NOVARTIS

Clinical Development

Dabrafenib (DRB436), Trametinib (TMT212)

Oncology Clinical Protocol CDRB436G2201 / NCT02684058

# Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)

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## List of abbreviations

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| ADL | Activities of daily living |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| AUC | Area under the curve |
| b.i.d. | *bis in diem*/twice a day |
| BAL | Bronchoalveolar lavage |
| BCC | Basal cell carcinoma |
| $C_{avg}$ | Average concentration |
| CBDCA | Carboplatin |
| CBR | Clinical benefit rate |
| [redacted] | [redacted] |
| Cmax | The observed maximum (peak) plasma concentration after drug administration |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CMO&PS | Chief Medical Office and Patient Safety |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| COG | Children's Oncology Group |
| CR | Complete response |
| CRF | Case report/record form; the term CRF can be applied to either EDC or paper |
| CRO | Contract research organization |
| CRP | C reactive protein |
| CSF | Cerebrospinal fluid |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CSR addendum | An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR |
| CTCAE | Common terminology criteria for adverse event |
| DILI | Drug-induced liver injury |
| DLT | Dose limiting toxicity |
| DMC | Data monitoring committee |
| DOR | Duration of response |
| DRESS | Drug reaction with eosinophilia and systemic symptoms |
| EBV | Epstein-Barr virus |
| EEA | European Economic Area |
| ECG | Electrocardiogram |
| eCRF | Electronic case report forms for EDC |
| ECHO | Echocardiogram |
| EDC | Electronic data capture |
| EMA | The European Medicines Agency |
| EU | European Union |
| eSAE | Electronic serious adverse event |
| FAS | Full analysis set |
| FFPE | Formalin-fixed, paraffin-embedded |
| FDA | Food and Drug Administration |
| GBM | Glioblastoma multiforme |
| GDPR | General Data Protection Regulation |

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|---|---|
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HGG | High Grade Glioma |
| HPMC | Hydroxypropylmethyl cellulose |
| HSV | Herpes simplex virus |
| i.v. | intravenous(ly) |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System |
| IUD | Intrauterine device |
| IUS | Intrauterine system |
| Kg | Kilogram |
| LCH | Langerhans Cell Histiocytosis |
| LFT | Liver function test |
| LGG | Low Grade Glioma |
| MAP | Master analysis plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| NGS | Next-generation sequencing |
| NSCLC | Non-small cell lung cancer |
| q.d. | *omnia die*/once a day |
| ORR | Overall response rate |
| OS | Overall survival |
| PAS | Pharmacokinetic analysis set |
| PD | Progression of disease |
| PFS | Progression free survival |
| PHI | Protected Health Information |
| PK | Pharmacokinetics |
| p.o. | *per os*/by mouth/orally |
| POS | Probability of success |
| PPS | Per-protocol set |
| PR | Partial Response |
| PRO | Patient reported outcomes |
| PTC | Papillary Thyroid Cancer |
| PXA | Pleomorphic Xanthoastrocytoma |
| QT | Q to T interval (ECG) |
| QTcF | QT interval corrected using Fridericia method |
| RANO | Response Assessment in Neuro-Oncology Criteria |
| RAP | The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses |
| REB | Research Ethics Board |
| RP2D | Recommended phase two dose |
| RPED | Retinal pigment epithelial detachment |
| RoW | Rest of world |
| RR | Response rate |

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| R Value | ALT/ALP in x ULN |
| RVO | Retinal vein occlusion |
| SAE | Serious adverse event |
| SC | Steering committee |
| SCAR | Severe cutaneous adverse reactions |
| SIADH | Syndrome of inappropriate antidiuretic hormone secretion |
| SmPC | Summary of product characteristics |
| SOC | Standard of care |
| SOP | Standard operating procedure |
| TBIL | Total bilirubin |
| TTR | Time to response |
| ULN | Upper limit of normal |
| VCR | Vincristine |
| WBC | White blood cells |
| WHO | World Health Organization |

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## Glossary of terms

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| Assessment | A procedure used to generate data required by the study |
| Biologic Samples | A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient |
| Control drug | A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Cohort | A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days) |
| Dose level | The dose of drug given to the patient (total daily or weekly etc.) |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Investigational drug | The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug." |
| Investigational treatment | Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage |
| Medication number | A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study |
| Other study treatment | Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment |
| Subject Number (Subject No.) | A unique identifying number assigned to each patient who enrolls in the study |
| Period | A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Personal Data | Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples. |
| Randomization number | A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Stage related to study timeline | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Stage in cancer | The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body |
| Stop study participation | Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued and post treatment follow-up is complete, whichever is later |
| Study treatment | Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.<br>In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination. |
| Study treatment discontinuation | Point/time when patient permanently stops taking study treatment for any reason |
| Supportive treatment | Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium. |

