 days prior to the first dose of study medication, until 4 weeks after the last dose of study medication. In dogs and in rats, testicular degeneration/depletion has been observed in repeat dose studies (up to 13 weeks duration) with no clear evidence of recovery following off-treatment periods of up to 4 weeks duration. Spermatid retention was observed in mice in a 14 day study. Male subjects enrolled or in follow-up in clinical trials are informed of the potential risk for impaired spermatogenesis, which may be irreversible.

Cardiovascular effects: Data from preclinical studies with dabrafenib suggest the potential for cardiovascular effects, including cardiac valve effects in the 28 day dog study, coronary vascular effects in the 7 day dog study, hepatic vascular effects in a 10 day rat study, increased incidence of minimal cardiomyopathy in male rats and mild increases in heart rate in single dose studies in dogs and rats. In a 13-week oral toxicity study in dogs right atrial wall thickening characterized microscopically by fibrovascular proliferation (transmural granulation tissue) was observed. In the ongoing monotherapy clinical studies, 3 (<1%) non-serious valvular abnormalities meeting stopping criteria have been identified to date; two of these subjects had baseline valvular abnormalities Additionally, a blinded independent review of available echocardiogram results from subjects participating in the phase 2 BREAK-2 study was performed to further examine the effect of dabrafenib on valvular function. No persistent findings suggestive of a drug effect were observed. Because valvular abnormalities were observed in a minority of subjects in the integrated dabrafenib population, and the results of the central analysis in BREAK-2 were not suggestive of a drug effect, valvular toxicity is no longer considered an AE of special interest for dabrafenib. Subjects with clinically significant baseline cardiac abnormalities are excluded from the study. Safety evaluations include physical examination, 12-lead electrocardiogram (ECG) and echocardiogram (ECHO) monitoring as well as AE reporting.

Respiratory Effects: Lobar bronchoalveolar inflammation has been observed in dogs, with shallow and/or labored breathing noted during the treatment phase in 2 dogs given dabrafenib for 13 weeks. Respiratory changes are being monitored through medical history and physical examination. There have been no corresponding clinical findings identified in clinical trials to date.

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
● To determine the safe and tolerable dabrafenib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures to the dabrafenib adult dose, in subjects with BRAF V600 mutation positive tumors	● Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs in Part 1 and Part 2. ● Cmax, area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration [AUC(0-τ] and AUC(0-inf) of dabrafenib
Secondary	
● To characterize the pharmacokinetics of dabrafenib, and its metabolites	● Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) (dabrafenib only), Cmax, tmax and t½ of dabrafenib and its metabolites, as appropriate
● To characterize the longer term safety and tolerability of dabrafenib	● AEs; ECG; changes in laboratory values and vital signs
● To assess any preliminary anti-tumor activity of dabrafenib	● Tumor response as defined in Appendix 2 by investigator assessment
● To determine the effect of age and weight on the pharmacokinetics of dabrafenib using a population pharmacokinetics approach	● CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates
Exploratory	
[redacted]	
● To determine the palatability of dabrafenib in pediatric subjects	● Palatability questionnaire data

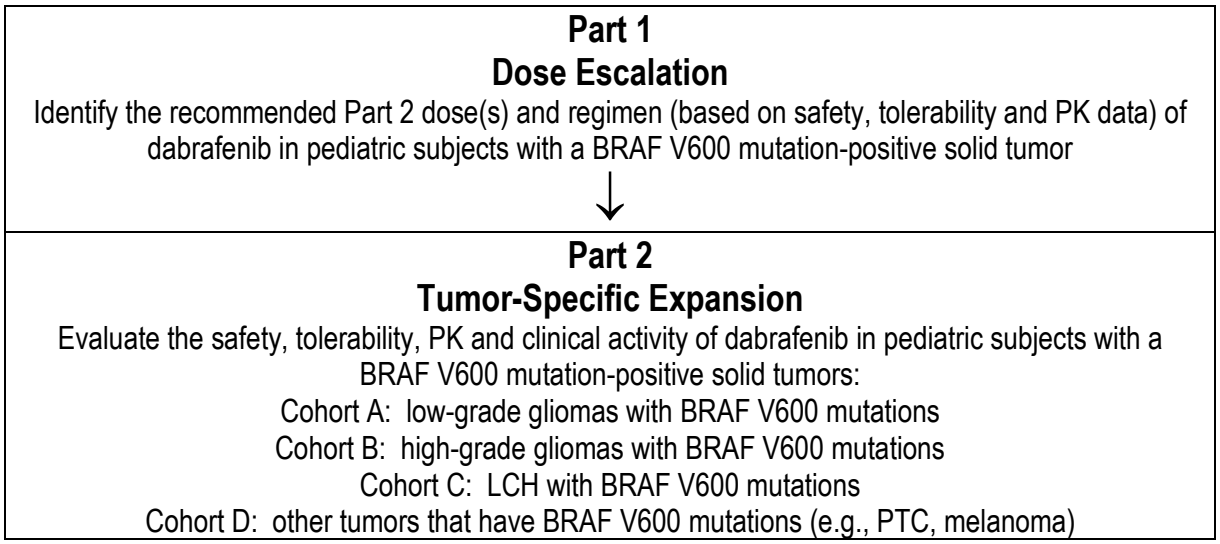
3 INVESTIGATIONAL PLAN

3.1 Study Design/Schematic

This is a 2-part, Phase I/IIa, multi-center, open label, study in pediatric subjects with advanced BRAF V600 mutation-positive solid tumors (Figure 3-1). Subjects will participate in only 1 part. Part 1 will be a dose escalation study in subjects with any BRAF V600 mutation-positive solid tumor using a modified Rolling 6 Design (RSD). Part 2 will be an expansion study to further evaluate the safety / tolerability profile and clinical activity of dabrafenib in 4 tumor-

specific pediatric populations. Approximately 6 to 18 subjects are **estimated** for Part 1, and approximately 65 subjects are planned for Part 2 (at least 10 evaluable subjects in each of 4 cohorts; evaluable for the purpose of clinical activity analysis is defined as a subject with a pre-dose and at least 1 post-dose disease assessment). The HGG cohort will continue recruitment until enrollment on another pediatric HGG study is available (expected by the end of 2018 and no later than mid 2019).

Figure 3-1 Study Design



The screening visit will be completed within 21 days prior to administration of the first dose of study medication. No study specific procedure will start before the signature of the informed consent form (and assent, according to institutional guidelines). Screening assessments may be carried out over more than one day provided that all required assessments are completed within 21 days prior to the first dose of study drug. Screening assessments may be repeated once at the discretion of the investigator.

Safety and PK assessments will be performed at regular intervals as outlined in the Time and Events Tables (Table 3-7 and Table 3-9). 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 2). Additional details for the conduct of Part 1 and Part 2 are provided in Section 3.1.1 and Section 3.1.2, respectively.

Guidelines for dabrafenib dose modifications are outlined in Section 3.7. Dabrafenib treatment may be delayed for up to 7 days to allow for resolution of toxicity. For treatment delays >7 days due to toxicity, subjects should be withdrawn from dabrafenib permanently (unless the investigator determines that clinical benefit from continued administration of dabrafenib outweighs any risks associated with continued use).

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

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

3.1.1 Part 1 – Dose Escalation

Part 1 is a repeat dose, dose escalation study. The RSD (Skolnik, 2008) builds on the classic 3+3 design, but allows for continued recruitment of subjects while the data from the first 3 subjects in each cohort is collected (up to 6 subjects per cohort). For dose escalation decisions, all available data are used to inform the decision. The starting dose will be 3 mg/kg with dose levels for subsequent dose levels (+1 and +2 Dose Levels) as outlined in Table 3-1.

Table 3-1 Dabrafenib Dose Levels [a]

Dose Level	**Total Daily Dose (mg/kg) [c]**
-2 Dose Level	1.5 mg/kg
-1 Dose Level	2.25 mg/kg
Starting Dose Level [b]	3 mg/kg
+1 Dose Level	3.75 mg/kg
+2 Dose Level	4.5 mg/kg
+3 Dose Level	5.25 mg/kg
+4 Dose Level	6.0 mg/kg

a. Intermediate and additional dose levels may be explored based on emerging PK and safety data.

b. Starting dose level. The first cohort of subjects will receive approximately 80% of the adult mg/kg dose (doses will be rounded based on the smallest 10mg capsule increments for subjects receiving capsules). The adult dose is 3.75 mg/kg given as 2 divided doses.

c. The total daily dose will be split evenly into a morning and evening dose (BID dosing). The total daily dose will not exceed 300 mg (150 mg BID).

The actual weight-adjusted dose to be administered for a given dose level may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose for a given dose level. Dosing frequency may also be adjusted based on emerging PK and/or safety data. Cohorts may be added in order to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as those described for other study subjects.

Up to 6 subjects can be enrolled concurrently at one dose level dependent upon the number of subjects enrolled at the current dose level, the number of subjects who have experienced a dose limiting toxicity (DLT, see Section 3.3) at the current dose level, and the number of subjects enrolled but with data pending at the current dose level. Dose escalation schematic is in Appendix 1.

For example, if 3 subjects are enrolled at a dose level and all 3 subjects have been fully evaluated for the first 28 days (including Day 15 PK) and no DLTs were observed, a fourth subject can be enrolled at the next higher dose level (i.e., **dose escalation**). If all 3 subjects have NOT been fully evaluated for the first 28 days or 1 DLT occurred, the fourth subject will be enrolled at the same dose level. If 2 or more DLTs are observed, the fourth subject will be enrolled at the next

lower dose level (i.e., **de-escalated**). Similarly, the process is repeated for the fifth and sixth subjects in a cohort.

Beyond the sixth subject in an ongoing cohort, additional subjects wanting to be enrolled before the next cohort is open for enrollment, can be enrolled at the previous lower dose level.

On Day 1, serial blood samples for PK analysis will be collected in subjects ≥10 kg in weight after the first dose of dabrafenib. A second dose may be administered on Day 1 if the timing is in compliance with Section 3.6. Twice a day dosing will begin on Day 2. PK samples in subjects ≥10 kg in weight will also be collected on Day 15. For subjects <10 kg in weight, blood samples for PK analysis will be collected after repeated administration on Day 15 only.

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 3.8).

Treatment with dabrafenib will be continued until disease progression, until the subject is no longer obtaining clinical benefit from continued treatment, they develop an unacceptable toxicity, the study is terminated, or the subject withdraws consent or begins a new therapy. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 9.1.

3.1.1.1 Dose Escalation

Dose escalation decisions will take into account all available safety and PK data (from the current and all previous cohorts, if available) and will be documented.

If a subject is withdrawn before the first 28 days in Part 1 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 at the time the next available subject enrolls in the study.

The dose in Part 1 will be escalated until the maximum tolerated dose (MTD) is reached (based on toxicity, Section 3.4) **OR** in the absence of reaching the MTD, the dose in which the median AUC(0-τ) is between approximately 4000 ng*h/mL and approximately 5500 ng*h/mL. The proportion of subjects who achieve an AUC(0-12) ≥ 4000 ng*h/mL also will be considered when selecting the dose for Part 2. In the absence of meeting criteria for MTD, if less than 80% of subjects in an age group (≤2 yrs, >2 and ≤12 yrs, >12 yrs) achieve an AUC(0-12) ≥ approximately 4000 ng*h/mL **OR** if fewer than two subjects in a specific age group have been evaluated at a given dose level, the study sponsor and study team will review all available safety and PK data and determine if further Part 1 evaluation of a specific age group is required before these subjects may enroll in Part 2. Intermediate doses may be explored.

3.1.2 Part 2: Tumor-Specific Expansion

Part 2 will have four disease-specific cohorts of subjects with tumors known to have BRAF V600 activation (cohort 1: pediatric low-grade gliomas, cohort 2: pediatric high-grade gliomas cohort 3: Langerhans cell histiocytosis, and, cohort 4: miscellaneous tumors such as melanoma and PTC). At least 40 patients will be recruited into Part 2, with at least 10 patients each for cohort 1, 2 and 3, and up to 10 patients in cohort 4. The HGG cohort will continue recruitment until enrollment on another pediatric HGG study is available (expected by the end of 2018 and

no later than mid 2019). The study will attempt to enroll at least 5 children in each cohort who are <6 years of age.

On Day 1, serial blood samples for PK analysis will be collected in subjects ≥10 kg in weight after the first dose of dabrafenib. A second dose may be administered on Day 1 if the timing is in compliance with Section 3.6. Twice a day dosing will begin on Day 2. PK samples in subjects ≥10 kg in weight will also be collected on Day 15. For subjects <10 kg in weight, blood samples for PK analysis will be collected after repeated administration on Day 15 only.

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 3.8).

Treatment with dabrafenib will be continued until disease progression, until the subject is no longer obtaining clinical benefit from continued treatment, they develop an unacceptable toxicity, the study is terminated, or the subject withdraws consent or begins a new therapy. At the end of treatment, a final study visit will occur. Additional details on subject completion are provided in Section 9.1.

3.1.3 Study End

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 protocol is 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.

3.1.4 Follow-Up

Follow-up care will be offered to subjects from Part 1 and Part 2. Details are provided in Section 9.4.

3.2 Discussion of Study Design

Dabrafenib is not being developed for BRAF V600 wild-type (non-mutation positive) tumors for several reasons: 1) dabrafenib has 10-fold less affinity for wild-type BRAF protein; 2) data from the FTIH study showed no evidence of anti-tumor activity in BRAF V600 wild-type subjects and no evidence of anti-tumor activity in BRAF non-V600 mutation positive subjects (e.g., K601 mutations) and 3) there is pre-clinical data to indicate that inhibition of wild-type RAF with BRAF inhibitors could lead to paradoxically enhanced signalling in cells with wild-type BRAF via transactivation of dimerized RAF (Poulikakos, 2010). This enhanced signalling could manifest as cell proliferation in BRAF wild-type tumors.

Identification of BRAF V600 mutant pediatric tumors will be enabled by molecular genotyping assays which are available at many major academic pediatric oncology centres. In addition, a central genotyping assay has already been developed by GlaxoSmithKline (GSK), with an external partner, for use in the adult dabrafenib program. Because this central assay is DNA-based, it can be employed for any tissue, including those from pediatric tumors. Sites may enroll subjects based on genotyping performed at a local (non-central) laboratory using a standardized assay performed in a Clinical Laboratory Improvement Amendments (CLIA)-

approved (or equivalent) laboratory. Sites without access to local laboratory testing may enroll subjects based on genotyping performed at a central laboratory. For enrolled subjects with available archived tissue, BRAF V600 genotyping will also be performed at a central laboratory.

With regard to the dose escalation design, employing a modified RSD (as opposed to the commonly used 3+3 design) allows for more continuous accrual of subjects into the study and avoids delays in accruing and treating subjects with BRAF V600-mutant tumors as they are identified. In the 3+3 design, accrual is stopped until 3 subjects have been evaluated for a specified evaluation period (typically 28 days or more). With the modified RSD, suspension of subject accrual occurs less frequently and therefore the enrolment period is shortened. The ability to detect and respond to safety signals is the same in the modified RSD as in the 3+3 design (Skolnik, 2008).

Exposure-response relationships between plasma dabrafenib concentrations and clinical efficacy have been established in adult subjects with melanoma. Given that the available published data indicates that the histopathology, molecular pathology of melanoma is similar between adolescent patients and adult patients, and that the molecular biology of mutant BRAF activity is identical between adult patients and patients in the pediatric population, it should be possible to extrapolate adult response data to adolescent patients, if the pharmacologic exposures achieved in adolescent patients are similar. Also, no maximally tolerated dose has been identified in adult subjects with melanoma. Therefore, in addition to monitoring for DLTs, systemic exposure to dabrafenib will be used to determine the optimal dose in the pediatric population.

In the absence of compelling pre-clinical and clinical data to indicate a similar likelihood of response in pediatric BRAF V600 mutation-positive non-melanoma tumors to that seen in adult BRAF V600 mutation-positive melanoma, the introduction of new agents such as dabrafenib into pediatric oncology treatment regimens typically occurs in later lines of therapy. In keeping with this standard, this study will be conducted in subjects who have experienced recurrent, refractory, or progressive disease after receiving at least 1 standard therapy. One exception will be for subjects with metastatic melanoma (i.e., subjects with metastatic and surgically unresectable disease can be enrolled as first-line therapy) since there is sufficient clinical data from Phase III adult studies with dabrafenib to allow this treatment option.

The study will use the currently available dabrafenib capsule strengths (50 mg and 75 mg) from the adult program for children who are able to reliably swallow capsules. In addition, two lower strength capsules (10 mg and 25 mg),a powder for oral suspension formulation, and dispersible tablet formulation are available for pediatric subjects who may have difficulty swallowing larger capsules. **In France, children younger than 6 years and children 6 years and older with a risk of choking when swallowing capsules are required to use the oral suspension formulation or dispersible tablet formulation.**

3.3 Dose Limiting Toxicity Definitions

The DLT evaluable population is defined as those subjects in Part 1 fulfilling the ‘All Subjects’ population criteria and having received an adequate treatment in 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 drug doses, exclusive of missed doses due to treatment-related toxicity. For those subjects who are either withdrawn or dose reduced due to toxicity during the first 28 days will be included in the DLT evaluable population.

An AE will be considered a DLT if it occurs within the **first 28 days of treatment** with dabrafenib, and if it is considered by the investigator to be related to treatment with dabrafenib, and if meets at least one of the following additional criteria:

- Grade 4 hematologic AE (specifically neutropenia, anemia, thrombocytopenia and lymphopenia);
- Grade 3 or 4 non-hematologic AE. Grade 3 nausea, vomiting, and diarrhea will only be considered dose limiting if uncontrolled with standard supportive measures. Cutaneous SCC is not considered a DLT;
- Treatment delay of greater than 7 consecutive days due to unresolved AE
- Ejection fraction less than the lower limit of normal (LLN) with an absolute decrease of >10% from baseline with confirming assessment within 7 days;
- A Grade 2 or greater non-hematological AE that in the judgment of the investigator and Novartis Medical Lead is dose limiting;
- AEs requiring a dose reduction.

3.4 Maximum Tolerated Dose (MTD)

An MTD has not been identified for dabrafenib in the adult population. This does not preclude the identification of an MTD in the pediatric population. As such, in the current study employing a modified RSD, if **dose de-escalation** occurs (due to the occurrence of DLTs) resulting in 6 subjects being entered at the next lower dose level, and there are ≤1 DLT in that next lower dose level (see Appendix 1), then the MTD will have been defined (Skolnik, 2008).

3.5 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 in accordance with the randomization schedule generated prior to the start of the study, using validated software.

3.6 Investigational Product and Other Study Treatment Dosage/Administration

In France, children younger than 6 years and children 6 years and older with a risk of choking when swallowing capsules will be required to use the powder suspension formulation or the dispersible tablets.

Capsules: Dabrafenib capsules will be supplied by Novartis (for subjects able to reliably and consistently swallow capsules).

Powder for oral suspension: Dabrafenib will be supplied by Novartis 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 Novartis or its authorized agent. Detailed instructions for constitution and dosing will be provided in the SPM.

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 dispersion. 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 (supplied in the SPM) based on weight and dose level will be used to prescribe dabrafenib to minimize inter-subject dosing variability.

Investigational product details are provided in Table 3-2.

Table 3-2 Investigational Product

Formulation description:	HPMC Dabrafenib capsules	Dabrafenib powder for oral suspension	Dabrafenib Dispersible Tablets for oral suspension
Dosage form:	Capsule	Powder for oral suspension	Dispersible Tablet
Unit dose strengths:	10 mg, 25 mg, 50 mg and 75 mg	150 mg (in stickpack) 10 mg/mL (as oral suspension)	10mg
Route/ Frequency:	Oral / BID	Oral / BID	Oral / BID

Physical description:	10 mg: opaque capsules composed of a white body and cap 25 mg: opaque capsules composed of a pink body and cap 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 silver laminated foil stickpacks.	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	Novartis
Method for individualizing dosage:	Unit dose capsules	Administered using oral syringes (1, 5, and 20 mL sizes)	Administered using dosing cup / PP oral liquid dispenser

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.

Dabrafenib should be administered under fasting conditions, either approximately 1 hour before or approximately 2 hours after a meal. 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, dabrafenib can be administered with a small non-fat meal (e.g., small amount of apple juice/sauce, a piece of dry toast). Subjects and their parents should be advised to avoid administering dabrafenib with milk or high-fat, high-calorie foods.

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.

The total daily dose will not exceed 300 mg (150 mg BID).

3.7 Dose Adjustment/Stopping Criteria

All dose adjustments will be made by a Novartis Medical Lead in collaboration with the investigator.

3.7.1 Dabrafenib Intra-Subject Dose Escalation

In certain circumstances in Part 1 of this study, a subject's dose level may be increased up to the highest dose level that is open to enrollment. Only subjects who have completed their DLT assessment period (28 days), who have tolerated treatment, but have measured AUC(0-12) less than target level, may be eligible for escalation. Decisions to increase a subject's current dose will be based on all available data, including safety data and PK data for that subject, and must be agreed by the investigator and the Novartis Medical Lead. Predicted exposure AUC(0-12) at the escalated dose may not exceed 6000 ng*h/mL. Documentation of the dose escalation agreement and predicted exposure must be kept in the study files for the subject.

Dose escalation is only allowed in subjects who are willing to consent to additional PK sampling at the escalated dose level. Additional PK samples will be collected on Day 15 following administration of the escalated dose.

Intra-subject dose escalation will not occur in Part 2.

Subjects will be summarized based on the treatment level to which they were originally assigned.

3.7.2 Dabrafenib Dose Modifications/Interruption for Toxicity

The severity of adverse events will be graded utilizing the National Cancer Institute (NCI) CTCAE, version 4.0. The following sections include:

- Supportive guidelines for managing common toxicities
- General dose modification guidelines for toxicities related to study treatments
- Specific management guidelines for pyrexia, cardiovascular adverse events, and cutaneous squamous cell carcinoma/keratoacanthoma

Investigators should also refer to the dabrafenib Investigator's Brochure for the most current product safety information.

3.7.3 General supportive guidelines

3.7.3.1 Dose Modification for General Toxicities

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

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

are provided separately in Section 3.7.8. Additionally, please refer to the SPM for additional dose modification guidance.

Table 3-3 Dose Modification Guidelines - General

CTCAE Grade	Action and Dose Modificationa,b
Grade 1 or Grade 2 (tolerable)	Continue study treatments at same dose level (no dose modification) and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	
1st, 2nd, or 3rd occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at next lower dose level
4th or greater occurrence	Discontinue treatment.
Grade 4	
1st occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level or discontinue at discretion of investigator
All other occurrences	Discontinue treatments

a. Treatments should be discontinued if more than 3 dose reductions are required.

b. Approval from the Novartis Medical Lead is required to restart study treatments after ≥21 days interruption

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered.

3.7.4 Dose Modification Guidelines - Adverse Events of Special Interest

3.7.4.1 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. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration or hypotension, serum creatinine and other evidence of renal function (e.g. creatinine clearance, BUN) should be monitored carefully during and following severe events of pyrexia. Pyrexia accompanied by hypotension, dehydration requiring intravenous fluids, renal insufficiency and/or severe (≥ Grade 3) rigors/chills in the absence of an obvious infectious cause should be reported as a SAE.

Guidelines regarding management and dose reduction for pyrexia considered to be related to dabrafenib are provided in Table 3-4.

Table 3-4 Mandatory Dose Modification and Recommended Clinical Management for Pyrexia

Occurrence [a,b]	Recommended adverse event management guidelines	Mandatory dose modification requirements
Any	● Clinical evaluation for infection and hypersensitivity[c] ● Laboratory (local lab) work-upc ● Hydration as required[d]	
1st Event[b]:	● Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration, or hypotension[e]	● Interrupt dabrafenib ● Once pyrexia resolves to baseline, restart dabrafenib at the same dose level ● If fever was associated with dehydration, hypotension, or renal insufficiency, reduce dabrafenib to the next lower dose level. [g]
2nd Event [e]	● Same as for 1st event, and ● Within 3 days of onset of pyrexia ● Optimize anti-pyretic therapy ● Consider oral corticosteroids for at least 5 days or as clinically indicated[f]	● Same as 1st 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 ● Once pyrexia resolves to baseline, restart dabrafenib reduced by one dose level[g]

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.

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 after 3 episodes of pyrexia complicated by rigors, severe chills etc., 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

3.7.4.2 Renal insufficiency

Cases of renal insufficiency have occurred in adult subjects receiving dabrafenib. Prior to start of study treatment, concomitant medications must be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications may 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 3-5.

Table 3-5 Mandatory Dose Modification 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 subject has fever: treat pyrexia as per Table 5 (please note NSAIDs can induce renal insufficiency, especially in subjects 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% from baseline: Continue dabrafenib at current dose
	• If creatinine rise is ≥ 25% but < 50% from baseline: • Monitor creatinine at least twice weekly, can decrease frequency if creatinine rise < 25% from baseline • Avoid nephrotoxic agents	• If creatinine rise is ≥ 25% but < 50% from baseline: • Continue dabrafenib at current dose
	• 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 • May restart dabrafenib at reduced dose if creatinine rise returns to < 25% from baseline • If creatinine rise is ≥ 100% from baseline, permanently discontinue dabrafenib
2nd occurrence	• See guidance for first occurrence	• Permanently discontinue dabrafenib

3.7.4.3 Dose Modifications and Management Guideline for New Malignancies

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 (refer to Section 11.7). [redacted]

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. Monitoring of the skin can be performed by a qualified local physician (e.g. subject's general practitioner) at the discretion of the investigator during non-clinic visits or visits where only dermatologic assessment is to be performed and subject has extensive travel requirement. If possible, the same local physician should perform each exam throughout the study to ensure consistency between evaluations.

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 (Sievert, 2013). 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. [redacted]

Refer to Appendix 6 for French country specific dermatological follow up.

3.7.4.4 Guidelines for prolonged QTc

Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided in Table 3-6.

Table 3-6 Withholding and Stopping Criteria for QTc-Prolongation

QTc Prolongation	Required adverse event management guidelines	Mandatory dose modification requirements
QTcB ≥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	• Interrupt study treatment (dabrafenib) until QTcB 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 treatment.

	● Consider evaluation with cardiologist (recommended).	● If event recurs, permanently discontinue study treatments.
Abbreviations: ECG = electrocardiogram; msec = milliseconds; QTcB = QT duration corrected for heart rate by 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		

3.7.5 Management Guidelines for Additional AEs

- **Palmar Plantar Erythrodysesthesia** (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.
- **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 iridocylitis) of > 6 week duration.
- **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.

3.7.6 Left Ventricular Ejection Fraction Stopping Criteria

ECHO must be performed at baseline and at follow-up visit(s) per the schedule in the Time and Events Table. Subjects who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline **and** the ejection fraction is below the institution's LLN should temporarily discontinue dabrafenib and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until LVEF recovery to above institutional lower limit of normal and within 10% of baseline.

- If the LVEF recovers (defined as ≥ LLN **and** absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks**, after consultation and approval of the Medical Lead,** the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, monitoring of LVEF will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

- If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (LVEF to above institutional LLN and symptom resolution) within 4 weeks, the subject may restart dabrafenib at a reduced dose in consultation with the Medical Lead (if in the opinion of the investigator, the subject was receiving or likely to receive clinical benefit with continued treatment).

All events of LVEF meeting the stopping criteria should be reported as SAEs (refer to Section 11.7).

Copies of all ECHO(s) will be required for possible central review. Copies of all cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is below the institution's LLN will also be required for possible central review. Details for central collection of ECHOs will be provided in the SPM.

3.7.7 Valvular Toxicity Stopping Criteria

Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTC AE v4.0) should temporarily discontinue Dabrafenib and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks, **after consultation and approval of the Medical Lead,** the subject may be restarted on Dabrafenib at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue Dabrafenib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) valvular toxicity must discontinue dabrafenib. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart Dabrafenib at a reduced dose **after consultation and approval of the Medical Lead**.

Copies of all ECHO(s) will be required for possible central review. Details for central collection of ECHOs will be provided in the SPM. Copies of all cardiology consultations performed on subjects who experience a valvular toxicity will also be required by Novartis for review.

3.7.8 Liver Chemistry Stopping Criteria

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

Liver chemistry stopping criteria 1-5 are defined as:

1. Alanine aminotransferase (ALT) ≥3 times the upper limit of normal (xULN) and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and International Normalized Ratio (INR) >1.5, if INR measured)
   NOTE: If serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. ALT ≥8xULN
3. ALT ≥5xULN but <8 xULN persists for ≥2 weeks
4. ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
5. ALT ≥5xULN but <8 xULN and cannot be monitored weekly for >2 weeks.

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

- **Immediately** discontinue subject from study treatment.
- Report the event to Novartis **within 24 hours** of learning its occurrence.
- Complete the liver event electronic case report form (eCRF) and SAE data collection tool if the event also meets the criteria for an SAE.
- All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
- NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow up assessments (Section 12), and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required or Novartis Medical Governance approval of drug restart is granted, as described in Section 12).

  - For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment
- Do not restart investigational product unless written approval is granted by Novartis Medical Governance (details for restarting investigational product are described in Section 12), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 12).
- Subjects meeting criterion 5 should be monitored as frequently as possible.

In addition, for subjects meeting criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 12), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries [ALT, aspartate aminotransferase (AST), alkaline phosphatase, bilirubin] resolve, stabilize or return to within baseline values.

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

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hours** for repeat liver chemistries and liver event follow up assessments (refer to Section 12).
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
- Subjects meeting criterion 5 should be monitored as frequently as possible.

3.8 Time and Events Schedule

Table 3-7 Part 1 and Part 2 Treatment Phase: Screening through Day 21 (See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 21			
VISIT		Screen	Pre-dose Day 1	Pre-dose Day 8	Pre-dose Day 15	Pre-dose Day 22
VISIT WINDOW (±days		-21	N/A	±2	±2	±2
Baseline Assessments						
Informed consent/assent		X				
Tumor tissue for V600 testing	Local testing for inclusion in the study; can be from archival tissue or if no archival tissue is available, from fresh biopsy; the local BRAF test result will be subject to retrospective central confirmation. BRAF testing may be completed prior to the 21 day screening period. Availability of tissue suitable for central testing must be documented prior to first dose.	X				
Demographic data	Record date of birth, gender, race and ethnicity	X				
Register subject	Using an interactive voice response system	X	X			
Height/Weight	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 14 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			
Disease characteristics	Record date of diagnosis, primary tumor type, histology, stage, etc.	X				
Prior anti-cancer therapy & radiation		X				
Prior surgical procedures		X				
Past and current medical conditions	Medical history will be assessed as related to the eligibility criteria listed in Section 4.2. Cardiovascular medical history/risk factors will also be assessed at baseline	X				

STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 21			
VISIT		Screen	Pre-dose Day 1	Pre-dose Day 8	Pre-dose Day 15	Pre-dose Day 22
VISIT WINDOW (±days		-21	N/A	±2	±2	±2
Alcohol consumption	Alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2	X				
Past and current tobacco use	Tobacco use will be assessed as related to the eligibility criteria listed in Section 4.2	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
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
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	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		X	X	X
Echocardiogram (ECHO)	Copies of all ECHOs will be collected for possible central review. 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).	X			X	
Concomitant medications	See Section 8 for list of prohibited and cautionary medications.	X	X	X	X	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X

STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 21			
VISIT		Screen	Pre-dose Day 1	Pre-dose Day 8	Pre-dose Day 15	Pre-dose Day 22
VISIT WINDOW (±days		-21	N/A	±2	±2	±2
Palatability questionnaire	For suspension - see SPM for additional details; subjects ≥12 years of age may complete the questionnaire independently (if able) while subjects younger than 12 years of age should work with their caregiver to supply feedback and the caregiver then completes the questionnaire. The questionnaire may be completed after the first dose of study drug but must be completed no later than Day 8 (±3 days)			X		
Blood Sampling						
Chemistry	Evaluations performed by a local laboratory. No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	X
Hematology	Evaluations performed by a local laboratory. No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	X
Urinalysis		X	X	X	X	X
Spot urine protein/Cr ratio, spot urine albumin	Early morning specimen preferred	X	X	X	X	X
PK sampling	For details, see Table 3-8		X (see Table 3-8)		X (see Table 3-8)	
Clinical Activity Assessments [redacted]						
Target and non-target lesion assessment	1. Must be identified at time of screening scan.	X				
Brain MRI (glioma subjects ONLY)	If an MRI of the brain was obtained within 35 days of the first dose, this can be used as screening MRI. CT with contrast allowed only if brain MRI is contraindicated). Glioma patients are not required to have CT of chest, abdomen and pelvis unless clinically indicated.	X				
LCH Assessment and LCH Scoring	LCH Assessment and LCH Scoring (Donadieu, 2004)	X				

STUDY PHASE		**SCREEN**	**TREATMENT DAYS 1 through 21**			
VISIT		**Screen**	**Pre-dose Day 1**	**Pre-dose Day 8**	**Pre-dose Day 15**	**Pre-dose Day 22**
VISIT WINDOW (±days		-21	N/A	±2	±2	±2
Performance status (Karnofsky/Lansky)	See Appendix 3	X	X	X	X	X
Study Medication						
Dispense oral study medication and assess compliance	Dispense a 2 to 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations. Two doses may be administered the first day if the time between doses is in compliance with protocol Section 3.6		X			
Collection of Scans obtained prior to study						
For subjects with a diagnosis of LGG only (enrolled in all parts)	Collection of efficacy assessments (imaging scans, primarily MRI) from one of the most recent prior chemotherapy and/or targeted therapy regimen to include the baseline assessment and a time point closest to 6 months following initiation of that therapy.	To be collected within 1 month of the subject enrolling in the study, or within 1 month of this amendment being approved, whichever is the later.				

1. MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram; PK = pharmacokinetic

Table 3-8 PK Sampling Table for Day 1 and Day 15 (Part 1 and Part 2)

	Day 1			Day 15[a]							
hour	**0.5**	**2**	**4**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**
COLLECTION WINDOW	± 5 min	± 5 min	± 20 min	-30 min	± 5 min	± 5 min	± 5 min	± 20 min	± 20 min	± 20 min	± 20 min
Subjects ≥25 kg											
PK (2 mL samples)	X	X	X	X	X	X	X	X	X	X	X
Subjects <25 kg and ≥10 kg											
PK (1 mL samples)	X	X	X				X	X			
PK (2 mL samples)				X		X			X		X
Subjects <10 kg											

PK (1 mL samples)							X		X		
PK (2 mL samples)				X							

Plasma concentrations of dabrafenib and all metabolites (hydroxy-dabrafenib, desmethyl-dabrafenib, and carboxy-dabrafenib) will be measured in the 2 mL blood samples. Plasma concentrations of dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib will be measured in 1 mL blood samples. Carboxy-dabrafenib will not be measured in the 1 mL blood sample.

[a] Subjects who are approved for intra-subject dose escalation must provide PK samples on day 15 at the higher dose level.

Table 3-9 Part 1 and Part 2 Treatment Phase: Week 4 (Day 29) through End of Study

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28+	Weeks 48+	Final Visit[2]
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
Safety Assessments										
Brief Physical examination	Will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated]	X	X	X		X	X	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X
Urine or Serum Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations, height, weight	X	X	X	X	X	X	Every 4 weeks	Week 48 then 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. Monitoring of the skin can be performed by a qualified local physician at the discretion of the investigator during non-clinic visits or dermatologic assessment only visits after Week 48. If possible, the same local physician should perform each exam throughout the study to ensure consistency between evaluations.		X		X		X	Week 32 then every 8 weeks	Week 48 then every 8 weeks	X

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28+	Weeks 48+	Final Visit[2]
VISIT WINDOW (±days)		±3	±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	Week 36	Week 48 then every 12 weeks	X
Echocardiogram (ECHO)	Copies of all ECHOs 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 (ECHO to be performed by the same operator throughout the study, where possible, 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. French subjects please see Appendix 5 for echocardiogram schedule.		X	X	X		X	Week 36	Week 48 then every 12 weeks	X
Concomitant medications	See Protocol Section 8 for list of prohibited and cautionary medications.	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Blood Sampling										
Chemistry	Evaluations performed by a local laboratory; Chemistry assessment should be performed at Week 36 for subjects with LCH for the LCH scoring assessment.	W4, W5, W6, W7	X	X	X	X	X	Week 32 then every 8 weeks; (also Week 36 for LCH only)	Week 48 then every 12 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	X	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X

STUDY PHASE		TREATMENT WEEK 4+							
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28+	Weeks 48+	Final Visit[2]
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
Urinalysis		X	X	X	X	X	X	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X
Spot urine protein/Cr ratio, spot urine albumin	Early morning specimen preferred	X	X	X	X	X	X	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X
Clinical Activity and Biomarker Assessments										
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	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X
Response for LGG, HGG, and other solid tumors	**Target/non-target lesions:** 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	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X
Response for LCH	Response assessment for LCH include RECIST 1.1, LCH assessment, and LCH Scoring (Donadieu, 2004).			X			X	At week 36	Week 48 then every 12 weeks	X
[redacted]										
Performance status (Karnofsky/Lansky)	See Appendix 3	X	X	X	X		X	Week 32 then every 8 weeks	Week 48 then every 12 weeks	X

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28+	Weeks 48+	Final Visit[2]
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
Study Medication										
Dispense oral study medication and assess compliance	Dispense a 2 to 12 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	X	Every 2-4 weeks	Every 4-12 weeks	
Post Treatment Follow-up – See Section 9.4										
Dermatologic skin monitoring after IP discontinuation	Follow up dermatologic skin assessments should be performed every 2 to 3 months for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy. (see Appendix 6 for French guidelines)									

1. MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram.
2. Final study visit within 28 days after last dose of study drug.

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 6 to 18 subjects will be enrolled in Part 1. In Part 2, each expansion cohort will attempt to enroll at least 10 evaluable subjects; evaluable for the purpose of clinical activity analysis is defined as a subject with a pre-dose and at least 1 post-dose disease assessment. The HGG cohort will continue recruitment until enrollment on another pediatric HGG study is available (expected by the end of 2018 and no later than mid 2019). It is estimated that approximately 35 subjects with HGG will be enrolled into Part 2.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the Novartis investigational product or other study treatment that may impact subject eligibility is provided in the IB.

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.

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Written informed consent – a signed informed consent and/or assent (as age appropriate) will be obtained according to institutional guidelines;
2. Male or female ≥12 months and <18 years of age at the time of signing the informed consent form;
3. 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.
4. At least one evaluable lesion;
5. 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);
6. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale (Yates, 1908) (Appendix 3);
7. NOTE: Subjects with a performance status of <50% can be enrolled if the subject's confinement to bed and inability to carry out activities is due solely to cancer-related pain, as assessed by the investigator.

8. Females of child-bearing potential must be willing to practice acceptable methods of birth control (see Section 7.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study medication. Sexually active males (including those that have had a vasectomy), who do not agree to abstinence, must be willing to use a condom during intercourse while taking the study drug, and for 4 weeks after stopping treatment and should not father a child in this period.
9. Must have adequate organ function as defined by the following values:
    - 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
10. Adequate renal and metabolic function defined as:
    - Calculated eGFR (Schwartz formula, http://www.medcalc.com/pedigfr.html), or radioisotope GFR ≥90 mL/min/1.73 m2; or
    - A serum creatinine within the institutional reference range upper limit of normal (for age/gender, if available);
11. Adequate liver function defined as:
    - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
    - AST and ALT ≤2.5 x ULN; AST/ALT may be <5 x ULN at baseline if disease under treatment involves the liver (requires radiographic confirmation of liver involvement)
12. Adequate cardiac function defined as:
    - LVEF of either ≥50% by ECHO or greater than institutional LLN by ECHO (while not receiving medications for cardiac function)
    - Corrected QT (QTcB) interval <450 msecs.

4.2.2 Exclusion Criteria

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

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. **Part 2 ONLY**: Previous treatment with dabrafenib, another RAF inhibitor, or a MEK inhibitor (exception: prior treatment with sorafenib is permitted);
2. Malignancy OTHER than the BRAF mutant malignancy under study
3. Had chemotherapy or radiotherapy within 3 weeks (or 6 weeks for nitrosoureas or mitomycin C) prior to administration of the first dose of study treatment;
4. The subject has received an investigational product within the following time period prior to the first dosing day in the current study: 28 days or 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is warranted by the data);
5. History of another malignancy;

Exception: (a) Subjects who have been successfully treated and are disease-free for 3 years, (b) a history of completely resected non-melanoma skin cancer, (c) successfully treated *in situ* carcinoma, or (d) CLL in stable remission, are eligible

6. Current use of a prohibited medication (Section 8.2) or herbal preparation or requires any of these medications during the study;
7. Unresolved toxicity greater than NCI CTCAE v4.0 (NCI, 2009) Grade 2 or higher from previous anti-cancer therapy, including major surgery, except those that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profile of dabrafenib (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy);
8. Has leukaemia;
9. History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib and its excipients;
10. Autologous or allogeneic stem cell transplant within 3 months prior to enrolment [NOTE: subjects with evidence of active graft versus host disease are excluded];
11. History of myocardial infarction, severe or unstable angina, peripheral vascular disease or familial QTc prolongation;
12. Abnormal cardiac valve morphology (≥ grade 2) documented by echocardiogram (NOTE: subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study);
13. Moderate valvular thickening;
14. Known, uncontrolled cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks;
15. Uncontrolled medical conditions (e.g., diabetes mellitus, hypertension, liver disease or uncontrolled infection), psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol; or unwillingness or inability to follow the procedures required in the protocol;
16. Presence of active GI disease or other condition (e.g., small bowel or large bowel resection) 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;
17. Hepatitis B Virus, or Hepatitis C Virus infection (subjects with laboratory evidence of Hepatitis B Virus clearance may be enrolled);
18. Pregnant females as determined by positive human chorionic gonadotropin (hCG) test at screening or prior to dosing;
19. Lactating females who are actively breast feeding.

4.3 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.

4.4 Withdrawal from Study and Missing Visits

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 appropriately be 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.

5 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

5.1 Hypotheses and Treatment Comparisons

With respect to the primary objectives and endpoints, the primary focus will be on determining the MTD (or recommended dose based on available safety, PK, and response data), the safety profile, and PK/PD relationship of dabrafenib in paediatric subjects with advanced BRAF V600-mutation positive solid tumors. Most analyses will be descriptive [redacted].

5.2 Sample Size Considerations

5.2.1 Sample Size Assumptions

5.2.1.1 Part 1 Dose Escalation

A minimum of 3 subjects will be evaluated at each dose level for determination of an appropriate pediatric dose using the modified RSD. It is estimated that approximately 6 to 18 subjects will be enrolled into Part 1.