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| Treatment group | A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled. |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints |
| Withdrawal of study consent | Withdrawal of consent from study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data |

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## Protocol summary:

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| **Title** | Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG) |
| **Brief title** | Study of efficacy and safety of dabrafenib in combination with trametinib in pediatric patients with *BRAF* V600 mutation positive LGG or relapsed or refractory HGG tumors |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | Relapsed, refractory or resistant pediatric HGG lacks a standard of care. Multiple chemotherapies and targeted agents have been studied in this setting but none have demonstrated activity. Targeted agents in this disease setting have shown a lack of efficacy.<br>Preliminary results from [BRF116013, CDRB436A2102, data cut off of 12-Sept-2017] showed that 14 of 31 patients (45%) with relapsed or refractory *BRAF* V600 mutant HGG had central independent radiologic review confirmed responses (CRs + PRs) following dabrafenib monotherapy. These results indicate that dabrafenib may offer improvement in treatment outcome for these patients. For this reason, the historical response rate (RR) in *BRAF* V600 mutant pediatric relapsed refractory HGG may be higher than that observed in unselected populations, where the RR is less than 12%.<br>Pediatric patients with *BRAF* V600 mutant LGG that is progressing following optimal surgical resection often require systemic treatment. The standard of care in this setting has been a regimen of carboplatin and vincristine, which may not be as effective in patients whose tumor harbors the *BRAF* V600 mutation, with lower response rate, PFS and OS than those without this mutation. Furthermore, in patients with *BRAF* V600 mutant LGG who have failed prior systemic chemotherapy, independently confirmed response of dabrafenib monotherapy exceeds historical expectations for this subgroup of patients.<br>The combination of dabrafenib with trametinib in adults with *BRAF* V600 mutant melanoma, non-small cell lung cancer (NSCLC) and other tumors have resulted in improved efficacy over dabrafenib monotherapy and suggests that greater efficacy may also be seen in the pediatric patients with a *BRAF* V600 mutant malignancy.<br>Given the high unmet medical need in pediatric HGG and LGG, the encouraging efficacy of dabrafenib monotherapy in pediatric patients with *BRAF* V600 mutant HGG and LGG, and the improved efficacy seen in adult cancer studies upon the addition of trametinib to dabrafenib, this study aims to demonstrate the effectiveness of dabrafenib with trametinib in pediatric patients with *BRAF* V600 mutant LGG and relapsed refractory HGG. |
| **Primary Objective(s)** | The primary objective of the HGG cohort is to evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria.<br>The primary objective of the LGG cohort is to compare the anti-tumor activity of dabrafenib in combination with trametinib to the combination of carboplatin and vincristine, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria. |
| **Secondary Objectives** | **HGG Cohort:**<br>1. Evaluate ORR by investigator assessment<br>2. Evaluate duration of response (DOR) by investigator and central independent assessment<br>3. Evaluate progression free survival (PFS) by investigator and central independent assessment<br>4. Evaluate time to response (TTR) by investigator and central independent assessment |

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| | 5. Evaluate clinical benefit rate (CBR) by investigator and central independent assessment<br>6. Evaluate overall survival (OS)<br>7. Evaluate the safety and tolerability profile of dabrafenib in combination with trametinib in the study population<br>8. Evaluate the palatability of dabrafenib oral suspension and trametinib oral solution<br>9. Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population<br>**LGG Cohort:**<br>10. Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator assessment.<br>11. Evaluate the DOR of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and independent assessment.<br>12. Evaluate PFS of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and independent assessment.<br>13. Evaluate TTR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and independent assessment.<br>14. Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment.<br>15. Evaluate the overall survival of dabrafenib in combination with trametinib versus carboplatin with vincristine.<br>16. Evaluate the safety and tolerability of dabrafenib in combination with trametinib versus carboplatin with vincristine.<br>17. Evaluate the palatability of dabrafenib oral suspension and trametinib oral solution<br>18. Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population.<br>19. Assess patient reported outcomes of dabrafenib in combination with trametinib versus carboplatin with vincristine. |
| **Study design** | CDRB436G2201 combines two pediatric glioma cohorts into a single multi-center, global, open-label, phase II study. The HGG cohort is a single arm part evaluating the effect of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation positive relapsed, refractory HGG. Approximately 40 patients will be enrolled to receive oral dabrafenib twice daily and trametinib once daily based on weight, age and appropriate dose level.<br>The LGG cohort is a randomized part comparing the anti-tumor activity of dabrafenib in combination with trametinib to the combination of carboplatin and vincristine in children and adolescents with *BRAF* V600 mutation positive LGG. Approximately 102 patients will be randomized in a 2:1 ratio to either dabrafenib plus trametinib or carboplatin with vincristine. For the LGG cohort, patients randomized to carboplatin with vincristine control arm will be allowed to crossover to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression.<br>All patients will be followed for survival for at least 2 years after the last patient first study treatment (except if consent is withdrawn, patient death, lost to follow-up or study is discontinued). An interim analysis for futility for the HGG cohort will be implemented to allow possible termination of recruitment into the HGG cohort in the event that there is insufficient efficacy. An independent DMC will be instituted to review safety data during the study for all patients in LGG and HGG cohorts.<br>For full details of study design refer to Section 4. |
| **Population** | This study will be conducted in two cohorts of pediatric patients, HGG cohort and LGG cohort. |