5.2.1.2 Part 2 Cohort Expansion

The sample size for Part 2 is based on feasibility, practicality, and what would be sufficient for the characterization of the safety of dabrafenib and the plasma pharmacokinetics for the populations enrolled. Each of the 4 expansion cohorts will attempt to enroll at least 10 evaluable subjects; the HGG cohort will continue recruitment until enrollment on another pediatric HGG study is available (expected by the end of 2018 and no later than mid 2019). It is estimated that approximately 35 subjects with HGG will enroll into Part 2.

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 5-1. 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 dabrafenib in high grade glioma subjects, the chance declaring the cohort as having insufficient clinical activity after 10 subjects is approximately 20%.

Table 5-1 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

5.2.2 Sample Size Re-estimation

The HGG cohort in Part 2 will continue recruitment after 10 subjects are enrolled until enrollment on another study is available (expected by the end of 2018 and no later than mid 2019). The exact number of subjects recruited to the HGG cohort will depend on both the recruitment rate of subjects with HGG and the time it takes to begin recruitment to the new study. It is estimated that around 35 subjects with HGG will be recruited prior to the full opening of the new study based on the current plans, although the actual figure could be higher or lower than this. As promising efficacy has already been demonstrated with the initial subjects enrolled in this cohort, the additional increase in enrollment is to ensure that subjects can have access to a beneficial treatment, while also providing important additional refinement of the response rate estimate. For illustration, the improvement of precision in response rate estimate is shown in the Table below with the 95% exact binomial confidence intervals (CIs) at N=35 compared to the 95% CIs at N=10.

Table 5-2 Exact Binomial 95% Confidence Intervals around Potential Observed Objective Responses Rates for 10 and 35 Subjects

Observed # of Responses (Response Rate) (N=10)	Exact 95% Confidence Interval (%) (N=10)	Observed # of Responses (Response Rate) (N=35)	Exact 95% Confidence Interval (%) (N=35)
1 (10%)	0.3, 44.5	4 (11%)	3.2, 26.7
2 (20%)	2.5, 55.6	7 (20%)	8.4, 36.9
3 (30%)	6.7, 65.2	11 (31%)	16.9, 49.3
4 (40%)	12.2, 73.8	14 (40%)	23.9, 57.9
5 (50%)	18.7, 81.3	18 (51%)	34.0, 68.6
6 (60%)	26.2, 87.8	21 (60%)	42.1, 76.1

Observed # of Responses (Response Rate) (N=10)	Exact 95% Confidence Interval (%) (N=10)	Observed # of Responses (Response Rate) (N=35)	Exact 95% Confidence Interval (%) (N=35)
7 (70%)	34.8, 93.3	25 (71%)	53.7, 85.4

5.3 Data Analysis Considerations

All data will be summarized or listed. Subjects will be summarized based on the treatment level to which they were originally assigned. Additionally, selected analyses and summaries will be provided by age group as appropriate.

Complete details will be provided in the Statistical and Analysis Plan (SAP).

5.3.1 Analysis Populations

Populations will be considered for the analysis as follows:

The '**All Treated**' population is defined as all subjects who receive at least 1 dose of study treatment. An incorrect treatment schedule or drug administration or an early termination of treatment will not result in exclusion of subjects from this population.

The '**Safety**' population consists of all subjects who receive at least 1 dose of study treatment. All safety data will be analyzed using the Safety population.

The '**DLT Evaluable**' population is defined as those subjects in Part 1 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 drug 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 3.3, will also be included in the DLT evaluable population regardless of exposure.

The '**PK Population**' is defined as those subjects fulfilling the All Treated population criteria who contribute PK samples.

5.3.2 Interim Analysis

Safety and PK data will be examined while the study is being conducted for dose escalation decisions.

At the time of Amendment 7, an unplanned interim analysis was performed after all subjects with LGG had enrolled in Part 2 and completed at least 6 months of treatment or had discontinued treatment earlier. The interim analysis included analysis of all Part 1 subjects and other disease cohorts from Part 2 were analyzed as appropriate. This interim analysis was used for decision making of future development options and for publications. No statistical hypothesis testing was planned or conducted.

An interim analysis is planned after all subjects with LCH have enrolled in Part 2 and have completed at least 1 year of treatment or have discontinued treatment earlier. The results will be used for decision making of 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. The data for all Part 1 and Part 2 subjects may also be analyzed at this interim. In addition, safety and tolerability will be monitored closely on a continued basis.

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

5.3.3 Final Analyses

5.3.3.1 Safety and Tolerability Analyses

All relevant safety data will be summarized or listed based on the Safety population.

All safety data will be reported according to the initial treatment regimen the subject received (initial dose of dabrafenib). Additionally, selected analyses and summaries will be provided by age group as appropriate. AEs will be summarized by maximum toxicity grade for each initial dose level of dabrafenib. The toxicity grade for laboratory data will be calculated using NCI CTCAEv4.0 or higher (NCI, 2009). The lab data will then be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy (done for each initial dose level of dabrafenib).

DLTs will be summarized.

5.3.3.1.1 Extent of Exposure

Extent of exposure of dabrafenib will depend on tolerability of the subjects to the doses administered and the course of their disease. The number of subjects exposed to dabrafenib will be summarized for each dose level administered.

5.3.3.1.2 Adverse Events

AEs will be coded and grouped by body system. AEs will be summarized by frequency and proportion of total subjects, event type and body system. Separate summaries will be given for all AEs, drug-related AEs, SAEs, and AEs leading to withdrawal from the study.

Adverse events (AEs) and toxicities will be graded according to the NCI-CTCAE, Version 4.0. Summaries of the number of toxicity grades for both laboratory and non-laboratory data will be presented. If the AE is listed in the NCI-CTCAE, Version 4.0, the maximum grade will be summarized. Otherwise, the maximum intensity will be summarized.

5.3.3.1.3 Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade (version 4.0). For laboratory tests where grades are not defined by CTCAE v4.0, results will be categorized as low/normal/high based on laboratory normal ranges. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded; no visit windows will be applied. Unscheduled data will be included in "post-baseline" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study medication. Further details will be provided in the SAP.

5.3.3.1.4 Other Safety Measures

Performance status (Karnofsky/Lansky) assessments will be summarized by the originally assigned dose level. Vital signs, ECG, and ECHOs will be summarized at all measured time points. A descriptive summary including change from baseline pre-dose will also be presented. Further details will be provided in the SAP.

5.3.3.2 Pharmacokinetic Analyses

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

All 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 pharmacokinetics of dabrafenib and its metabolites. PK parameters estimated in the population PK analysis will include: apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and absorption rate (ka). Data may be pooled with PK data from adult studies.

5.3.3.3 Efficacy Analyses

Anti-tumor activities will be calculated based on clinical evidence and the investigator-determined response assessment algorithms as described in Appendix 2. Where appropriate, the lesion data will be listed for each subject. For subjects with solid tumors, the percent change from baseline and nadir will be calculated for each subject and listed, along with their calculated response [complete response (CR), partial response (PR), stable disease and progression of disease (PD)] according to response criteria in Appendix 2. Response data will be summarized by disease cohort and by dose using the All Treated population. If the data warrant, the response data may also be summarized by the dose level of dabrafenib. For the LGG, HGG, and other solid tumors disease cohorts, response will also be assessed by an independent reviewer, and this data will be used to provide supportive analyses.

Additionally, all efficacy analyses will also be performed on the subset of central laboratory confirmed BRAF mutant subjects, excluding subjects who were centrally confirmed to be BRAF Wild-Type. In the event that central confirmation of mutation status is not obtained, the local laboratory testing result for BRAF mutation status will be utilized.

Response Rate (RR) with 95% exact confidence intervals will be calculated as the proportion of subjects with best overall response of confirmed CR or PR, as defined in Appendix 2, relative to the total number of subjects treated in each expansion cohort. In the case of LCH subjects, the RR is the number of subjects assessed to have treatment response relative to the total number of subjects treated in that cohort. See Appendix 2 for further information.

In addition to the frequentist analysis approach mentioned above, RR will be compared to the target RR using Bayesian posterior probabilities. A posterior estimate of RR will be calculated for each expansion cohort along with associated 95% credible intervals as calculated on

posterior probabilities. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior and the likelihood (i.e., the data). Since dabrafenib has not yet been tested previously in the clinic for these pediatric indications, a Beta (0.005, 0.005) prior is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows: Let p denote the RR for the treatment. The number of responses in the current n subjects, x, follows a binomial distribution: Binomial (n, p). Taking the Bayesian method and combining the non-informative prior and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e., p ~Beta(0.005+x, 0.005+n-x) with the posterior mean (0.005+x)/(0.01+n).

Based on this posterior distribution of the RR, the probability that the RR ≥10% ≥ 15%, ≥20%, ≥ 25%, ≥30% and ≥40% will be calculated as the reference for decision-making of stopping for futility or considering further development for each of the expansion cohorts. Since there is no formal hypothesis to be tested, no formal decision rule will be formulated for the final analysis.

5.3.3.4 Other Analyses

Nonlinear mixed effects modelling techniques may be employed to define dosing requirements to achieve comparable exposure in pediatric patients relative to adults. [redacted] Complete details will be provided in the SAP.

6 STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 3.8). Detailed procedures for obtaining each assessment are provided in the Study Procedures Manual (SPM).

The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme. The total volume of trial related blood loss will not exceed 3% of the total blood volume during any 4 week period, and will not exceed 1% of the total blood volume at any single time. Please see the SPM for details around calculation for total blood volume of blood will be collected over the duration of the study, including any extra assessments that may be required.

Procedures conducted as part of the subject's routine clinical management (e.g., 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.

6.1 Demographic/Medical History Assessments

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

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2.

Additional retrospective data will be collected, if available, on subjects 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.

6.2 Critical Baseline Assessments

6.2.1 Confirmation of BRAF Mutation Positive Status

Subjects with BRAF V600 mutation- positive tumors as determined by local testing conducted in a CLIA-approved facility (or equivalent) may be enrolled on the study. Archived tumor tissue sample will be collected at screening for retrospective confirmation of the BRAF mutation status. If an archived tumor tissue sample is not available, fresh tumor tissue should be collected for the assessment and confirmation of BRAF V600 mutation status in a CLIA approved facility (see SPM for further details on sample collection).

6.2.2 Baseline Documentation of Target and Non-target Lesions

All baseline lesion assessments must be performed within 21 days of the first dose of study medication (or within 35 days for MRIs). Guidance on baseline documentation of target and non-target lesions will be provided (by tumor type) in the SPM or Imaging Manual.

6.2.3 Independent review of HGG tumor histology

A central review of tumor histology and grade will be performed by an independent pathologist for all subjects with HGG diagnosis.

Slides and/or blocks collected during the study will be used for the central review.

6.3 Safety and Tolerability

Planned time points for all safety assessments are listed in the Time and Events Table (Section 3.8).

Physical and Dermatological Examinations

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities
- Height and weight will also be measured and recorded.
- A brief physical examination will include height and weight, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) [and neurological exam as clinically indicated].

Dermatological Examination/Skin Biopsy/Photography

- A full body dermatological examination will be performed by a dermatologist [or suitably qualified personnel (i.e., physician or supervised physician assistant)] to identify abnormal skin lesions. All findings will be identified during screening (photography of suspect lesions at screening is recommended). Dermatological examinations should include examination of skin and assessment of any skin changes. Wherever possible, the same personnel should perform these examinations. Follow-up skin examinations by a referral dermatologist should be conducted if clinically indicated.
- Skin photography of new non-melanoma skin lesions or non-melanoma lesions that change while on study is recommended. Refer to the SPM for details regarding the lesion documentation by photography.
- Biopsy in or around skin lesions that change during the study may be requested by Novartis, if clinically indicated. [redacted]
- Dermatological examinations should be performed every 2 months during treatment, and every 2-3 months for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Monitoring of the skin can be performed by a qualified local physician at the discretion of the investigator during non-clinic visits or dermatologic assessment only visits. If possible, the same local physician should perform each exam throughout the study to ensure consistency between evaluations. 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

- During treatment subjects should be monitored as clinically appropriate. Complete blood cell counts should be performed as clinically indicated. Following discontinuation of dabrafenib monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy, whichever comes first. Any non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE and treated according to standard clinical practice.
- See Appendix 6 for French country specific guidelines.

Vital Signs

- Vital sign measurements will include systolic and diastolic blood pressure, temperature and pulse rate.
- If a subject develops a fever, refer to Section 3.7.1 for management guidelines.

Electrocardiogram (ECG)

- A single 12-lead ECG will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and

QTcB intervals. Refer to Section 3.7.4.4 for QTcB withdrawal criteria and additional QTcB readings that may be necessary.

Echocardiography (ECHO)

- ECHOs will be performed to assess cardiac ejection fraction. The echocardiographer's evaluation should include an evaluation of left ventricular ejection fraction. Post-dose ECHOs should be compared to baseline to note if there are any changes.
- Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% absolute decrease in LVEF from baseline and whose cardiac ejection fraction is less than institution's LLN will be required by Novartis for review.

Clinical Laboratory Assessments

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

Hematology			
Platelet Count:	Red blood cell (RBC) Indices (at screening and if hemoglobin decrease ≥2 g/dL compared to baseline):		Automated White Blood Cell (WBC) Differential:
RBC Count	MCV		Neutrophils
WBC Count (absolute)	MCH		Lymphocytes
Hemoglobin	MCHC		Monocytes
	Reticulocyte Count		Eosinophils
			Basophils
Clinical Chemistry			
BUN	Potassium	AST	Total and direct bilirubin [a]
Creatinine	Chloride	ALT	Uric Acid
Glucose	Total CO_2	Alkaline phosphatase	Albumin
Sodium	Calcium		Total Protein
Magnesium	Phosphate		
Other tests			
Pregnancy tests			
Amylase and lipase [monitor via local laboratory where appropriate to evaluate certain AEs (i.e., abdominal pain, pancreatitis, etc.)]			
Creatine phosphokinase (CPK) at screening and pre-dose Day 1 only			
Liver gamma GT for subject with LCH to complete the LCH scoring system (see Appendix 2)			

a. Direct bilirubin is required only if the total bilirubin is elevated (> or = 2 times the ULN)

Palatability

For subjects ≥12 years of age who receive the suspension, the subject will complete a form 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, 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. Additional details (and an example questionnaire) are provided in the SPM.

6.4 Pregnancy

6.4.1 Time period for collecting pregnancy information

All pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until 5 terminal half-lives post-last dose.

6.4.2 Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Novartis within 24 hours of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to Novartis as described in Section 11.7. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

6.4.3 Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Novartis within 24 hours of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

6.5 Pharmacokinetics

6.5.1 Blood Sample Collection

Blood samples for PK analysis of dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, will be collected at the time points indicated in Section

3.8, Time and Events Table. 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 (hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib) will be determined from the 2 mL blood samples collected. Plasma concentrations of dabrafenib and certain metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) will be determined from the 1 mL blood samples collected. Carboxy-dabrafenib will not be determined from the 1 mL blood sample.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM).

6.5.2 Sample Analysis

Until 31 Dec 2015 plasma analysis was performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics, Platform Technology and Sciences, GSK and raw data is stored in the GlaxoSmithKline Archives until transfer to Novartis archive. Since 1 Jan 2016 plasma analysis is performed under the management of Novartis DMPK and raw data are stored in the archives of the analytical site until transfer to Novartis archive.

Concentrations of dabrafenib and its metabolites (hydroxy-dabrafenib, desmethyl-dabrafenib, and carboxy-dabrafenib) will be determined in plasma samples using validated analytical methods. Once the plasma has been analyzed for dabrafenib and its metabolites, any remaining plasma may be analyzed qualitatively for other circulating metabolites or quantitatively to perform long term stability evaluation or cross validation and the results reported under a separate DMPK protocol.

6.6 Anti-tumor Assessment

Disease progression and response evaluations will be determined according to the appropriate guidelines (Appendix 2).

See the Time and Events Table (Section 3.8) for the schedule of assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window is permitted to allow for flexible scheduling (see Time and Events Table, Section 3.8).

Confirmation of CR and partial response (PR) are required per protocol. Complete response/PR confirmation assessments may take place at Week 16 (but not earlier than week 12) if initial response was seen at the Week 8 assessments. Initial responses (CR/PR) that occur at Week 16 (or after) should be confirmed not less than 4 and not more than 8 weeks after the initial response. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments). If the criteria for a CR or PR are not confirmed, then stable disease can be considered the best response if it has been demonstrated for a minimum of 12 weeks.

The response scans/assessments may also be independently reviewed to confirm the investigator-assessed responses. Details related to disease assessment acquisition and transfers are provided in the SPM and are to be applied to baseline and all subsequent assessments.

6.6.1 Assessment of Subject Completion

If the last radiographic assessment was more than 16 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.

[redacted]

7 LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1 Contraception Requirements

7.1.1 Female Subjects

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during dosing and for 4 weeks after stopping treatment with dabrafenib. This includes female pediatric subjects who are menarchal or who become menarchal during the study. 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.
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. 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.

All menstruating female subjects (as required per local requirements and/or regulations) must have a negative serum pregnancy test within 7 days prior to the first dose of study medication, preferably as close to the first dose as possible, If serum pregnancy test is performed within 7 days of first dose of study drug, it does not need to be repeated on Day 1 (pre-dose). All female subjects who begin to menstruate during the study must have a negative serum pregnancy test (as required per local requirements and/or regulations) during the study and for 4 weeks following the last dose of study drug.

NOTES:

- Oral contraceptives are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib.
- 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]
- 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.

7.1.2 Male Subjects

Male subjects (including those that have had a vasectomy) taking dabrafenib in the study must use a condom during intercourse while taking the drug and not to father a child during the study and for the period of 4 weeks following stopping of study treatment.

7.2 Meals and Dietary Restrictions

Subjects no longer need to abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges (orange marmalade) or pommelos within 7 days prior to the first dose of dabrafenib until the end of the study.

Dabrafenib should be administered under fasting conditions, either approximately 1 hour before or approximately 2 hours after a meal. If it is not possible for a subject to tolerate the fasting conditions noted above, dabrafenib can be administered with a small non-fat meal (e.g., small

amount of apple juice/sauce, a piece of dry toast). Subjects and their parents should be advised to avoid administering dabrafenib with milk or high-fat, high-calorie foods. 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.

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.

7.3 Caffeine, Alcohol, and Tobacco

- On PK sampling days, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, energy drinks) for 24 hours prior to the start of collection of the samples and until collection of the last sample.
- On PK sampling days, subjects will abstain from alcohol for 24 hours prior to the start of collection of the samples and until collection of the last sample.
- Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit.

7.4 Activity

Subjects will abstain from strenuous exercise (e.g., competitive sports) for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies.

8 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1 Permitted Medications and Non-Drug Therapies

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

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

Immunization is permitted while on dabrafenib if subject has been on treatment and is deemed stable.

8.2 Prohibited Medications and Non-Drug Therapies

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

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs;
- 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 8-1) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the Novartis 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 8-1 Prohibited Medications

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, 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

8.3 Medications to be Used with Caution

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

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 8-2 and in the SPM.
- Therapeutic level dosing of warfarin can be used with approval by the Novartis Medical Lead and close monitoring of PT/INR by the site. 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.

Table 8-2 Medications to be used with Caution

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide

Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, digoxin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone

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

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

9 COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

9.1 Subject Completion

A subject will be considered to have completed the study if the subject dies, otherwise progresses during the study treatment (or is not clinically benefiting from continued treatment), is withdrawn due to an unacceptable toxicity, withdraws consent or begins a new therapy. A final study visit within 28 days after last dose of study drug should be completed.

9.2 Subject Withdrawal Criteria

Refer to Section 3.7 for dose adjustment/stopping criteria.

A subject may withdraw from study treatment at any time at his/her own request, at the request of his/her parents, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons.

9.3 Subject Withdrawal Procedures

9.3.1 Subject Withdrawal from Study

A subject will be considered to have withdrawn from the study if the subject has not died or progressed and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.

9.3.2 Subject Withdrawal from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable AE (including meeting stopping criteria for liver chemistry defined in Section 3.7.8 or for hematologic and other non-hematologic toxicity as described in Section 3.7.2). Treatment beyond disease progression may be considered if the investigator determines that the subject is still clinically benefiting from study treatment and the subject or their parent (guardian) is willing to continue study drug, following consultation with the study Medical Lead. In this case, the study treatment as well as the study procedures may be continued until study treatment

discontinuation. These subjects will be considered as having progressive disease (as of the date of the scan showing progression).

Study medication may also be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol that result in a significant risk to the patient's safety;
- request of the subject or parent/guardian's request
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

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

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

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

All subjects who discontinue from study treatment will have a Final Visit (as defined in Table 10) which should be completed at the time of discontinuation (within 28 days after last dose of study drug). Subjects will be offered post study treatment follow-up as specified in Section 9.4. 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.

9.3.3 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.

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.

9.4 Treatment after the End of the Study

After study participation in the current study and for subjects still benefitting from treatment with dabrafenib, subjects will be given the option to transition to the rollover study, where subjects continue receiving dabrafenib alone as specified in rollover study, provided subjects are still benefiting from dabrafenib.

Subjects who are no longer receiving 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 2 to 3 months according to the instructions in Section 6.3.

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

10 STUDY TREATMENT

Study treatment dosage and administration details are listed in Section 3.6.

10.1 Blinding

This will be an open label study.

10.2 Packaging and Labeling

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

10.3 Preparation/Handling/Storage/Accountability

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 Novartis.

Dabrafenib dispersible tablets will be dispersed in a defined 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. 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.

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to Novartis and the amount supplied and/or administered to and returned by subjects. The required accountability units for this study will be number of capsules, number of dispersible tablets, or weight of suspension. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the SPM.

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.

10.4 Assessment of Compliance

When 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.

When dosing occurs outside the clinic, parents/subjects will be provided a supply of study drug (powder stickpacks, dispersible tablets, or capsules). On each return visit to the clinic, the parent/subject will return all unused study drug in its dispensed container, and the study site staff will note the number of capsules, number of tablets, or number of stickpacks returned in the source documents.

10.5 Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than the highest dose tested in pediatric clinical studies without reaching a manageable specific toxicity, the investigator should contact a Novartis Medical Lead immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Haemodialysis is not expected to enhance the elimination of dabrafenib as it is highly bound to plasma proteins.

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

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

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

11 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

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 start of Study Treatment and until the end of the follow-up period.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a Novartis product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded and reported to Novartis within 24 hours, as indicated in Section 11.6.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify Novartis.

11.1 Definition of Adverse Events

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

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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

- Any clinically significant abnormal laboratory findings or other abnormal 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.
- 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.
- 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.

11.2 Definition of Serious Adverse Events

If an event is not an AE per Section 11.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

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-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity, or
   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.
f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).
   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the

criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury

h. Protocol-specific SAEs: LVEF meeting stopping criteria; any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and new primary melanoma); basal cell carcinoma (BCC) is required to be reported as a protocol-specific SAE for all non-melanoma indications.

11.3 Method of Detecting AEs and SAEs

Care will 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 "How does your child seem to feel?"
- "Have you had any (other) medical problems since your last visit/contact?" or "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 "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

11.4 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the subject's medical records to Novartis in lieu of completion of the Novartis, AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are requested by Novartis. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to Novartis.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

11.5 Evaluating AEs and SAEs

11.5.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

11.5.2 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

11.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by Novartis to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Novartis with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to Novartis within the designated reporting time frames.

11.7 Prompt Reporting of SAEs to Novartis

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Novartis within 24 hours. Any follow-up information on a previously reported SAE will also be reported to Novartis within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying Novartis of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 11.5.2, Assessment of Causality.

The primary mechanism for reporting SAEs to Novartis will be the electronic data collection tool. If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to a Novartis Medical Lead. Then the site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to their Novartis protocol contact by telephone.

Novartis contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Lead Contact Information page.

11.8 Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

12 LIVER CHEMISTRY FOLLOW-UP PROCEDURES

Refer to the diagram in Appendix 4 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 3.7.8:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody.

- Blood sample for PK analysis, obtained within 96 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the ECRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum CPK and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

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

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.

12.1 Liver Chemistry Monitoring Criteria

For subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, do the following:

- Notify the Novartis Medical Lead within 24 hours of learning of the abnormality to discuss subject safety
- Continue investigational product
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet any of the liver chemistry stopping criteria 1 - 5 in Section 3.7.8, then proceed as described above

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, then monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Refer to Appendix 4 for algorithm of liver chemistry stopping and follow up criteria.

12.2 Restarting Investigational Product

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

Approval by Novartis for drug restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by Novartis in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by Novartis.

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

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

Approval by Novartis for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug is approved by Novartis in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by Novartis.

Subjects approved by Novartis for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

13 STUDY CONDUCT CONSIDERATIONS

13.1 Posting of Information on Publicly Available Clinical Trial Registers

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

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 applicable country-specific regulatory requirements including those required under a US IND.

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

The study will also be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent/assent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from parent(s), LAR or subject prior to participation in the study.

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

13.2.1 Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety 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 IEC/IRB is notified.

13.3 Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and Novartis procedures, Novartis personnel (or designated Clinical Research Organization [CRO]) will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Novartis requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

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

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

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

13.4 Quality Assurance

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

13.5 Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and Novartis Standard Operating Procedures.

In addition, Novartis reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If Novartis determines such action is needed, Novartis will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, Novartis will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, Novartis will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

13.6 Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a Novartis audit or regulatory inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these 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 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 at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

13.7 Provision of Study Results to Investigators, Posting of Information on Publically 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. Investigators 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 investigators with the full summary of the study results. Investigators are encouraged to share the summary results with the study subjects, as appropriate.

Novartis aims to post a results summary to the Novartis Clinical Trial Results website (novartisclinicaltrials.com) and other publicly available registers no later than six (6) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication .When publication is not feasible, please refer to the Novartis Clinical Trial Results website (novartisclinicaltrials.com) for a summary of the trial results.

13.8 Data Management

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

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

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures with the objective of resolving errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. All AEs and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and a custom dictionary. Laboratory data (i.e., hematology and clinical chemistry) will be stored in a database maintained by the central laboratory and transferred to Novartis at agreed times.

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

14 REFERENCES

Alessandri AJ, Goddard KJ, Blair GK, et al. Age is the major determinant of recurrence in paediatric differentiated thyroid carcinoma. *Med Paediatr Oncol*. 2000;35(1):41-6.

Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. *Hematol Oncol Clin North Am.* 1998;12(2):247-258.

Badalian-Very G, Vergilio J, Degar BA, MacConaill LE, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010;116(11):1919-1923.

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

[redacted]

Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature*. 2010;467:7315(596-599).

Cancer Research UK 2010. CancerStats – Childhood Cancer – Great Britain & UK. http://info.cancerresearchuk.org/cancerstats/

CBTRUS (2010). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumours Diagnosed in the United States in 2004-2006. Source: Central Brain Tumour Registry of the United States, Hinsdale, IL. www.cbtrus.org

Clinical Trials Facilitation Group. 2014. Recommendations related to contraception and pregnancy testing. Available at: hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. [Accessed 20 February 2017].

Corrias A, Mussa A, Baronio F, Arrigo T, et al. Diagnostic features of thyroid nodules in paediatrics. Arch Paediatr Adolesc Med. 2010;164(8):714-719.

Daniotti M, Ferrari A, Frigerio S, Casieri P, et al. Cutaneous melanoma in childhood and adolescence shows frequent loss of INK4A and gain of KIT. *J Invest Dermatol.* 2009;129:1759–1768.

deVries E, et al. Skin cancer incidence and survival in European children and adolescents (1978–1997). Report from the Automated Childhood Cancer Information System project. *Eur J Cancer*. 2006;42:2170-2182.

Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, et al. (2011) BRAF V600E Mutations Are Common in Pleomorphic Xanthoastrocytoma: Diagnostic and Therapeutic Implications. PLoS ONE 6(3): e17948. doi:10.1371/journal.pone.0017948

Donadieu J, Piguet C, Bernard F, Barkaoui M, Ouache M, Bertrand Y, et al. A new clinical score for disease activity in Langerhans cell histiocytosis. *Pediatr Blood Cancer.* 2004;43:770-776.

Dougherty M, Santi M, Brose M, Ma C, et al. Activating mutations in BRAF characterize a spectrum of paediatric low-grade gliomas. Neuro Oncol. 2010 Feb 14. [Epub ahead of print]. PMID: 20156809.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.

European Medicines Agency (EMA), 2009. ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

European Medicines Agency. 2006; Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. European Medicines Agency , London, United Kingdom. ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf.

Ferlay J, et al. Estimates of the cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010;46(4):765-81.

Flesch G, et al. Overview of the clinical pharmacokinetics of oxcarbazepine. Clin Drug Investig. 2004;24(4):185-203.

Forshew T, Tatevossian RG, Lawson ARJ, Ma J, et al. Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. *J Pathol*. 2009;218:172-181.

BRF112680: A Phase I, Open-Label, Multiple-Dose, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of the BRAF Inhibitor GSK2118436 in Subjects with Solid Tumors. Report Date March 2012.

GlaxoSmithKline. Worldwide Epidemiology Project WEUKBRE5092. 2010. Available upon request.

Hauschild A, Grob J, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. Published online 25June2012.

Hawkins MM, Wilson LM, Stovall MA, Marsden HB, et al. Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. *BMJ*. 1992;304(6832):951-958.

Hudson MM, Tyc VL, Srivastava DK, Gattuso J, et al. Multi-component behavioral intervention to promote health protective behaviors in childhood cancer survivors: the protect study. *Med Pediatr Oncol*. 2002;39(1):2-1; discussion 2.

Jacob K, Albrecht S, Sollier C, Faury D, et al. Duplication of 7q34 is specific to juvenile pilocytic astrocytomas and a hallmark of cerebellar and optic pathway tumours. *Brit J Cancer*. 2009;101:722–733.

[redacted].

Kumagai A, Namba H, Saenko VA, Ashizawa K, et al. Low frequency of BRAF T1796A mutations in childhood thyroid carcinomas. *J Clin Endocrinol Metab.* 2004;89:4280–4284.

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

MacConaill LE, Campbell CD, Kehoe SM, Bass AJ, et al. Profiling Critical Cancer Gene Mutations in Clinical Tumor Samples. *PLoSONE*. 2009;4(11):e7887.

Melck AL, Yip L, Carty SE. The utility of BRAF testing in the management of papillary thyroid cancer. The Oncologist. 2010;15:1285–1293.

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

National Cancer Institute (NCI). 9 January 2012. Langerhans Cell Histiocytosis Treatment PDQ http://www.cancer.gov/cancertopics/pdq/treatment/lchistio/HealthProfessional/

National Cancer Institute (NCI). 11 May 2012. Melanoma Treatment PDQ http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional

National Cancer Institute (NCI). 9 May 2012. Thyroid Cancer Treatment PDQ http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional

Nikiforova MN, Nikiforov YE. Molecular diagnostics and predictors in thyroid cancer. *Thyroid*. 2009;19(12):1351-1361.

Pfister S, Janzarik WG, Remke M, Ernst A, et al. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. *J Clin Invest*. 2008;118:1739–1749.

Poulikakos PI, Zhang C, Bollag G, Shokat KM and Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature* 2010; 464:427-430.

Prados MD, Edwards MS, Rabbitt J, Lamborn K, et al. Treatment of paediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. *J Neurooncol*. 1997;32(3):235–241.

Qaddoumi I, Sultan I, Broniscer A. Paediatric low-grade gliomas and the need for new options for therapy. *Cancer Biol Ther*. 2009;8:1-7.

Rosenbaum E, Hosler G, Zahurak M, Cohen Y, et al. Mutational activation of BRAF is not a major event in sporadic childhood papillary thyroid carcinoma. *Modern Pathol*. 2005;18:898-902.

Satoh T, Smith A, Sarde A, et al. B-RAF mutant alleles associated with Langerhans cell histiocytosis. *PLoS ONE*. 2012;7:4.

Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the histiocyte society. *Paediatr Dermatol*. 2008;25(3):291-295.

Schiffman JD, Hodgson JG, VandenBerg SR, Flaherty P, et al. Oncogenic BRAF mutation with CDKN2A inactivation is characteristic of a subset of paediatric malignant astrocytomas. *Cancer Res.* 2010;70(2):512–519.

Sievert AJ, Lang SS, Boucher KL, Madsen PJ, Slaunwhite E, Choudhari N, Kellet M, Storm PB, Resnick AC. Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. Proc Natl Acad Sci USA 2013; 110:5957–5962.

Skolnik J, Barret J, Jayaraman B, et al. Shortening the Timeline of Pediatric Phase I Trials: The Rolling Six Design. *J Clin Onc*. 2008; 26:190-196.

Stalemark H, Laurencikas E, Karis J, Gavhed D, et al. Incidence of Langerhans cell histiocytosis in children: a population-based study. *Paediatr Blood Cancer*. 2008;51:76-81.

Stockschlaeder M, Sucker C. Adult Langerhans cell histiocytosis. *Eur J Haematol.* 2006;76(5):363-368.

Sugiyama I, Murayama N, Kuroki A, Kota J, Iwano S, Yamazaki H, Hirota T, et al. Evaluation of cytochrome P450 inductions by anti-epileptic drug oxcarbazepine, 10-hydroxyoxcarbazepine, and carbamazepine using human hepatocytes and HepaRG cells. Xenobiotica. 2016 Sep;46(9):765-74

Surveillance, Epidemiology, and End Results (SEER) Program. 2010. www.seer.cancer.gov Trileptal SPC; http://www.medicines.org.uk/EMC/searchresults.aspx?term=trileptal&searchtype=QuickSearch

U.S. Food and Drug Administration. 2000; Guidance for industry. E11 Clinical investigation of medicinal products in the pediatric population. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM129477.pdf

United Nations, Projected 2010 Population Estimates. http://esa.un.org/unpp/.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. *J Clin Oncol.* 2010; 28:1963-1972.

Wen PY, Chang S, Van den Bent, MJ, et al. Response Assessment in Neuro-Oncology Clinical Trials. *J Clin Oncol.* 2017; 35(21):2439-2449.

Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky Performance Status. *Cancer.* 1908;45:2220-2224.

Zhao L, Lee, J, et al. The superiority of the time-to-event continual reassessment method to the rolling six design in pediatric oncology Phase I trials. *Clinical Trials*. 2011;8:361-369.

15 APPENDICES

15.1 Appendix 1: Modified Rolling Six Design Dose Escalation Procedures

Dose Escalation Procedure

Number of Subjects Enrolled	Number of Subjects with a DLT	Number of Subjects with Data Pending	Decision
1	--	--	Same dose level
2	2	--	De-escalate
	Other	--	Same dose level
3	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
4	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
5	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
6	≥2	--	De-escalate
	≤1	0	Escalate[a]
	0	1	Escalate[a]
	Other	--	Suspend

a. Modified from the Zhao, 2011 publication

15.2 Appendix 2: Response Criteria

Response criteria for subjects with solid tumors and measurable disease

Anti-tumor activity will be assessed based on clinical evidence and the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria for solid tumors (Eisenhauer, 2009).

Evaluation of Target Lesions

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

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

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

stable disease the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of Non-target Lesions

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

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

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

New Lesions

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

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

Evaluation of Overall Response

Table 15-1 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 15-1 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

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

NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, PD=progressive disease, NA= not applicable, and NE=not evaluable

Note:

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

Evaluation of Best Overall Response

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

- To be assigned a status of stable disease, follow-up disease assessment must have met the SD criteria at least once after first dose of study medication at a minimum interval of 12 weeks.
- If the minimum time for stable disease is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of stable disease and stable disease does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after a stable disease assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed at Week 16 if initial response was seen at the Week 8 scan. Initial responses (CR/PR) that occur Week 16 or after should be confirmed not less than 4 and not more than 8 weeks after the criteria for response are first met.

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 V11, 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 (Wen, 2010). These criteria are noted in section 15.2.

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) 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.

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 v11. This review is in addition to the previously performed review using RANO (Wen, 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 0mm 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.
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

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**

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
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.

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.

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 (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
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	2 1

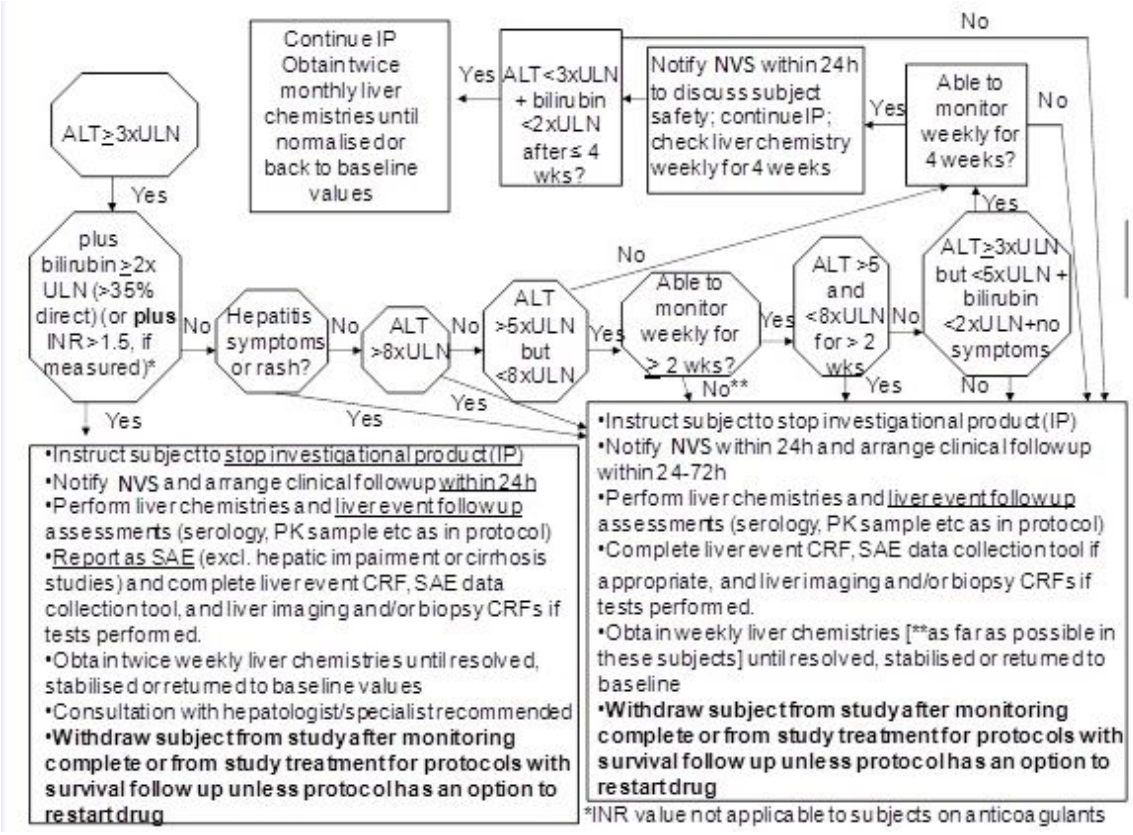
Variable	Modality	Score
	0-2 cm maximum diameter	0
Nodes (>2 cm)	Yes	1
	No	0
Liver	Below umbilicus	2
	Enlarged, above umbilicus	1
	Not enlarged	0
Spleen	Below umbilicus	2
	Enlarged, above umbilicus	1
	Not enlarged	0
Liver (enzymes)	>10 ULN	2
	3-10 ULN	1
	<3 ULN	0
Liver (gamma GT)	>10 ULN	2
	3-10 ULN	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

15.3 Appendix 3: Performance Status Criteria / Scoring System

Karnofsky (age >=16 years of age) and Lansky (age <16 years) Performance Scores (Yates, 1908)

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
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 or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more 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	Required 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.

15.4 Appendix 4: Liver Safety Algorithms



15.5 Appendix 5: Country Specific Amendment 2 for France

TITLE PAGE

Division: Worldwide Development
Retention Category: GRS019
Information Type: Protocol Amendment

Title:	Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Pediatric Subjects Aged 1 Month to <18 years with Advanced BRAF V600-Mutation Positive Solid Tumors

Compound Number: GSK2118436

Effective Date: 13-DEC-2012

Protocol Amendment Number: 02
Subject: Dabrafenib, pediatrics, V600-mutation positive, BRAF, dose escalation
Authors:

Revision Chronology:

2012N131371_00	2012-JUL-24	Original
2012N131371_01	2012-OCT-19	Amendment No. 01 corrected Inclusion Criteria #6 to ensure consistency with the contraception requirements as outlined in Section 7.1.1; the requirement for male contraception was deleted since the risk of embryofetal developmental toxicity as a consequence of exposure to female pregnant partners is very low. In addition, the dose escalation procedure table provided in Appendix 1 was changed to ensure that escalation of dose when 6 subjects are enrolled occurs only if there are ≤1 subject with a DLT and no subject data pending, and to fix the reference and formatting.
2012N131371_02	2012-DEC-13	Amendment No. 02 is a country-specific amendment for France which prohibits children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules from inclusion in the study in France (pending availability of an oral suspension formulation); changes the QTc stopping criteria to 500 msec for French subjects (as compared to 530 msec); adds cardiac monitoring by echocardiogram (ECHO) at Week 4; and highlights that ECHOs are to be performed by the same operator throughout the study, where possible.

Sponsor Signatory:

[redacted] MD
[redacted]

Date

Sponsor Information Page

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	[redacted] M.D.	[redacted]	Mobile: [redacted]		GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426-0989 Email: [redacted]
Secondary Medical Monitor	[redacted] M.D.	[redacted]	Mobile: [redacted]		GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426-0989 Email:

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Numbers:

IND No.: 105,032
EudraCT Number: 2012-001499-12

Investigator PROTOCOL Agreement Page

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

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

LIST OF ABBREVIATIONS

ANSM	Agence Nationale de Securite du Medicament et des Produits de Sante
ECHO	echocardiogram
ECG	electrocardiogram
msec	millisecond

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

Amendment 02

Where the Amendment Applies

Amendment 02 is a country specific amendment for France. Bolded text indicates new language, and strikethrough text indicates deleted language.

Summary of Amendment Changes with Rationale

Amendment No. 02 is a country-specific amendment for France. Amendment 02 prohibits children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules from inclusion in the study in France (pending availability of an oral suspension formulation). In addition, Amendment 02 changes the QTc stopping criteria to 500 msec for French subjects (as compared to 530 msec) and adds cardiac monitoring by echocardiogram (ECHO) at Week 4 as requested by the French Agency [the Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM)]. It is noted in the Study Procedures Manual, and highlighted in this country-specific amendment, that ECHOs are to be performed by the same operator throughout the study, where possible.

List of Specific Changes

Change #1, Section 3.2, Discussion of Study Design: in response to ANSM review of the protocol.

Previous Text (last paragraph in Section)

The study will use the currently available dabrafenib capsule strengths (50 mg and 75 mg) from the adult program for children who are able to reliably swallow capsules. In addition, two lower strength capsules (10 mg and 25 mg) and an oral suspension formulation are available for pediatric subjects who may have difficulty swallowing larger capsules. The suspension will only be available at those sites that are capable of and meet the applicable regulatory requirements to prepare the suspension.