[redacted]

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| | For the HGG cohort, approximately 40 male or female children or adolescent patients between ≥12 months and <18 years of age with *BRAF* V600 mutation positive, refractory or relapsed HGG after having received at least one previous standard therapy will be enrolled.<br>For the LGG cohort, approximately 102 male or female children or adolescent patients between ≥12 months and <18 years of age with *BRAF* V600 mutation positive LGG with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression. |
| **Inclusion criteria** | **Key Inclusion criteria:**<br>- Male or female ≥12 months and <18 years of age. Patient must weigh ≥7 kg at the time of enrollment.<br>- Locally determined HGG or LGG as defined by WHO histological classification system, revised 2016.<br>• For HGG cohort only: locally confirmed histologic diagnosis of High Grade Glioma (Grade III or IV), including anaplastic pleomorphic xanthoastrocytoma (aPXA) and anaplastic ganglioglioma.<br>• For LGG cohort only: locally confirmed histologic diagnosis of Low Grade Glioma (Grade I or II).<br>- HGG cohort: Relapsed, progressed, or failed to respond to frontline therapy.<br>- LGG cohort: Patients with progressive disease following surgical excision, or non-surgical candidates with necessity to begin systemic treatment because of a risk of neurological impairment with progression.<br>- *BRAF* V600 mutation-positive tumor assessed locally, or at a Novartis designated central reference laboratory if local *BRAF* V600 testing is unavailable.<br>- Locally determined and centrally confirmed measurable disease with minimal bi-perpendicular diameter that must be at least twice the imaging slice thickness to be used for efficacy assessments.<br>- Tumor tissue must be provided for central confirmatory testing of *BRAF* mutational status (LGG and HGG cohorts), and for HGG histopathology (HGG cohort only).<br>- Karnofsky/Lansky performance score of ≥50%.<br>- Adequate bone marrow function per central or local lab in the absence of growth factor support.<br>- Adequate renal function, liver function, and cardiac function.<br>- If receiving glucocorticoids, patient must be on a stable or weaning dose for at least **7** days prior to first dose of study treatment. |

[redacted]

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| **Exclusion criteria** | **Key Exclusion criteria:**<br>- Malignancy OTHER than *BRAF* V600 mutant HGG or LGG.<br>- Previous treatment with dabrafenib or another RAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor.<br>- HGG patients: Cancer therapy (chemotherapy with delayed toxicity, immunotherapy, biologic therapy, vaccine therapy) or investigational drugs within 3 weeks preceding the first dose of study treatment. LGG patients: Any systemic anticancer therapy (chemotherapy, immunotherapy, biologic therapy or vaccine therapy) or investigational drugs prior to enrollment.<br>- HGG patients: Radiotherapy to CNS glioma lesions within 3 months prior to first dose of study treatment, unless there is clear evidence of radiologic progression outside of the field of radiation. LGG patients: Radiotherapy to CNS glioma lesions at any point prior to enrollment.<br>- History of malignancy with confirmed activating RAS mutation or with *BRAF* fusion such as BRF-KIAA1549.<br>- Current use of a prohibited medication or herbal preparation or requires any of these medications during the study. See Section 6.4 for details.<br>- Unresolved toxicity greater than NCI CTCAE v 4.03 grade 2 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 the study treatment (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy).<br>- History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib, trametinib and their excipients. For LGG patients only: history of allergic reactions or contraindications to the use of carboplatin or vincristine (refer to local product label or SmPC)<br>- Autologous or allogeneic stem cell transplant within 3 months prior to the first dose of study treatment [NOTE: patients with evidence of active graft versus host disease are excluded regardless of elapsed time].<br>- History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease.<br>- 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.<br>- 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.<br>- A history of Hepatitis B Virus or Hepatitis C Virus infection (patients with laboratory evidence of cleared Hepatitis B Virus and/or Hepatitis C Virus may be enrolled).<br>- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (e.g. are menstruating), unless they are using highly effective methods of contraception during dosing of study treatment and for 16 weeks after stopping study medication with trametinib monotherapy or dabrafenib in combination with trametinib, and 2 weeks after stopping treatment with dabrafenib monotherapy, whichever is longer. Note: Hormonal-based methods are not permitted as a method of contraception due to potential drug-drug interactions with dabrafenib.<br>- Women who are pregnant or actively breast feeding.<br>- Sexually active males (including those that have had a vasectomy) unless they use a condom during intercourse while on study and for 16 weeks after stopping study treatment, and agree not to father a child during this period.<br>- A history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy. See Section 5.3 for details |