Revised Text:

The study will use the currently available dabrafenib capsule strengths (50 mg and 75 mg) from the adult program for children who are able to reliably swallow capsules. In addition, two lower strength capsules (10 mg and 25 mg) and an oral suspension formulation are available for pediatric subjects who may have difficulty swallowing larger capsules. The suspension will only be available at those sites that are capable of and meet the applicable regulatory requirements to prepare the suspension. **In France, children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules cannot be included in the study, pending availability of an oral suspension formulation.**

Change #2, Section 3.6, Investigational Product and Other Study Treatment Dosage/Administration; rationale for change: in response to ANSM review of the protocol.

Previous Text

Capsules: Dabrafenib capsules will be supplied by GSK (for subjects able to reliably and consistently swallow capsules).

Suspension: Bottles of bulk GSK2118436B drug substance with bottles of individual excipients (4 components) will be supplied by GSK for on-site extemporaneous compounding of a suspension formulation (for subjects unable to swallow capsules). Only sites meeting local, applicable regulations regarding extemporaneous compounding will be permitted to enroll subjects requiring suspension administration. Detailed preparation instructions are supplied in the SPM. The suspension will be administered with an oral dosing syringe supplied by GSK (oral syringes, 1 mL, 5 mL, and 20 mL for single use).

Revised Text (added to beginning of section):

In France: Children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules cannot be included in the study, pending availability of an oral suspension formulation.

Capsules: Dabrafenib capsules will be supplied by GSK (for subjects able to reliably and consistently swallow capsules).

Suspension: Bottles of bulk GSK2118436B drug substance with bottles of individual excipients (4 components) will be supplied by GSK for on-site extemporaneous compounding of a suspension formulation (for subjects unable to swallow capsules). Only sites meeting local, applicable regulations regarding extemporaneous compounding will be permitted to enroll subjects requiring suspension administration. Detailed preparation instructions are supplied in the SPM. The suspension will be administered with an oral dosing syringe supplied by GSK (oral syringes, 1 mL, 5 mL, and 20 mL for single use).

Change #3, Section 3.7.8, QTc Stopping Criteria; rationale for change: in response to ANSM review of the protocol.

Previous Text:

A subject that meets the criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study [QT duration corrected for heart rate by Bazett's formula (QTcB)].

- QTcB >500 msec or uncorrected QT >600 msec
- If subject has underlying bundle branch block then the QTcB withdrawal criteria depends on the baseline value:

Baseline QTcB value (with underlying bundle branch block)	QTcB withdrawal criteria
<450 ms	>500 ms
450-480 ms	≥530 ms

Withdrawal decisions are to be based on an average QTcB value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (e.g., 5 minutes between each ECG), and then use the averaged QTcB values of the 3 ECGs to determine whether the subject should be discontinued from the study.

Revised Text:

Withholding and Stopping Criteria for QTc Prolongation for Subjects Enrolled in France

QTc-Prolongation[1] Action and Dose Modification

QTc-Prolongation[1]	Action and Dose Modification
QTcB ≥501 msec	Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline
	Restart at current dose level[2]
	If event recurs, permanently discontinue study treatment

1. Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula
1. 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.
2. 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.

Change #4, Section 3.8, Time and Events Schedule (Table 10); rationale for change: add ECHO at Week 4 in response to ANSM review of the protocol.

Previous Table:

Table 10 Part 1 and Part 2 Treatment Phase: Week 4 through End of Study

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 25-56	Weeks 57+	Final Visit
VISIT WINDOW (±days)		±3	±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		Every 8 weeks	Every 12 weeks	X
Urine Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	X	X	X	Every 4 weeks	Every 4 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			Every 12 weeks	Every 12 weeks	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			X			X	Every 12 weeks	Every 12 weeks	X

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 25-56	Weeks 57+	Final Visit
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
Echocardiogram (ECHO)	Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is less than the nstitution'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	X		X	Every 8 weeks	Every 8 weeks	X
Concomitant medications	See Protocol Section 8 for list of prohibited and cautionary medications.	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	X	X	X
Blood Sampling										
Chemistry	Evaluations performed by a local laboratory	X	X	X	X	X	X	Every 8 weeks	Every 8 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	X	Every 8 weeks	Every 8 weeks	X
Clinical Activity [redacted] Assessments										
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 8 weeks	Every 12 weeks (or as per standard of care)	X

STUDY PHASE		TREATMENT WEEK 4+							
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 25-56	Weeks 57+	Final Visit
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
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 8 weeks	Every 12 weeks	X
[redacted]										
Performance status (Karnofsky/Lansky)	See Appendix 3	X	X	X	X		X	Every 8 weeks	Every 12 weeks	X
Study Medication										
Dispense oral study medication and assess compliance	Dispense a 2 to 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	X	Every 2-4 weeks	Every 2-4 weeks	
Post Treatment Follow-up – See Section 9.4										

1. MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram

Revised Table:

Table 10 Part 1 and Part 2 Treatment Phase: Week 4 through End of Study

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 25-56	Weeks 57+	Final Visit
VISIT WINDOW (±days)		±3	±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		Every 8 weeks	Every 12 weeks	X
Urine Pregnancy test	For menstruating females and as required per local applicable regulations	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	X	X	X	Every 4 weeks	Every 4 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			Every 12 weeks	Every 12 weeks	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			X			X	Every 12 weeks	Every 12 weeks	X

STUDY PHASE		TREATMENT WEEK 4+								
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 25-56	Weeks 57+	Final Visit
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
Echocardiogram (ECHO)	Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is less than the nstitution's LLN will be collected for possible central review (**ECHO to be performed by the same operator throughout the study, where possible;** 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	X	X		X	Every 8 weeks	Every 8 weeks	X
Concomitant medications	See Protocol Section 8 for list of prohibited and cautionary medications.	X	X	X	X	X	X	Every 4 weeks	Every 4 weeks	X
Adverse events	Adverse event assessment should be continuous	X	X	X	X	X	X	X	X	X
Blood Sampling										
Chemistry	Evaluations performed by a local laboratory	X	X	X	X	X	X	Every 8 weeks	Every 8 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	X	Every 8 weeks	Every 8 weeks	X
Clinical Activity [redacted] Assessments										
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 8 weeks	Every 12 weeks (or as per standard of care)	X

STUDY PHASE		TREATMENT WEEK 4+							
Visit		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 25-56	Weeks 57+	Final Visit
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
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 8 weeks	Every 12 weeks	X
[redacted]										
Performance status (Karnofsky/Lansky)	See Appendix 3	X	X	X	X		X	Every 8 weeks	Every 12 weeks	X
Study Medication										
Dispense oral study medication and assess compliance	Dispense a 2 to 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.	X	X	X	X	X	X	Every 2-4 weeks	Every 2-4 weeks	
Post Treatment Follow-up – See Section 9.4										

1. MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram

15.6 Appendix 6 French Country Guidelines for additional dermatological monitoring while on therapy and after IP discontinuation

This Section applies to subject 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 non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE and treated according to standard clinical practice.

15.7 Appendix 7: Protocol Amendment Changes

Amendment 07

WHERE THE AMENDMENT APPLIES

Amendment 07 applies to all sites conducting the study

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Section(s)	Change	Rationale
Title page	Title page replaced as per Novartis requirements	Change in study sponsorship from GSK to Novartis
Sponsor Information Page	GSK contact information has been replaced with Novartis details	Change in study sponsorship from GSK to Novartis
Sponsor signatory	Change of sponsor signatory	Change in study sponsorship from GSK to Novartis
Multiple	The term 'GSK medical monitor' has been replaced by Novartis Medical Lead	To align with the change of sponsorship from GSK to Novartis.
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	Make administrative changes	To align with the change of sponsorship from GSK to Novartis.

LIST OF SPECIFIC CHANGES

1. INTRODUCTION

1.1. Background

Previous text:

Complete safety, clinical activity and pharmacokinetic (PK) data for clinical and non-clinical studies conducted with dabrafenib are provided in the Investigator Brochure (IB) [GlaxoSmithKline Document Number 2012N136095_00]. A summary of safety, clinical activity and PK data are also provided below.

Revised text:

Complete safety, clinical activity and pharmacokinetic (PK) data for clinical and non-clinical studies conducted with dabrafenib are provided in the Investigator Brochure (IB) ~~[GlaxoSmithKline Document Number 2012N136095_00]~~. A summary of safety, clinical activity and PK data are also provided below.

1.1.1.1 BRF112680 (FTIH)

Previous text:

In addition, data from a small number of adult subjects with BRAF V600 mutation-positive solid tumors other than melanoma, who were enrolled in an expansion cohort in the FTIH study, suggested that dabrafenib may have beneficial effects in these subjects as well [GlaxoSmithKline Document Number RM2009/00673/00]. There were 7 subjects enrolled with colorectal cancer (CRC), 10 subjects with thyroid cancer, 1 subject with NSCLC and 1 subject with ovarian cancer. A summary of investigator-assessed unconfirmed response for CRC and thyroid cancer are summarized in Table 1 and Table 2, respectively. The NSCLC subject was enrolled in Part 2 (150 mg BID) and reported an unconfirmed partial response (PR) at 6 weeks followed by disease progression at 12 weeks. The ovarian cancer subject was enrolled in Part 1 (100 mg BID) and reported stable disease before progressing at approximately 36 weeks.

Revised text:

In addition, data from a small number of adult subjects with BRAF V600 mutation-positive solid tumors other than melanoma, who were enrolled in an expansion cohort in the FTIH study, suggested that dabrafenib may have beneficial effects in these subjects as well [BRF112680~~GlaxoSmithKline Document Number RM2009/00673/00~~]. There were 7 subjects enrolled with colorectal cancer (CRC), 10 subjects with thyroid cancer, 1 subject with NSCLC and 1 subject with ovarian cancer. A summary of investigator-assessed unconfirmed response for CRC and thyroid cancer are summarized in Table 1 and Table 2, respectively. The NSCLC subject was enrolled in Part 2 (150 mg BID) and reported an unconfirmed partial response (PR) at 6 weeks followed by disease progression at 12 weeks. The ovarian cancer subject was enrolled in Part 1 (100 mg BID) and reported stable disease before progressing at approximately 36 weeks.

5 Hypotheses and Treatment Comparisons

Previous text:

With respect to the primary objectives and endpoints, the primary focus will be on determining the MTD (or recommended dose based on available safety, PK, and response data), the safety profile, and PK/PD relationship of dabfabranib in paediatric subjects with advanced BRAF V600-mutation positive solid tumors. Most analyses will be descriptive or exploratory.

Revised text:

With respect to the primary objectives and endpoints, the primary focus will be on determining the MTD (or recommended dose based on available safety, PK, and response data), the safety profile, and PK/PD relationship of ~~dabfabranib~~ dabrafenib paediatric subjects with advanced BRAF V600-mutation positive solid tumors. Most analyses will be descriptive or exploratory.

5.2.1.2 Part 2 Cohort Expansion

Previous text:

The sample size for Part 2 is s based on feasibility, practicality, and what would be sufficient for the characterization of the safety of dabfabranib and the plasma pharmacokinetics for the populations enrolled. Each of the 4 expansion cohorts will attempt to enrol at least 10 evaluable subjects. Therefore, an estimated 40 subjects will be enrolled into Part 2.

Revised text:

The sample size for Part 2 is ~~s~~ based on feasibility, practicality, and what would be sufficient for the characterization of the safety of ~~dabfabranib~~ dabrafenib and the plasma pharmacokinetics for the populations enrolled. Each of the 4 expansion cohorts will attempt to enrol at least 10 evaluable subjects. Therefore, an estimated 40 subjects will be enrolled into Part 2.

Section 6.2.1. Confirmation of BRAF Mutation Positive Status

Previous text:

Subjects with V600 mutation- positive tumors as determined by local testing conducted in a CLIA-approved facility (or equivalent) may be enrolled on the study. Archived tumor tissue sample will be collected at screening for retrospective confirmation of the BRAF mutation status using the bioMerieux (bMx) BRAF mutation assay (THxID assay) being developed by GSK in collaboration with bMx. If an archived tumor tissue sample is not available, fresh tumor tissue should be collected for the assessment and confirmation of BRAF V600 mutation status in a CLIA approved facility (see SPM for further details on sample collection).

Revised text:

Subjects with V600 mutation- positive tumors as determined by local testing conducted in a CLIA-approved facility (or equivalent) may be enrolled on the study. Archived tumor tissue sample will be collected at screening for retrospective confirmation of the BRAF mutation status ~~using the bioMerieux (bMx) BRAF mutation assay (THxID assay) being developed by GSK in collaboration with bMx~~. If an archived tumor tissue sample is not available, fresh tumor tissue should be collected for the assessment and confirmation of BRAF V600 mutation status in a CLIA approved facility (see SPM for further details on sample collection).

Section 6.4.2. Action to be taken if Pregnancy occurs

Previous text:

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 11.7. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

Revised text:

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to **Novartis**~~GSK~~ within **24 hours** 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to **Novartis**~~GSK~~. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to **Novartis**~~GSK~~ as described in Section 11.7. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

Section 6.4.2. Action to be taken if Pregnancy occurs in a female partnet of a male study subject

Previous text:

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Revised Text:

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to **Novartis within 24**

hours ~~GSK within 2 weeks~~ of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to ~~GSK~~**Novartis**. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Section 6.5.2. Sample Analysis

Previous text:

Plasma analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics, Platform Technology and Sciences, GSK. Concentrations of 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 Archives, GlaxoSmithKline. Once the plasma has been analyzed for 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.

Revised Text:

~~Plasma analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics, Platform Technology and Sciences, GSK. Concentrations of 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 Archives, GlaxoSmithKline. Once the plasma has been analyzed for 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.~~

Until 31 Dec 2015 plasma analysis was performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics, Platform Technology and Sciences, GSK and raw data is stored in the GlaxoSmithKline Archives, until transfer to Novartis archive. Since 1 Jan 2016 plasma analysis is performed under the management of Novartis DMPK, and raw data are stored in the archives of the analytical site until transfer to Novartis archive.

Concentrations of dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) will be determined in plasma samples using validated analytical methods. Once the plasma has been analyzed for dabrafenib and its metabolites (GSK2285403, GSK2298683 and GSK2167542) any remaining plasma may be analyzed qualitatively for other circulating metabolites or quantitatively to perform long term stability evaluation or cross validation and the results reported under a separate DMPK protocol.

Section 13.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Previous text:

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

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

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent/assent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from parent(s), LAR or subject prior to participation in the study.

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

Revised Text:

Prior to initiation of a study site, **Novartis** ~~GSK~~ will obtain ~~favorable opinion/~~approval to conduct the study from the appropriate regulatory agency ~~to conduct the study~~ in accordance with ~~any~~ applicable country-specific regulatory requirements ~~prior to a site initiating the study in that country~~ **including those required under a US IND**.

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

The study will also be conducted in accordance with ~~ICH~~ Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and ~~favorable opinion/~~approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent/assent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from parent(s), LAR or subject prior to participation in the study.

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

Section 13.3. Quality Control (Study Monitoring)

Previous text:

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors 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 GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

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

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

Revised Text:

In accordance with applicable regulations including GCP, and **Novartis**~~GSK~~ procedures, **Novartis personnel (or designated Clinical Research Organization [CRO])** ~~GSK monitors~~ 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**~~GSK~~ requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

Novartis (or designated CRO) personnel will monitor the study to ensure that the: ~~GSK will monitor the study and site activity to verify that the:~~

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

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

Section 13.6. Records Retention

Previous text:

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

Revised Text:

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** ~~GSK~~ audit or **regulatory** inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

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

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.

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

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

Section 13.7. Provision of Study Results to Investigators, Posting to the Clincal Trials Register and Publication

Previous text:

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

GSK will also provide investigators with the full summary of the study results. Investigators are encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 6 months after the last subject's last visit [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

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

Revised Text:

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

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

~~GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 6 months after the last subject's last visit [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK~~

~~Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.~~

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary. **Novartis aims to post a results summary to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) and other publicly available registers no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication .When publication is not feasible, please refer to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) for a summary of the trial results.**

Section 13.8. Data Management

Previous text:

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

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. 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. Subject initials will not be collected or transmitted to GSK according to GSK policy.

Revised Text:

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

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

~~Management of clinical data~~ **Clinical data management** will be performed in accordance with applicable ~~GSK~~ standards and data cleaning procedures **with the objective of resolving errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report**. ~~to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events~~ **All AEs** and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) **and a custom dictionary.**~~and an internal validated medication dictionary, GSKDrug~~. **Laboratory data (i.e., hematology and clinical chemistry) will be stored in a database maintained by the central laboratory and transferred to Novartis at agreed times.**

eCRFs (including queries and audit trails) will be retained by **Novartis** ~~GSK~~, and copies will be sent to the investigator to maintain as the investigator copy. ~~Subject initials will not be collected or transmitted to GSK according to GSK policy.~~

Amendment 06

WHERE THE AMENDMENT APPLIES

Amendment 06 applies to all sites conducting the study.

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Title changed to specify children and adolescents instead of specific years (corrected to align with previous protocol changes).

Administrative change (i.e. addition of information for an abbreviation and an additional 3 abbreviations added).

Background updated to reflect approval for dabrafenib in many jurisdictions.

Study rationale updated to increase lower age to ≥12 months from >1 month (corrected to align with previous protocol changes) and to specify refractory disease.

Summary of risk management updated to remove paragraph on glucose-6-phosphate dehydrogenase.

Clarification of the dose escalation rules for selection of the appropriate dose by age group in the absence of MTD.

Correction of units for exposure criterion.

Update of dose modification guidelines for clarity and in accordance with the most recent information available for dabrafenib. Rash guidelines have not been proven to be effective. Addition of new section on management guidelines for additional AEs, added according to the 02 May 2014 Asset language changes.

Addition of LCH assessments to the time and events schedule, and addition of the LCH scoring system, to establish baseline disease burden.

Addition of follow-up skin assessments to the time and events schedule and safety assessments, including French country specific guidelines, to provide additional safety oversight of the patient.

Clarification of timing for final study visit in the time and events schedule. Inclusion criterion 10 updated to replace references to liver metastases with liver involvement.

Exclusion criterion 7 updated to include major surgery as previous anti-cancer therapy.

Exclusion criterion 17 updated to remove history of known HIV, as risk to patients is minimal and they will not be excluded; reference to HIV patients' ineligibility removed from prohibited medications and non-drug therapies section.

Exclusion criterion 18 (subjects with known G6PD deficiency) removed as further information indicates that this is no longer a risk.

Dermatological examinations clarified for safety monitoring. The time for stable disease to be considered best response reduced to 12 weeks from 16 weeks.

[redacted]

Removal of the restriction on foods that may inhibit cytochrome (CYP) 3A4 activity, as further information indicates that this is no longer a risk, and inclusion of all dietary information for clarity.

Clarification that children that are breastfeeding may continue to breast feed on demand, but that if child is breast fed during collection of PK samples the time of breastfeeding should be recorded.

Addition in section on treatment after the end of the study of reference to Section 6.3 for follow up instructions for subjects who discontinue.

Overdose section updated to provide additional guidance in accordance with the most recent information available for dabrafenib.

SAE definition of protocol-specific SAEs updated for clarity and modified based on additional understanding of the compound.

New appendix added in Section 15.6 (Appendix 6 French Country Guidelines for additional dermatological monitoring while on therapy and after IP discontinuation).

LIST OF SPECIFIC CHANGES

Title

Previous text:

Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Pediatric Subjects Aged 1 Month to <18 Years with Advance BRAF V600-Mutation Positive Solid Tumors.

Revised text:

Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects with Advanced BRAF V600-Mutation Positive Solid Tumors.

Abbreviations corrected and added

eGFR	Calculated Glomerular Filtration Rate
PPE	**Palmar** Plantar erythrodysaethesia **Syndrome**
QTc	QT duration corrected for heart rate
UPC	Urine Protein:Creatinine Ratio

Section 1.1. Background

Previous text:

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 biomarker (phosphorylated extracellular signal-related kinase [pERK]) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutation-positive tumor cell lines, achieved proximal biomarker suppression and tumor regression in BRAF mutant xenograft models, and has demonstrated significant anti-tumor efficacy in BRAF V600-mutation positive tumors, including melanoma, papillary thyroid cancer, and non-small cell lung cancer. Dabrafenib is currently being developed in adult subjects with BRAF V600 mutation-positive advanced or metastatic melanoma, and is being studied in subjects with other BRAF V600 mutation-positive tumor types.

Revised text:

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 biomarker (phosphorylated extracellular signal-related kinase [pERK]) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutation-positive tumor cell lines, achieved proximal biomarker suppression and tumor regression in BRAF mutant xenograft models, and has demonstrated significant anti-tumor efficacy in BRAF V600-mutation positive tumors, including melanoma, papillary thyroid cancer, and non-small cell lung cancer. Dabrafenib is **currently approved in many jurisdictions for** adult subjects with BRAF V600 mutation-positive advanced or metastatic melanoma, and is being studied in subjects with other BRAF V600 mutation-positive tumor types.

Section 1.2. Study Rationale

Previous text:

The proposed study is a Phase I/IIa, open-label study to determine the safety, tolerability, and pharmacokinetics of oral dabrafenib in pediatric subjects aged 1 month to less than 18 years of age with advanced BRAF V600 mutation positive advanced solid tumors. As noted above, dabrafanib has demonstrated promising efficacy in adults with BRAF V600 mutation-positive advanced or metastatic melanoma as well as other tumors types with BRAF V600 mutations. For patients with recurrent gliomas, LCH, melanoma, or PTC, the 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. Recent data identifying BRAF V600 activating mutations in pediatric melanoma, gliomas, LCH, and PTC coupled with the recent

development of specific BRAF inhibitors may allow for the development of a new therapeutic opportunity for children, and is the primary rationale for this study.

Revised text:

The proposed study is a Phase I/IIa, open-label study to determine the safety, tolerability, and pharmacokinetics of oral dabrafenib in pediatric **and adolescent** subjects aged **≥12** months to less than 18 years of age with advanced BRAF V600 mutation positive advanced solid tumors. As noted above, dabrafanib has demonstrated promising efficacy in adults with BRAF V600 mutation-positive advanced or metastatic melanoma as well as other tumors types with BRAF V600 mutations. For patients with **refractory,** recurrent gliomas, LCH, melanoma, or PTC, the 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. Recent data identifying BRAF V600 activating mutations in pediatric melanoma, gliomas, LCH, and PTC coupled with the recent development of specific BRAF inhibitors may allow for the development of a new therapeutic opportunity for children, and is the primary rationale for this study.

Section 1.3. Summary of Risk management

The following paragraph has been deleted:

Glucose-6-phosphate dehydrogenase: Subjects with a history of known glucose-6-phosphate dehydrogenase (G6PD) deficiency are excluded from clinical trials as they may develop nonimmune hemolytic anemia in response to dabrafenib which contains a sulfonamide, a potential risk factor for subjects with this deficiency. No cases of hemolytic anemia have been reported to date in dabrafenib clinical trials.

Section 3.1.1.1. Dose Escalation

Previous text:

The dose in Part 1 will be escalated until the maximum tolerated dose (MTD) is reached (based on toxicity, Section 3.4) **OR** in the absence of reaching the MTD, the dose in which the median AUC(0-τ) is between approximately 4000 ng*h/mL and approximately 5500 ng*h/mL. The proportion of subjects who achieve an AUC(0-12) ≥ 4000 ng*h/mL also will be considered when selecting the dose for Part 2. In the absence of meeting criteria for MTD, if <80% of subjects in an age group (≤2 yrs, >2 and ≤12 yrs, >12 yrs) fail to achieve an AUC(0-12) ≥ approximately 4000 ng*h/mL **OR** if fewer than two subjects in a specific age group have been evaluated at a given dose level, the study sponsor and study team will review all available safety and PK data and determine if further Part 1 evaluation of a specific age group is required before these subjects may enroll in Part 2. Intermediate doses may be explored.

Revised text:

The dose in Part 1 will be escalated until the maximum tolerated dose (MTD) is reached (based on toxicity, Section 3.4) **OR** in the absence of reaching the MTD, the dose in which the median AUC(0-τ) is between approximately 4000 ng*h/mL and approximately 5500 ng*h/mL. The proportion of subjects who achieve an AUC(0-12) ≥ 4000 ng*h/mL also will be considered when selecting the dose for Part 2. In the absence of meeting criteria for

MTD, if **less than** 80% of subjects in an age group (≤2 yrs, >2 and ≤12 yrs, >12 yrs) **achieve** an AUC(0-12) ≥ approximately 4000 ng*h/mL **OR** if fewer than two subjects in a specific age group have been evaluated at a given dose level, the study sponsor and study team will review all available safety and PK data and determine if further Part 1 evaluation of a specific age group is required before these subjects may enroll in Part 2. Intermediate doses may be explored.

Section 3.7.1. Dabrafenib Intra-Subject Dose Escalation

Previous text:

In certain circumstances in Part 1 of this study, a subject's dose level may be increased up to the highest dose level that is open to enrollment. Only subjects who have completed their DLT assessment period (28 days), who have tolerated treatment, but have measured AUC(0-12) less than target level, may be eligible for escalation. Decisions to increase a subject's current dose will be based on all available data, including safety data and PK data for that subject, and must be agreed by the investigator and the GSK medical monitor. Predicted exposure AUC(0-12) at the escalated dose may not exceed 6000 µg*h/mL. Documentation of the dose escalation agreement and predicted exposure must be kept in the study files for the subject.

Revised text:

In certain circumstances in Part 1 of this study, a subject's dose level may be increased up to the highest dose level that is open to enrollment. Only subjects who have completed their DLT assessment period (28 days), who have tolerated treatment, but have measured AUC(0-12) less than target level, may be eligible for escalation. Decisions to increase a subject's current dose will be based on all available data, including safety data and PK data for that subject, and must be agreed by the investigator and the GSK medical monitor. Predicted exposure AUC(0-12) at the escalated dose may not exceed 6000**ng***h/mL. Documentation of the dose escalation agreement and predicted exposure must be kept in the study files for the subject.

Section 3.7.3. General supportive guidelines

The following subsection has been deleted:

3.7.3.1. Skin Toxicity (Rash, Palmar-Plantar Erythrodysesthaesia syndrome)

Rash and Palmar-Plantar Erythrodysesthaesia Syndrome (PPES) are frequently observed in subjects receiving dabrafenib therapy. Guidelines for management are based on experience with other MEK inhibitors and EGFR inhibitors [Balagula, 2010; Lacouture, 2012] and include:

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

Additional measures for PPES should include:

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

Dose modification may also be required (refer toTable 5 - General Dose Modification Guidelines).

Section 3.7.4. Dose Modification for General Toxicities to Section 3.7.9. Liver Chemistry Stopping Criteria

Previous text:

3.7.4. Dose Modification for General Toxicities

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

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

TABLE 5 DOSE MODIFICATION GUIDELINES - GENERAL

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

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

b. Approval from the GSK Medical Monitor is required to restart study treatments after ≥21 days interruption

If the AE does not resolve to at least Grade 1 in ≤7 days, withdrawal from the study is recommended. However, if the investigator and a GSK Medical Monitor agree that the subject has benefited from treatment and further treatment will continue to benefit the subject in a manner that outweighs the risk posed by the AE, then treatment can continue with at least a 25% dose reduction for next cycle of treatment. If well tolerated at the reduced dose and both the investigator and a GSK medical monitor agree with favorable benefit risk for this subject, the previous dose level can be resumed in subsequent cycles. Any dose modification or interruption will be recorded.

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:

- Renal insufficiency – Please refer to Table 6.

TABLE 6 GUIDELINES FOR RENAL INSUFFICIENCY

For subjects with creatinine increase of ≥50% from baseline or eGFR [(a)] decrease of >25% from baseline:	

1st occurrence	• Interrupt dabrafenib
	• If subject has fever: treat pyrexia as per Table 7 (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration
	• Pediatric nephrology consult is recommended
	• Re-check within 24 hours
	  • If <50% increase in creatinine or ≤25% decrease in eGFR from baseline then may restart dabrafenib
	  • If ≥50% increase in creatinine from baseline or eGFR decrease of >25% from baseline
	  - Recommend monitor creatinine at least twice weekly
	  - May restart dabrafenib if creatinine/eGFR returns to baseline with approval of medical monitor.
	  - If creatinine<50% increase from baseline or eGFR returns to ≤25% decrease from baseline may restart dabrafenib at a reduced dose with approval of the medical monitor

2nd occurrence	• Follow above recommendations. • If restart of dabrafenib is approved by medical monitor ○ Upon restart reduce dabrafenib by one dose level
3rd occurrence	▪ Permanently discontinue dabrafenib

For subjects with creatinine increase of ≥100% from baseline or eGFR [(a)] decrease of >50% from baseline	

	• Interrupt dabrafenib
	• If subject has fever: treat pyrexia as per Table 7 (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration
	• Pediatric nephrology consultation recommended
	• Re-check within 24 hours
	  ○ If creatinine increase of ≥100% or eGFR decrease of >50% is confirmed, permanently discontinue dabrafenib
	  ○ If creatinine increase ≥50% or eGFR decrease >25% from baseline and ≤50% from baseline, continue to hold dabrafenib and follow guidelines above
	  ○ If creatinine increase <50% or eGFR is ≤25% decrease from baseline may restart dabrafenib

1. (a). eGFR calculated according to Schwartz formula (http://www.medcalc.com/pedigfr.html)

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

3.7.5. Dose Modification Guidelines - Adverse Events of Special Interest

3.7.5.1. Pyrexia

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

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, renal function should be monitored carefully (see Section 3.7.4).

Pyrexia accompanied by hypotension, dehydration requiring IV fluids, or severe (≥Grade 3) rigors/chills (in the absence of an obvious infectious cause) should be reported as an SAE (Section 11.7).

Guidelines regarding management and dose reduction for pyrexia considered to be related to dabrafenib are provided in Table 7. Pyrexia is defined as a body temperature equal to or above 38.5° Celsius or 101.3° Fahrenheit.

TABLE 7 MANAGEMENT AND DOSE MODIFICATION GUIDELINES FOR PYREXIA[a,b]

Occurrence	Action and Dose Modification
Any	• Consider clinical evaluation for infection and hypersensitivity if clinically warranted • Laboratory (local lab) work-up: CBC with differential, chemistry with creatinine, UA with microscopic • Hydration as required [c]
1st Event[b]:	• Administer anti-pyretic treatment if clinically indicated [d] • **Interrupt dabrafenib** • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level • If fever was associated with dehydration, hypotension, or renal insufficiency, reduce dabrafenib by one dose level
2nd Event [e]	• Same as for 1st event, and • Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated [e]
Subsequent Events:	• **Interrupt dabrafenib** • Once pyrexia resolves to baseline, **restart dabrafenib (consider dose reduction by one level)** [f] Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[g]

Occurrence	Action and Dose Modification
	• If corticosteroids have been tapered and pyrexia recurs, restart steroids • If corticosteroids cannot be tapered or escalating doses are required, consult medical monitor

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 when restarting after an interruption.

c. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.

d. 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

e. 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.

f. Dabrafenib should be reduced by one dose level at discretion of the investigator if pyrexia is accompanied by severe recurring rigors which cannot be managed by best supportive care, including increasing doses of oral steroids. Re-escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

3.7.5.2. Cutaneous squamous cell carcinoma (cuSCC) and keratoacanthoma (KA)

Both cuSCC and KA have been observed in subjects treated with dabrafenib [GlaxoSmithKline Document Number 2012N136095_00]. Dermatologic exams should be performed by the Investigator per Table 8 and Table 10, although referral to a Dermatologist is preferred to have evaluation at baseline, day 8, day 15, followed by week 8, 16, and every 12 weeks thereafter. If possible, the same Physician should perform each exam for the duration of the study (i.e. if the subject is referred to a Dermatologist for the screening exam, the Dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations. These 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 (refer to Section 11.7). [redacted] An additional examination should be considered 2 months after discontinuation of dabrafenib.

3.7.6. Liver Chemistry Stopping Criteria

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

Liver chemistry stopping criteria 1-5 are defined as:

1. Alanine aminotransferase (ALT) ≥3 times the upper limit of normal (xULN) and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and International Normalized Ratio (INR) >1.5, if INR measured)

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

2. ALT ≥8xULN
3. ALT ≥5xULN but <8 xULN persists for ≥2 weeks
4. ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
5. ALT ≥5xULN but <8 xULN and cannot be monitored weekly for >2 weeks.

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

- **Immediately** discontinue subject from study treatment.
- Report the event to GSK **within 24 hours** of learning its occurrence.
- Complete the liver event electronic case report form (eCRF) and SAE data collection tool if the event also meets the criteria for an SAE.
- All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
- NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow up assessments (Section 12), and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required or GSK Medical Governance approval of drug restart is granted, as described in Section 12.2).
    - For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment
- Do not restart investigational product unless written approval is granted by GSK Medical Governance (details for restarting investigational product are described in Section 12.2), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 12.2).

- Subjects meeting criterion 5 should be monitored as frequently as possible.

In addition, for subjects meeting criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 12), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries [ALT, aspartate aminotransferase (AST), alkaline phosphatase, bilirubin] resolve, stabilize or return to within baseline values.

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

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hours** for repeat liver chemistries and liver event follow up assessments (refer to Section 12).
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
    - Subjects meeting criterion 5 should be monitored as frequently as possible.

3.7.7. QTc Stopping Criteria

A subject that meets the criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study [QT duration corrected for heart rate by Bazett's formula (QTcB)].

- QTcB >500 msec or uncorrected QT >600 msec
- If subject has underlying bundle branch block then the QTcB withdrawal criteria depends on the baseline value:

Baseline QTcB value (with underlying bundle branch block)	QTcB withdrawal criteria
<450 ms	>500 ms
450-480 ms	≥530 ms

Withdrawal decisions are to be based on an average QTcB value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (e.g., 5 minutes between each ECG), and then use the averaged QTcB values of the 3 ECGs to determine whether the subject should be discontinued from the study.

Subjects recruited in France, please refer to Appendix 5 for French specific QTc stopping criteria Appendix 6.

3.7.8. Left Ventricular Ejection Fraction Stopping Criteria

ECHO must be performed at baseline and at follow-up visit(s) per the schedule in the Time and Events Table. Subjects who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline **and** the ejection fraction is below the institution's LLN should temporarily discontinue dabrafenib and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until LVEF recovery to above institutional lower limit of normal and within 10% of baseline.

- If the LVEF recovers (defined as ≥ LLN **and** absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, **after consultation and approval of the Medical Monitor**, the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, monitoring of LVEF will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (LVEF to above institutional LLN and symptom resolution) within 4 weeks, the subject may restart dabrafenib at a reduced dose in consultation with the Medical Monitor (if in the opinion of the investigator, the subject was receiving or likely to receive clinical benefit with continued treatment).

All events of LVEF meeting the stopping criteria should be reported as SAEs (refer to Section 11.7).

Copies of all ECHO(s) will be required for possible central review. Copies of all cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is below the institution's LLN will also be required for possible central review. Details for central collection of ECHOs will be provided in the SPM.

3.7.9. Valvular Toxicity Stopping Criteria

Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTC AE v4.0) should temporarily discontinue Dabrafanib and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks, **after consultation and approval of the Medical Monitor,** the subject may be restarted on Dabrafanib at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue Dabrafanib. 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 dabrafanib.

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 Dabrafanib at a reduced dose **after consultation and approval of the Medical Monitor**.

Copies of all ECHO(s) will be required for possible central review. Details for central collection of ECHOs will be provided in the SPM. Copies of all cardiology consultations performed on subjects who experience a valvular toxicity will also be required by GSK for review.

Revised text:

3.7.4. Dose Modification for General Toxicities

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

Investigators should always err on the side of caution in these settings if treatment-related toxicity is a possibility. Note that guidelines for management of hepatobiliary adverse events are provided separately in Section 3.7.9.

TABLE 5 DOSE MODIFICATION GUIDELINES - GENERAL

CTCAE Grade	Action and Dose Modification[a,b]
Grade 1 or Grade 2 (tolerable)	Continue study treatments at same dose level (no dose modification) and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	
1st, 2nd, or 3rd occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at next lower dose level
4th or greater occurrence	Discontinue treatment.
Grade 4	
1st occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level or discontinue at discretion of investigator
All other occurrences	Discontinue treatments

a. Treatments should be discontinued if more than 3 dose reductions are required.

b. Approval from the GSK Medical Monitor is required to restart study treatments after ≥21 days interruption

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered.

3.7.5. Dose Modification Guidelines - Adverse Events of Special Interest

3.7.5.1. 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 (see Section 3.7.4).

Guidelines regarding management and dose reduction for pyrexia considered to be related to dabrafenib are provided in Table 6

TABLE 6 MANAGEMENT AND DOSE MODIFICATION GUIDELINES FOR PYREXIA

Occurrence [a,b]	Action and Dose Modification
Any	• Clinical evaluation for infection and hypersensitivity[c] • Laboratory (local lab) work-up[c] • Hydration as required[d]
1st Event[b]:	• Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration, or hypotension[e] • **Interrupt dabrafenib** • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level • **If fever was associated with dehydration, hypotension, or renal insufficiency, reduce dabrafenib by one dose level[g]**

2nd Event [e]	• Same as for 1st event, and
	• Within 3 days of onset of pyrexia
	  • Optimize anti-pyretic therapy
	  • Consider oral corticosteroids for at least 5 days or as clinically indicated[f]

Subsequent Events:	• **Interrupt dabrafenib** • Once pyrexia resolves to baseline, **restart dabrafenib reduced by one dose level[g]** • Within 3 days of onset of pyrexia

	• Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f] • If corticosteroids have been tapered and pyrexia recurs, restart steroids • If corticosteroids cannot be tapered or escalating doses are required, consult medical monitor

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.

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 after 3 episodes of pyrexia complicated by rigors, severe chills etc, 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.

3.7.5.2. 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 7.

TABLE 7 RENAL INSUFFICIENCY GUIDELINES

For subjects with creatinine rise ≥50% from baseline :	

1 st occurrence	• If subject has fever: treat pyrexia as per Table 6 (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration
	• Pediatric nephrology consult is recommended
	• **Re-check within 24 hours**
	  • If creatinine rise is < 25% from baseline:
	  • Continue dabrafenib at current dose
	  • Monitor creatinine weekly for 4 weeks to ensure levels remain within 25% of baseline

For subjects with creatinine rise ≥50% from baseline :	
	• Discuss with medical monitor if dose interruption should be considered in the setting of significant concurrent illness • If creatinine rise is ≥ 25% but < 50% from baseline: • Continue dabrafenib at current dose • Monitor creatinine at least twice weekly, can decrease frequency if creatinine rise < 25% from baseline • Avoid nephrotoxic agents • Discuss with medical monitor if dose interruption should be considered in the setting of significant concurrent illness • If creatinine rise is ≥ 50% but < 100% from baseline: • Interrupt dabrafenib • Monitor creatinine at least twice weekly • Avoid nephrotoxic agents • May restart dabrafenib at reduced dose if creatinine rise returns to < 25% from baseline, or with approval of medical monitor[a] • If creatinine rise is ≥ 100% from baseline: • Permanently discontinue dabrafenib unless further therapy is approved by medical monitor[a]
2nd occurrence	• Permanently discontinue dabrafenib unless further therapy is approved by medical monitor[a]

[a] Case should be discussed with medical monitor and written final decision on further dosing should be based on individualized benefit/risk and assessment of alternate explanations of renal insufficiency.

3.7.5.3. Malignancies

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 (refer to Section 11.7). [redacted]

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. [redacted]

Refer to Appendix 6 for French country specific dermatological follow up.

3.7.5.4. Guidelines for prolonged QTc

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

TABLE 8 WITHHOLDING AND STOPPING CRITERIA FOR QTC-PROLONGATION

QTc Prolongation	Action and Dose Modifications
• QTcB ≥501 msec	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If event resolves restart 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.** Consider evaluation with cardiologist.

Abbreviations: ECG = electrocardiogram; msec = milliseconds; QTcB = QT duration corrected for heart rate by 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.

a. 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.

3.7.6. Management Guidelines for Additional AEs

- **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.
- **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.

3.7.7. Left Ventricular Ejection Fraction Stopping Criteria

ECHO must be performed at baseline and at follow-up visit(s) per the schedule in the Time and Events Table. Subjects who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline **and** the ejection fraction is below the institution's LLN should temporarily discontinue dabrafenib and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until LVEF recovery to above institutional lower limit of normal and within 10% of baseline.

- If the LVEF recovers (defined as ≥ LLN **and** absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks**, after consultation and approval of the Medical Monitor,** the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, monitoring of LVEF will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (LVEF to above institutional LLN and symptom resolution) within 4 weeks, the subject may restart dabrafenib at a reduced dose in consultation with the Medical Monitor (if in the opinion of the investigator, the subject was receiving or likely to receive clinical benefit with continued treatment).

All events of LVEF meeting the stopping criteria should be reported as SAEs (refer to Section 11.7).

Copies of all ECHO(s) will be required for possible central review. Copies of all cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is below the institution's LLN will also be required for possible central review. Details for central collection of ECHOs will be provided in the SPM.

3.7.8. Valvular Toxicity Stopping Criteria

Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTC AE v4.0) should temporarily discontinue Dabrafanib and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks, **after consultation and approval of the Medical Monitor,** the subject may be restarted on Dabrafanib at a reduced dose(s). For such subjects, monitoring of the valve via

ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue Dabrafanib. 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 dabrafanib. 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 Dabrafanib at a reduced dose **after consultation and approval of the Medical Monitor**.

Copies of all ECHO(s) will be required for possible central review. Details for central collection of ECHOs will be provided in the SPM. Copies of all cardiology consultations performed on subjects who experience a valvular toxicity will also be required by GSK for review.

3.7.9. Liver Chemistry Stopping Criteria

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

Liver chemistry stopping criteria 1-5 are defined as:

1. Alanine aminotransferase (ALT) ≥3 times the upper limit of normal (xULN) and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and International Normalized Ratio (INR) >1.5, if INR measured)

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

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

- **Immediately** discontinue subject from study treatment.
- Report the event to GSK **within 24 hours** of learning its occurrence.
- Complete the liver event electronic case report form (eCRF) and SAE data collection tool if the event also meets the criteria for an SAE.

- All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
- NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow up assessments (Section 12), and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required or GSK Medical Governance approval of drug restart is granted, as described in Section 12.2).
    - For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment
- Do not restart investigational product unless written approval is granted by GSK Medical Governance (details for restarting investigational product are described in Section 12.2), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 12.2).
- Subjects meeting criterion 5 should be monitored as frequently as possible.

In addition, for subjects meeting criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 12), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries [ALT, aspartate aminotransferase (AST), alkaline phosphatase, bilirubin] resolve, stabilize or return to within baseline values.

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

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hours** for repeat liver chemistries and liver event follow up assessments (refer to Section 12).
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;

Subjects meeting criterion 5 should be monitored as frequently as possible.

Section 3.8 Time and Events Schedule

Table 9 Part 1 and Part 2 Treatment Phase: Screening through Day 21 (See also PK sampling table for PK sampling schedule on Day 1 and Day 15):

The following row, under "Clinical Activity Assessments [redacted]", has been deleted:

STUDY PHASE	SCREEN	TREATMENT DAYS 1 through 21			
VISIT	Screen	Pre-dose Day 1	Pre-dose Day 8	Pre-dose Day 15	Pre-dose Day 22
VISIT WINDOW (±days	-21	N/A	±2	±2	±2
[redacted]					

Table 11 Part 1 and Part 2 Treatment Phase: Week 4 (Day 29) through End of Study:

The following row, under "Clinical Activity [redacted] Assessments", has been amended:

Response	**Target/non-target lesions:** 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. **LCH assessment:** required at week 12 (3 months) and week 26 (6 months).		X	X LCH	X		X	Every 8 weeks LCH at Week 26	Every 12 weeks	X

The following row under, "Post Treatment Follow-up – See Section 9.4" has been added:

Dermatologic skin monitoring after IP discontinuation	Follow up dermatologic skin assessments should be performed every 2 to 3 months for 6 months following discontinuation of dabrabenib or until initiation of another anti-neoplastic therapy. (see Appendix 6 for French guidelines)

The following footnote has been added:

2. Final study visit within 28 days after last dose of study drug.

Section 4.2.1. Inclusion Criteria

Previous text:

10. Adequate liver function defined as:
    - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
    - AST and ALT ≤2.5 x ULN; AST/ALT may be <5 x ULN at baseline if liver metastases are present (requires radiographic confirmation of liver metastases)

Revised text:

10. Adequate liver function defined as:
    - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
    - AST and ALT ≤2.5 x ULN; AST/ALT may be <5 x ULN at baseline **if disease under treatment involves the** liver (requires radiographic confirmation of liver **involvement**)

Section 4.2.2. Exclusion Criteria

Previous text:

7. Unresolved toxicity greater than NCI CTCAE v4.0 [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy except those that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profile of dabrafenib (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy);

Revised text:

7. Unresolved toxicity greater than NCI CTCAE v4.0 [NCI, 2009] Grade 2 or higher from previous anti-cancer therapy, **including major surgery,** except those that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profile of dabrafenib (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy);

Previous text:

17. A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus, or Hepatitis C Virus infection (subjects with laboratory evidence of Hepatitis B Virus clearance may be enrolled);
18. Subjects with known G6PD deficiency;

Revised text:

17. Hepatitis B Virus, or Hepatitis C Virus infection (subjects with laboratory evidence of Hepatitis B Virus clearance may be enrolled);
18. Note: this criterion was deleted in Protocol Amendment 6;

Section 6.3 Safety and Tolerability

New bullet point added under the subheading “Dermatological Examination/Skin Biopsy/Photography”:

Revised text:

- Dermatological examinations should be performed every 2 months during treatment, and every 2-3 months 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.

New subheading added:

Revised text:

Non-cutaneous secondary/recurrent malignancy

- During treatment subjects should be monitored as clinically appropriate. Complete blood cell counts should be performed as clinically indicated. Following discontinuation of dabrafenib monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy, whichever comes first. Any non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE and treated according to standard clinical practice.
- See Appendix 6 for French country specific guidelines.

Section 6.6. Anti-tumor Assessment

Previous text:

Confirmation of CR and partial response (PR) are required per protocol. Complete response/PR confirmation assessments may take place at Week 16 (but not earlier than week 12) if initial response was seen at the Week 8 assessments. Initial responses (CR/PR) that occur at Week 16 (or after) should be confirmed not less than 4 and not more than 8 weeks after the initial response. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments). If the criteria for a CR or PR are not confirmed, then stable disease can be considered the best response if it has been demonstrated for a minimum of 16 weeks.

Revised text:

Confirmation of CR and partial response (PR) are required per protocol. Complete response/PR confirmation assessments may take place at Week 16 (but not earlier than week 12) if initial response was seen at the Week 8 assessments. Initial responses (CR/PR) that occur at Week 16 (or after) should be confirmed not less than 4 and not more than 8 weeks after the initial response. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments). If the criteria for a CR or PR are not confirmed, then stable disease can be considered the best response if it has been demonstrated for a minimum of **12** weeks.

[redacted]

[redacted]

Section 7.2 Meals and Dietary Restrictions

Previous text:

7.2. Meals and Dietary Restrictions

Subjects shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges (orange marmalade) or pommelos within 7 days prior to the first dose of dabrafenib until the end of the study, as these have been shown to inhibit cytochrome (CYP) 3A4 activity.

Revised text:

7.2. Meals and Dietary Restrictions

Subjects **no longer need to** abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges (orange marmalade) or pommelos within 7 days prior to the first dose of dabrafenib until the end of the study.

Dabrafenib should be administered under fasting conditions, either approximately 1 hour before or approximately 2 hours after a meal. If it is not possible for a subject to tolerate the fasting conditions noted above, dabrafenib can be administered with a small non-fat meal (e.g., small amount of apple juice/sauce, a piece of dry toast). Subjects and their parents should be advised to avoid administering dabrafenib with milk or high-fat, high-calorie foods. 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.

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.

Section 8.2. Prohibited Medications and Non-Drug Therapies

Previous text:

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known HIV are ineligible for study participation);

Revised text:

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs;

Section 9.4. Treatment after the End of the Study

Previous text:

After study participation in the current study and for subjects still benefitting from treatment with dabrafenib, subjects will be given the option to transition to the rollover study (BRF114144), where subjects continue receiving GSK2118436 alone as specified in rollover study BRF114144, provided subjects are still benefiting from GSK2118436.

Subjects who are no longer receiving dabrafenib will be offered Follow-Up from GSK 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.

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

Revised text:

After study participation in the current study and for subjects still benefitting from treatment with dabrafenib, subjects will be given the option to transition to the rollover study (BRF114144), where subjects continue receiving GSK2118436 alone as specified in rollover study BRF114144, provided subjects are still benefiting from GSK2118436.

Subjects who are no longer receiving dabrafenib will be offered Follow-Up from GSK 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 2 to 3 months according to the instructions in Section 6.3.

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

Section 10.5. Treatment of Study Treatment Overdose

Previous text:

In the event of a dabrafenib overdose, defined as administration of more than the highest dose tested in pediatric clinical studies without reaching a manageable specific toxicity, the investigator should contact a GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

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

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

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

Revised text:

In the event of a dabrafenib overdose, defined as administration of more than the highest dose tested in pediatric clinical studies without reaching a manageable specific toxicity, the investigator should contact a GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Haemodialysis is not expected to enhance the elimination of dabrafenib as it is highly bound to plasma proteins.

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

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

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

Section 11.2. Definition of Serious Adverse Events

Previous text:

h. Protocol-specific SAEs: SCC, LVEF meeting stopping criteria; treatment emergent malignancies [basal cell carcinoma (BCC) is not required to be reported as a protocol-specific SAE and it should be reported as an AE or SAE based on the discretion of the investigator.); and pyrexia accompanied by hypotension, dehydration requiring IV fluids, renal insufficency and/or severe (≥Grade 3) rigors/chills in the absence of an obvious infectious cause.

Revised text:

h. Protocol-specific SAEs: LVEF meeting stopping criteria; **any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and new primary melanoma);** basal cell carcinoma (BCC) is required to be reported as a protocol-specific SAE **for all non-melanoma indications**.

Section 15.2. Appendix 2: Response Criteria

New table added:

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
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

Variable	Modality	Score
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

Section 15.6

New appendix added:

15.6. Appendix 6 French Country Guidelines for additional dermatological monitoring while on therapy and after IP discontinuation

This Section applies to subject 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 non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE and treated according to standard clinical practice.

Amendment 05

WHERE THE AMENDMENT APPLIES

Amendment 05 applies to all sites conducting the study

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Administrative change (i.e. additional abbreviation added) Clarification of the dose escalation rules to allow selection of the appropriate dose by age group in the absence of MTD. To permit intra-subject dose escalation during Part 1; intra-subject dose escalation determined on case by case basis after evaluation of PK and safety; subjects who are allowed to dose escalate will be required to have additional PK samples collected 15 days after starting the higher dose level; incorporated instructions for due diligence in contacting subjects who may be lost to follow up. Clarification of the DLT evaluable population and PK population. T&E table updated to clarify that ECHOs will be collected for all subjects.Correction made to Appendix 1.

LIST OF SPECIFIC CHANGES

Abbreviation added

eCRF	Electronic Case Report Form

Section3.1.1.1 Table 3 Dabrafenib Dose Levels

Previous Text

Dose Level	Total Daily Dose (mg/kg) [c]
-2 Dose Level	1.5 mg/kg
-1 Dose Level	2.25 mg/kg
Starting Dose Level [b]	3 mg/kg
+1 Dose Level	3.75 mg/kg
+2 Dose Level	4.5 mg/kg

Revised Text

Dose Level	Total Daily Dose (mg/kg) [c]
-2 Dose Level	1.5 mg/kg
-1 Dose Level	2.25 mg/kg
Starting Dose Level [b]	3 mg/kg
+1 Dose Level	3.75 mg/kg
+2 Dose Level	4.5 mg/kg
+3 Dose Level	5.25 mg/kg
+4 Dose Level	6.0 mg/kg

Section 3.1.1.1 Dose Escalation

Previous Text:

The dose in Part 1 will be escalated until the maximum tolerated dose (MTD) is reached (based on toxicity, Section 3.4) **OR** in the absence of reaching the MTD, the dose in which

the median AUC(0-τ) is between approximately 4000 ng*h/mL and approximately 5500 ng*h/mL, whichever occurs first.

Revised Text:

The dose in Part 1 will be escalated until the maximum tolerated dose (MTD) is reached (based on toxicity, Section 3.4) **OR** in the absence of reaching the MTD, the dose in which the median AUC(0-τ) is between approximately 4000 ng*h/mL and approximately 5500 ng*h/mL. The proportion of subjects who achieve an AUC(0-12) ≥ 4000 ng*h/mL also will be considered when selecting the dose for Part 2. In the absence of meeting criteria for MTD, if <80% of subjects in an age group (≤2 yrs, >2 and ≤12 yrs, >12 yrs) fail to achieve an AUC(0-12) ≥ approximately 4000 ng*h/mL **OR** if fewer than two subjects in a specific age group have been evaluated at a given dose level, the study sponsor and study team will review all available safety and PK data and determine if further Part 1 evaluation of a specific age group is required before these subjects may enroll in Part 2. Intermediate doses may be explored.

Section 3.1.2. Part 2 Tumor-Specific Expansion

Previous Text

The study ~~will aim~~ to enrol at least 5 children in each cohort who are <6 years of age.

Revised Text

The study will enrol at least 5 children in each cohort who are <6 years of age.

Section 3.7.1 Dabrafenib Intra-Subject Dose Escalation

Previous Text

In certain circumstances, a subject's dose level may be increased up to the highest dose level that has previously been confirmed by the investigator and GSK Medical Monitor as not exceeding the MTD.

In Part 1, intra-subject dose escalations will not be allowed until Part 2 is open for enrolment and a recommended Part 2 dose has been selected. For any subject who enrolled during Part 1 and remains on study when Part 2 is opened, each subject may be considered for dose escalation on a case by case basis.Intra-subject dose escalation will not occur in Part 2.

Intra-subject dose escalation will not occur in Part 2

Revised Text

In certain circumstances in Part 1 of this study, a subject's dose level may be increased up to the highest dose level that is open to enrollment. Only subjects who have completed their DLT assessment period (28 days), who have tolerated treatment, but have measured AUC (0-12) less than target level, may be eligible for escalation. Decisions to increase asubject's current dose will be based on all available data, including safety data and PK data for that subject, and must be agreed by the investigator and the GSK medical monitor. Predicted exposure AUC (0-12) at the escalated dose may not exceed 6000 □g*h/mL. Documentation

of the dose escalation agreement and predicted exposure must be kept in the study files for the subject.

Dose escalation is only allowed in subjects who are willing to consent to additional PK sampling at the escalated dose level. Additional PK samples will be collected on Day 15 following administration of the escalated dose

Intra-subject dose escalation will not occur in Part 2

Subjects will be summarized based on the treatment level to which they were originally assigned.

Section 3.7.4 Dose Modifications Guidelines – General Table 5

Previous Text

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

Dose Modification Guidelines – General

Revised Text

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

Section 3.7.5.2 Cutaneous squamous cell carcinoma (cuSCC) and keratoacanthoma (KA)

The following recommendation was included in the guidelines regarding general toxicities management.

An additional examination should be considered 2 months after discontinuation of dabrafenib.

Section 3.8 Time and Events Schedule

Table 8 Part 1 and Part 2 Treatment Phase: Screening through Day 21 (See also PK sampling table for PK sampling schedule on Day 1 and Day 15)

Additional wording added to clarify that all copies of ECHOS will be collected.

Copies **of all ECHOs will be collected for possible central review.** 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).

Table 9 PK Sampling Table for Day 1 and Day 15 (Part 1 and Part 2)

Footnote added: [1]Subjects who are approved for intra-subject dose escalation must provide PK samples on day 15 at the higher dose level.

Section 4.4 Withdrawal from Study and Missing Visits

New section added:

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 appropriately be 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.

Section 5.3 Data Analysis Considerations

Additional wording: Subjects will be summarized based on the treatment level to which they were originally assigned. Additionally, selected analyses and summaries will be provided by age group as appropriate.

Section 5.3.1 Analysis Populations

Previous Text:

The '**DLT Evaluable**' population is defined as those subjects 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 drug doses, exclusive of missed doses due to treatment-related toxicity. For those subjects who are either withdrawn or dose reduced due to toxicity during the first 28 days will be included in the DLT evaluable population.

The '**PK Population**' is defined as those subjects who contribute PK samples.

Revised Text

The '**DLT Evaluable**' population is defined as those subjects 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 drug 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 3.3, will also be included in the DLT evaluable population regardless of exposure.

The '**PK Population**' is defined as those subjects *fulfilling the All Treated population criteria who* who contribute PK samples.

Section 5.3.3.1 Safety and Tolerability Analyses

Additional text: Additionally, selected analyses and summaries will be provided by age group as appropriate.

Section 15.1 Appendix 1: Modified Rolling Six Design Dose Escalation Procedures

Previous table

Number of Subjects Enrolled	Number of Subjects with a DLT	Number of Subjects with Data Pending	Decision
1	--	--	Same dose level
2	2	--	De-escalate
	Other	--	Same dose level
3	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
4	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
5	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
6	≥2	--	De-escalate
	≤1	1	Suspend[1]
	≤1	0	Escalate[1]
	0	--	Escalate
	Other	--	Suspend

1. Modified from the Zhao, 2011 publication

Revised Table

Dose Escalation Procedure

Number of Subjects Enrolled	Number of Subjects with a DLT	Number of Subjects with Data Pending	Decision
1	--	--	Same dose level
2	2	--	De-escalate
	Other	--	Same dose level
3	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
4	≥2	--	De-escalate

Number of Subjects Enrolled	Number of Subjects with a DLT	Number of Subjects with Data Pending	Decision
	0	0	Escalate
	Other	--	Same dose level
5	≥2	--	De-escalate
	0	0	Escalate
	Other	--	Same dose level
6	≥2	--	De-escalate
	≤1	0	Escalate[a]
	0	1	Escalate[a]
	Other	--	Suspend

b. Modified from the Zhao, 2011 publication

Amendment 04

WHERE THE AMENDMENT APPLIES

Amendment 04 applies to all sites conducting the study.

Section 3.1.1.1 Dose Escalation

Previous text

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Amendment 04 expanded eligibility to include subjects with refractory disease. An allowance for BID dosing on Day 1 was added. Clarifications were made to glioma scan requirements and BRAF mutation testing timing. Pyrexia management guidelines and the section on prohibited and cautionary medications were updated.

LIST OF SPECIFIC CHANGES

Sponsor Information Page (page 4)

The [redacted] monitor was changed from [redacted], MD to [redacted], MD, PhD.

Section 3.1.1, Part 1 – Dose Escalation

The following changes were made to the 3rd from last paragraph:

On Day 1, ~~a single first dose will be administered, followed by the collection of~~ serial blood samples for PK analysis will be collected in subjects ≥10 kg in weight **after the first dose of dabrafenib. A second dose may be administered on Day 1 if the timing is in compliance with Section 3.6.**

Section 3.1.2, Part 2 – Tumor-Specific Expansion

The following changes were made to the 2nd paragraph:

On Day 1, ~~a single first dose will be administered, followed by the collection of~~ serial blood samples for PK analysis will be collected in subjects ≥10 kg in weight **after the first dose of dabrafenib. A second dose may be administered on Day 1 if the timing is in compliance with Section 3.6.**

Section 3.7.5.1, Pyrexia

Updated recommendations for any occurrence and aligned footnotes:

- **Consider** clinical evaluation for infection and hypersensitivity **if clinically warranted**
- Laboratory **(local lab) work-up: CBC with differential, chemistry with creatinine, UA with microscopic**
- Hydration as required[d]
- ~~Blood sample for cytokine analysis[e]~~

Section 3.8, Time and Events Schedule

Added the following clarification to comment on tumor tissue for V600 testing:

Local testing for inclusion in the study; can be from archival tissue or if no archival tissue is available, from fresh biopsy; **the local BRAF test result will be subject to retrospective central confirmation. BRAF testing may be completed prior to the 21 day screening period. Availability of tissue suitable for central testing must be documented prior to first dose**.

Added the following clarification to comment on brain MRI:

If an MRI of the brain was obtained within 35 days of the first dose, this can be used as screening MRI. CT with contrast allowed only if brain MRI is contraindicated). **Glioma patients are not required to have CT of chest, abdomen and pelvis unless clinically indicated.**

Added the following clarification to comment on study medication:

Dispense a 2 to 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations. **Two doses may be administered the first day if the time between doses is in compliance with protocol section 3.6.**

Section 4.2.1, Inclusion Criteria

Added refractory disease to inclusion criterion #3:

Recurrent disease, **refractory disease**, or progressive disease after having received at least one standard therapy for their disease

Section 8.1, Permitted Medications and Non-drug Therapies

Added to end of section:

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**.

Section 8.2, Prohibited Medications and Non-drug Therapies

Inserted new data to last bullet:

GSK2118436 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...

Inserted anti-retroviral agents **Ritonavir, Saquinavir, Atazanavir** to Table 12.

Section 8.3, Medications to be Used with Caution

Clarifications to second bullet:

Dabrafenib has been shown to induce CYP3A4 **and CYP2C9** in vivo using midazolam (**CYP3A4 substrate)** and S-warfarin (**CYP2C9** substrate). GSK2118436 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...

New information to third bullet:

Therapeutic level dosing of warfarin can be used with approval by the GSK Medical Monitor and close monitoring of PT/INR by the site. **Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib-mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued, 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

New fourth bullet:

Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in 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.

Updated Table 13:

CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 **or Transporter** Substrates that May be Affected by Induction

Rosuvastatin, pravastatin added to HMG-CoA reductase inhibitors

Digoxin to miscellaneous inhibitors

New section of table on **pH altering agents: dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine**

Amendment 03

WHERE THE AMENDMENT APPLIES

Amendment 03 applies to all sites conducting the study.

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

To take into account potential renal effects, Amendment 03 changed the lower age limit of inclusion criterion #2 from subjects 1 month old to ≥12 months old, adjusted criteria for adequate renal function in inclusion criterion #7, added guidelines for renal insufficiency and additional laboratory testing. Information on the new suspension formulation was incorporated. The section on dose modification was re-organized for consistency. The Time and Events Table was adjusted to include assessments on Day 21, Week 4 was clarified to be Day 29, and increased chemistry and urinalysis evaluations were added. The timing and volume of PK samples for subjects <25 kg and ≥10 kg was corrected.

LIST OF SPECIFIC CHANGES

Sponsor Information Page (page 4):

The [redacted] medical monitor was changed from [redacted], MD to [redacted], MD.

The IND No. was changed from 105, 032 to 117,898.

Section 1.2.2, Dose Rationale

Units corrected from µg*h/mL to ng*h/mL.

Section 1.3, Summary of Risk Management

Added the following paragraph to the section on acute renal failure:

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.

Section 3.1.1, Part 1 – Dose Escalation

Revised text:

Beyond the sixth subject in an ongoing cohort, additional subjects wanting to be enrolled before the next cohort is open for enrollment, can be enrolled at the previous lower dose level ~~(this is~~

~~to ensure that any subject eligible for enrolment is given a place in the study but is **not de-escalation**).~~

Section 3.1.1.1, Dose Escalation

Units corrected from µg*h/mL to ng*h/mL.

Section 3.1.1.2, Selection of Final Dose(s) for Part 2

Previous text:

~~After the selection of the dose to be administered in Part 2, consideration may be given based on the age of subjects (subjects younger than 2 years of age, subjects ≥2 years, subject older than 6 years of age, and subjects ≥6 years of age) enrolled in Part 1. That is, if the dose level for Part 2 is identified based on data from fewer than 2 subjects in an age group, Part 1 can remain open in an attempt to enrol subjects in a different age group to confirm the previously selected Part 2 dose (i.e., Part 1 and Part 2 may enrol concurrently if a sufficient number of subjects in a given age group have not been evaluated in Part 1). This will allow for selection of a different Part 2 dose for subjects in that particular age group, if necessary.~~

Revised text:

Data from all enrolled subjects will be considered at the time of Part 2 dose selection. However, if there are insufficient data in a specific age category at the time of Part 2 dose selection, additional patients in that age category may continue to be enrolled into Part 1. Age categories are ≥1 year but ≤5 years of age and ≥6 years but <18 years of age. Tolerability and PK data should be available from at least two subjects at the Part 2 dose in each age category before Part 1 of the protocol is considered fully enrolled for that age category. Once sufficient data are available for subjects from a given age category, all subsequent subjects in that age group should be enrolled into Part 2 of the protocol. With this approach, it is possible that the Part 2 dose will not be identical across age groups.

Section 3.1.2, Part 2: Tumor-Specific Expansion

Previous text:

Treatment with dabrafenib will be continued until disease progression or until subjects are no longer obtaining clinical benefit from continued treatment, until they develop an unacceptable toxicity, or until they withdraw consent or begins a new therapy.

Revised text:

Treatment with dabrafenib will be continued until disease progression, until the subject is no longer obtaining clinical benefit from continued treatment, they develop an unacceptable toxicity, **the study is terminated**, or the subject withdraws consent or begins a new therapy.

Section 3.2, Discussion of Study Design

Previous text:

In France, children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules cannot be included in the study, pending availability of an oral suspension formulation. ~~The suspension will only be available at those sites that are capable of and meet the applicable regulatory requirements to prepare the suspension~~.

Revised text:

In France, children younger than 6 years and children 6 years and older with a risk of choking when swallowing capsules are required to use the oral suspension formulation.

Section 3.3, Dose Limiting Toxicity Definitions

Deleted the following sentence:

~~**Isolated clinical laboratory value(s) considered NOT CLINICALLY SIGNIFICANT by the investigators are not AEs (and therefore, would not be DLTs).**~~

Section 3.4, Maximum Tolereated Dose (MTD)

Deleted the following paragraph:

~~If the identified MTD is identified due to a specific toxicity that can be managed with supportive care, an additional cohort of subjects may be enrolled at the dose level that exceeded MTD with institution of supportive care measures, and if tolerable, dose escalation may resume. A summary of the available safety data and a description of the plans for supportive measures with further enrolment at that dose level will be provided to Institutional Review Boards (IRBs)/Institutional Ethics Committee (IEC) prior to dosing, if required.~~

Section 3.6, Investigational Product and Other Study Treatment Dosage/Administration

Previous text:

In France, children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules cannot be included in the study, pending availability of an oral suspension formulation.

Revised text:

In France, children younger than 6 years and children 6 years and older with a risk of choking when swallowing capsules will be required to use the suspension formulation.

Previous text:

Suspension: Bottles of bulk GSK2118436B drug substance with bottles of individual excipients (4 components) will be supplied by GSK for on-site extemporaneous compounding of a suspension formulation (for subjects unable to swallow capsules). Only sites meeting local, applicable regulations regarding extemporaneous compounding will be permitted to enroll subjects requiring suspension administration. Detailed preparation instructions are supplied in the SPM. The suspension will be administered with an oral dosing syringe supplied by GSK (oral syringes, 1 mL, 5 mL, and 20 mL for single use.

Revised text:

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.

Previous text:

TABLE 15 INVESTIGATIONAL PRODUCT

	Dabrafenib capsules	**Dabrafenib powder for oral suspension**
Formulation description:	HPMC	Powder for reconstitution, for multi-dose use
Dosage form:	Capsule	Powder for oral suspension
Unit dose strengths:	10 mg, 25 mg, 50 mg and 75 mg	10 mg/mL (as oral suspension)
Route/ Frequency:	Oral / BID	Oral / BID
Physical description:	10 mg: opaque capsules composed of a white body and cap 25 mg: opaque capsules composed of a pink body and cap 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 white to slightly colored solid. Oral suspension is extemporaneously prepared by reconstituting the drug substance with an aqueous vehicle.
Manufacturer/ source of procurement:	GSK	GSK
Method for individualizing dosage:	Unit dose capsules	Administered using oral syringes

Dabrafenib capsules will be taken with approximately 3-5 mL/kg of water, twice a day. Subjects should be encouraged to take their doses at approximate 12 hour intervals and at similar times every day

Revised text:

TABLE 16 INVESTIGATIONAL PRODUCT

Formulation description:	Dabrafenib capsules	Dabrafenib powder for oral suspension
Dosage form:	Capsule	Powder for oral suspension
Unit dose strengths:	10 mg, 25 mg, 50 mg and 75 mg	**150 mg (in stickpack)** 10 mg/mL (as oral suspension)
Route/ Frequency:	Oral / BID	Oral / BID
Physical description:	10 mg: opaque capsules composed of a white body and cap 25 mg: opaque capsules composed of a pink body and cap 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 white to slightly colored solid. Oral suspension is extemporaneously prepared by reconstituting the drug substance with an aqueous vehicle~~ **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

Dabrafenib capsules will be taken with approximately ~~3.5 mL/kg of water~~ **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.

Section 3.7.1 Guidelines for Dabrafenib Dose Modification,

Entire section deleted and remaining sections reorganized for clarity.

~~3.7.1 Guidelines for Dabrafenib Dose Modification~~

~~In the event of a DLT (first 28 days of the study) or other clinically significant AE occurs in a subject, dabrafanib may be withheld and supportive therapy administered as clinically indicated. If the toxicity or AE resolves to either baseline or Grade 1 within 7 days of stopping treatment, treatment with dabrafenib may be restarted.~~

~~Dose reduction should be considered as clinically indicated. Table 17 describes the initial dose levels to be used for any necessary dose reductions. Additional levels for dose reduction for instances of toxicity may be added based on emerging PK and safety data.~~

~~Table 17 Dose Reductions Due to Toxicity~~

~~Dose Level~~	~~Total Daily Dose (mg/kg)[2]~~
~~0[1]~~	~~3 mg/kg~~
~~-1~~	~~2.25 mg/kg~~
~~-2~~	~~1.5 mg/kg~~

~~Starting dose level.~~

~~The total daily dose will be split evenly into a morning and evening dose (BID dosing).~~

~~If the AE does not resolve to at least Grade 1 in ≤7 days, withdrawal from the study is recommended. However, if the investigator and a GSK Medical Monitor agree that the subject has benefited from treatment and further treatment will continue to benefit the subject in a manner that outweighs the risk posed by the AE, then treatment can continue with at least a 25% dose reduction for next cycle of treatment. If well tolerated at the reduced dose and both the investigator and a GSK medical monitor agree with favorable benefit risk for this subject, the previous dose level can be resumed in subsequent cycles. Any dose modification or interruption will be recorded.~~

Section 3.7.4. Dose Modification for General Toxicities

Previous text:

- **Renal insufficiency** – ~~close monitoring of serum creatinine, treatment of associated pyrexia (see Table 7 Management and dose modification guidelines for pyrexia), and treatment interruption for increased serum creatinine >2 mg/dl (or >0.5 mg/dl above baseline). Nephrology consultation should also be obtained if no obvious cause for persistent creatinine elevation (e.g. volume depletion).~~

Revised text:

- **Renal insufficiency** – Please refer to Table 6.

TABLE 18 GUIDELINES FOR RENAL INSUFFICIENCY

For subjects with creatinine increase of ≥50% from baseline or eGFR [(a)] decrease of >25% from baseline:	

1st occurrence	• Interrupt dabrafenib
	• If subject has fever: treat pyrexia as per Table 7 (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration
	• Pediatric nephrology consult is recommended
	• Re-check within 24 hours
	  • If <50% increase in creatinine or ≤25% decrease in eGFR from baseline then may restart dabrafenib
	  • If ≥50% increase in creatinine from baseline or eGFR decrease of >25% from baseline
	  - Recommend monitor creatinine at least twice weekly
	  - May restart dabrafenib if creatinine/eGFR returns to baseline with approval of medical monitor.
	  - If creatinine<50% increase from baseline or eGFR returns to ≤25% decrease from baseline may restart dabrafenib at a reduced dose with approval of the medical monitor

2nd occurrence	• Follow above recommendations. • If restart of dabrafenib is approved by medical monitor

For subjects with creatinine increase of ≥50% from baseline or eGFR [(a)] decrease of >25% from baseline:	
	○ Upon restart reduce dabrafenib by one dose level
3rd occurrence	▪ Permanently discontinue dabrafenib
For subjects with creatinine increase of ≥100% from baseline or eGFR [(a)] decrease of >50% from baseline	
	• Interrupt dabrafenib • If subject has fever: treat pyrexia as per Table 7 (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration • Pediatric nephrology consultation recommended • Re-check within 24 hours • If creatinine increase of ≥100% or eGFR decrease of >50% is confirmed, permanently discontinue dabrafenib • If creatinine increase ≥50% or eGFR decrease >25% from baseline and ≤50% from baseline, continue to hold dabrafenib and follow guidelines above • If creatinine increase <50% or eGFR is ≤25% decrease from baseline may restart dabrafenib

(a). eGFR calculated according to Schwartz formula (http://www.medcalc.com/pedigfr.html)

Section 3.7.4. Dose Modification for General Toxicities

Revised text added after Table 5

If the AE does not resolve to at least Grade 1 in ≤7 days, withdrawal from the study is recommended. However, if the investigator and a GSK Medical Monitor agree that the subject has benefited from treatment and further treatment will continue to benefit the subject in a manner that outweighs the risk posed by the AE, then treatment can continue with at least a 25% dose reduction for next cycle of treatment. If well tolerated at the reduced dose and both the investigator and a GSK medical monitor agree with favorable benefit risk for this subject, the previous dose level can be resumed in subsequent cycles. Any dose modification or interruption will be recorded.

Section 3.8,Time and Events Tables

TABLE 8 PART 1 AND PART 2 TREATMENT PHASE: SCREENING THROUGH DAY 21 (SEE ALSO PK SAMPLING TABLE FOR PK SAMPLING SCHEDULE ON DAY 1 AND DAY 15)

Added assessments on Day 22, and urinalysis on Day 1, Day 8, Day 15, Day 21. Changes are in **bold.**

Revised text:

STUDY PHASE		**SCREEN**	**TREATMENT DAYS 1 through 22**			
VISIT		**Screen**	**Pre-dose Day 1**	**Pre-dose Day 8**	**Pre-dose Day 15**	**Pre-dose Day 22**
VISIT WINDOW (±days		-21	N/A	±2	±2	**±2**
Baseline Assessments						
Informed consent/assent		X				
Tumor tissue for V600 testing	Local testing for inclusion in the study; can be from archival tissue or if no archival tissue is available, from fresh biopsy; the local BRAF testing will be subject to subsequent verification by centralized testing.	X				
Demographic data	Record date of birth, gender, race and ethnicity	X				
Register subject	Using an interactive voice response system	X	X		~~X~~	
Height/Weight	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 14 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			
Disease characteristics	Record date of diagnosis, primary tumor type, histology, stage, etc.	X				
Prior anti-cancer therapy & radiation		X				
Prior surgical procedures		X				
Past and current medical conditions	Medical history will be assessed as related to the eligibility criteria listed in Section 4.2. Cardiovascular medical history/risk factors will also be assessed at baseline	X				
Alcohol consumption	Alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2	X				

STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 22			
VISIT		Screen	Pre-dose Day 1	Pre-dose Day 8	Pre-dose Day 15	Pre-dose Day 22
VISIT WINDOW (±days		-21	N/A	±2	±2	**±2**
Past and current tobacco use	Tobacco use will be assessed as related to the eligibility criteria listed in Section 4.2	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**
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**
Vital signs	Blood pressure, body temperature, pulse rate, respirations	X	X	X	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		X	X	**X**
Echocardiogram (ECHO)	Copies of all ECHOs 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).	X			X	
Concomitant medications	See Section 8 for list of prohibited and cautionary medications.	X	X	X	X	**X**
Adverse events	Adverse event assessment should be continuous	X	X	X	X	**X**
Palatability questionnaire	For suspension - see SPM for additional details; subjects ≥12 years of age may complete the questionnaire independently (if able) while subjects younger than 12 years of age should work with their caregiver to supply feedback and the caregiver then completes the questionnaire. The questionnaire may be completed after the first dose of study drug but must be completed no later than Day 8 (±3 days)			X		

STUDY PHASE		SCREEN	TREATMENT DAYS 1 through 22			
VISIT		Screen	Pre-dose Day 1	Pre-dose Day 8	Pre-dose Day 15	Pre-dose Day 22
VISIT WINDOW (±days		-21	N/A	±2	±2	**±2**
Blood Sampling						
Chemistry	Evaluations performed by a local laboratory. No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	**X**
Hematology	Evaluations performed by a local laboratory. No need to repeat at pre-dose Day 1 if screening assessments were performed within 14 days of first dose.	X	X	X	X	**X**
Urinalysis		**X**	**X**	**X**	**X**	**X**
Spot urine protein/Cr ratio, spot urine albumin	**Early morning specimen preferred**	**X**	**X**	**X**	**X**	**X**
PK sampling	For details, see PK sampling Table		X (see PK table)		X (see PK table)	
Clinical Activity Assessments [redacted]						
Target and non-target lesion assessment	1. Must be identified at time of screening scan.	X				
Brain MRI (glioma subjects ONLY)	If an MRI of the brain was obtained within 35 days of the first dose, this can be used as screening MRI. CT with contrast allowed only if brain MRI is contraindicated)	X				
Performance status (Karnofsky/Lansky)	See Appendix 3	X	X	X	X	**X**
[redacted]						
Study Medication						
Dispense oral study medication and assess compliance	Dispense a 2 to 4 week supply of the study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.		X (single dose)			

1. MRI = magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiogram; PK = pharmacokinetic

TABLE 9 PK SAMPLING TABLE FOR DAY 1 AND DAY 15 (PART 1 AND PART 2)

For subjects <25 kg and ≥10 kg, added 1 mL samples on Day 1 and some additional 2 mL samples on Day 15. For subjects <10 kg, added a 2 mL sample on Day 15. Changes are in **bold**.

Revised text:

	Day 1			Day 15							
hour	0.5	2	4	0	0.5	1	2	3	4	6	8
COLLECTION WINDOW	± 5 min	± 5 min	± 20 min	-30 min	± 5 min	± 5 min	± 5 min	± 20 min	± 20 min	± 20 min	± 20 min
Subjects ≥25 kg											
PK (2 mL samples)	X	X	X	X	X	X	X	X	X	X	X
Subjects <25 kg and ≥10 kg											
PK (1 mL samples)	**X**	**X**	**X**				X	**X**			
PK (2 mL samples)				**X**		**X**			**X**		X
Subjects <10 kg											
PK (1 mL samples)							X		X		
PK (2 mL samples)				**X**							

Plasma concentrations of dabrafenib and all metabolites will be measured in the 2 mL blood samples. Plasma concentrations of dabrafenib, GSK2285403 and GSK2167542 will be measured in 1 mL blood samples.

TABLE 10 PART 1 AND PART 2 TREATMENT PHASE: WEEK 4 (DAY 29) THROUGH END OF STUDY

Specified that Week 4 is Day 29 in the title, and added more frequent chemistry evaluations and urinalysis. Dermatologic exam every 8 weeks. Changes are in **bold.**

Revised text:

STUDY PHASE		**TREATMENT WEEK 4+**							
Visit		**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Weeks 25-56**	**Weeks 57+**	**Final Visit**
VISIT WINDOW (±days)		±3	±3	±7	±7	±7	±7	±7	±7	
Safety Assessments										
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	Every **8** weeks	Every **8** weeks	X
Blood Sampling										
Chemistry	Evaluations performed by a local laboratory	**W4, W5, W6, W7**	X	X	X	X	X	Every 8 weeks	Every 8 weeks	X
Hematology	Evaluations performed by a local laboratory	X	X	X	X	X	X	Every 8 weeks	Every 8 weeks	X
Urinalysis		**X**	**X**	**X**	**X**	**X**	**X**	**Every 4 weeks**	**Every 4 weeks**	
Spot urine protein/Cr ratio, spot urine albumin	**Early morning specimen preferred**	**X**	**X**	**X**	**X**	**X**	**X**	**Every 4 weeks**	**Every 4 weeks**	

Section 4.2.1, Inclusion Criteria,

Previous text:

2. Male or female between one month and <18 years of age (inclusive) at the time of signing the informed consent form;

Revised text:

2. Male or female ≥12 months and <18 years of age at the time of signing the informed consent form

Section 4.2.1, Inclusion Criteria,

Previous text:

7. Adequate renal and metabolic function defined as:

- Calculated creatinine clearance (Cockcroft-Gault), calculated GFR (revised Schwartz formula), or radioisotope GFR ≥ 60 mL/min/1.73 m2; or

Revised text:

7. Adequate renal and metabolic function defined as:

- Calculated eGFR (Schwartz formula, http://www.medcalc.com/pedigfr.html), or radioisotope GFR ≥90 mL/min/1.73 m^2; or

Section 4.2.2, Exclusion Criteria,

Revised text:

5. History of another malignancy;

Exception: (a) Subjects who have been successfully treated and are disease-free for 3 years, (b) a history of completely resected non-melanoma skin cancer, (c) successfully treated in situ carcinoma, or (d) CLL in stable remission, ~~or (e) indolent prostate cancer (definition: clinical stage T1 or T2a, Gleason score ≤6, and PSA < 10 ng/mL) requiring no or only anti-hormonal therapy with histologically confirmed tumour lesions that can be clearly differentiated from lung cancer target and non-target lesions~~ are eligible

Section 9.1, Subject Completion,

Revised text:

A final study visit **within 28 days after last dose of study drug** should be completed.

Section 9.3.2, Subject Withdrawal from Study Treatment,

Revised text:

All subjects who discontinue from study treatment will have a Final Visit (**as defined in Table 10) which should be completed at the time of discontinuation (within 28 days after last dose of study drug). Subjects** will be offered post study treatment follow-up as specified in Section 9.4

Section 10.3, Preparation/Handling/Storage/Accountability,

Previous text:

A description of the methods and materials required for preparation of the suspension formulation of dabrafenib are provided in the SPM.

Revised text:

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**.

Text deleted:

~~Dabrafenib suspension is to be stored at 2-8°C, protected from light. Maintenance of a temperature log (manual or automated) is required (after preparation).~~

Section 10.4, Assessment of Compliance,

Text deleted:

~~Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested~~

Section 11.4, Recording fo AEs and SAEs,

Text deleted:

~~Subject-completed health outcomes questionnaires and the collection of AE data are independent components of the study. Responses to each question in the health outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.~~

Appendix 2, Response Criteria

LCH Scoring System [Donadieu, 2004] table deleted.

Amendment 02

Amendment 02 was a country specific amendment for France. Please see Appendix 5.

Amendment 01

WHERE THE AMENDMENT APPLIES

Amendment 01 applies to all sites conducting the study.

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Amendment No. 01 corrected Inclusion Criteria #6 to ensure consistency with the contraception requirements as outlined in Section 7.1.1. In addition, the dose escalation procedure table provided in Appendix 1 was changed to ensure that escalation of dose when 6 subjects are enrolled occurs only if there are ≤1 subject with a DLT and no subject data pending, and to fix the reference and formatting.

LIST OF SPECIFIC CHANGES

Section 4.2.1, Inclusion Criteria (#6)

Rationale for change: The requirement for male contraception was deleted since the risk of embryofetal developmental toxicity as a consequence of exposure to female pregnant partners is very low.

Previous Text

6. Females of child-bearing potential and males with reproductive potential must be willing to practice acceptable methods of birth control (see Section 7.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study medication;

Revised Text

6. Females of child-bearing potential ~~and males with reproductive potential~~ must be willing to practice acceptable methods of birth control (see Section 7.1). Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study medication;

Appendix 1

Rationale for change: Changed to ensure that escalation of dose when 6 subjects are enrolled occurs only if there are ≤1 subject with a DLT and no subject data pending.

Previous Text

Appendix 1: Rolling Six Design Dose Escalation Procedures

DOSE ESCALATION PROCEDURE [SKOLNIK, 2008]

Number of Subjects Enrolled	Number of Subjects with a DLT	Number of Subjects with Data Pending	Decision
1	--	--	Same dose level
2	2	--	De-escalate[1]
	Other	--	Same dose level
3	≥2	--	De-escalate[1]
	0	0	Escalate
	Other	--	Same dose level
4	≥2	--	De-escalate[1]
	0	0	Escalate
	Other	--	Same dose level
5	≥2	--	De-escalate[1]
	0	0	Escalate
	Other	--	Same dose level
6	≥2	--	De-escalate[1]
	≤1	1	Escalate
	0	--	Escalate
	Other	--	Suspend

Revised Text

Appendix 1: Modified Rolling Six Design Dose Escalation Procedures

DOSE ESCALATION PROCEDURE ~~[SKOLNIK, 2008]~~

Number of Subjects Enrolled	Number of Subjects with a DLT	Number of Subjects with Data Pending	Decision
1	--	--	Same dose level
2	2	--	De-escalate~~[1]~~
	Other	--	Same dose level
3	≥2	--	De-escalate~~[1]~~
	0	0	Escalate
	Other	--	Same dose level
4	≥2	--	De-escalate~~[1]~~
	0	0	Escalate
	Other	--	Same dose level
5	≥2	--	De-escalate~~[1]~~
	0	0	Escalate
	Other	--	Same dose level
6	≥2	--	De-escalate~~[1]~~
	≤1	1	~~Escalate~~ **Suspend[1]**
	≤1	**0**	**Escalate[1]**
	0	--	Escalate
	Other	--	Suspend

1. Modified from the Zhao, 2011 publication