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| **Investigational and reference therapy** | Dabrafenib (DRB436) oral administration, twice daily based on weight, age and appropriate dose level. Trametinib (TMT212) oral administration, once daily based on weight and/or age. See dosing regimen in Section 6.1.1.<br>LGG patients randomized to receive carboplatin plus vincristine are administered one course of induction (10 weeks of chemotherapy with 2 weeks of rest) followed by 8 cycles of maintenance chemotherapy. Each maintenance cycle is 6 weeks. See dosing regimen in Section 6.1.2 |
| **Efficacy assessments** | **HGG and LGG cohorts:** Brain MRI every 8 weeks during the first 56 weeks and every 16 weeks thereafter while on treatment, during post-treatment follow-up, and at any time there is suspicion of clinical disease progression. Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed ≥4 weeks after the criteria for response are first met.<br>Tumor evaluation by RANO criteria as assessed by local investigator and central independent assessment. |
| **Safety assessments** | **HGG and LGG cohorts:**<br>Medical history<br>Physical examination, vital signs, height and weight, [redacted]<br>Performance status<br>Laboratory evaluations (hematology, clinical chemistry and urinalysis)<br>Monthly pregnancy testing for women of childbearing potential<br>Cardiac assessment, including ECG and cardiac imaging<br>[redacted]<br>Dermatology evaluation<br>Ophthalmologic exam<br>[redacted]<br>Adverse events, the severity, the seriousness, the relationship to study drug, and AEs of special interest |
| **Other assessments** | **HGG and LGG cohorts:**<br>Pharmacokinetics (PK) blood collection to summarize exposure (dabrafenib, dabrafenib metabolites and trametinib) [redacted]<br>Taste questionnaires for dabrafenib oral suspension and trametinib oral solution.<br>Tumor samples for confirmatory testing of HGG histopathology (HGG patients only)<br>Tumor samples for confirmatory testing of *BRAF* mutational status for both LGG and HGG patients.<br>[redacted]<br>Survival status follow-up<br>**LGG cohort only:**<br>Patient reported outcomes on PROMIS Parent Proxy Global 7+2 Health questionnaire |

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| **Data analysis** | **Data analysis to address the primary objective**:<br>The primary analysis will be performed on the full analysis set (FAS). For HGG cohort, point estimate and the exact binomial confidence intervals (CIs) of ORR by central independent assessment will be provided. The lower bound of the CIs will be used to provide evidence that the true ORR is greater than a certain specific response rate. For LGG cohort, the ORR by central independent assessment of the two treatment groups will be compared using Mantel Haenszel chi-square test at one-sided 2.5% level of significance. ORR will be summarized using descriptive statistics by treatment arm along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934).<br><br>**Data analysis to address secondary objectives:**<br>ORR per investigator assessment for HGG cohort and LGG cohort will also be analyzed.<br>TTR, DOR, CBR and PFS will be analyzed as per investigator and independent assessment. Confirmation of response is required for all response endpoints, as per RANO.<br>DOR, PFS and OS will be described using Kaplan-Meier methods and appropriate summary statistics.<br>**Efficacy:** The efficacy analysis will be performed on all patients who receive at least one dose of study treatment. Sensitivity analysis on the primary and secondary efficacy endpoints will be performed on the evaluable set of patients.<br>**Safety:**<br>The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. vital signs, ECG, ECHO) will be considered as required. The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation, unless otherwise specified. The safety analysis will be performed on patients receiving at least one dose of study treatment.<br>The palatability of dabrafenib oral suspension and trametinib oral solution will be evaluated.<br>The patient reported outcome for the LGG cohort will be summarized.<br><br>**Interim analysis:**<br>An interim analysis for futility will be implemented to allow possible termination of recruitment of the HGG cohort in the event that there is insufficient efficacy. The patients for inclusion in the formal interim analysis for futility will be determined shortly after 16 HGG patients in the FAS have been enrolled. The analysis will be conducted when this initial group of patients to be included in the analysis have all had at least 20 weeks of follow-up or have withdrawn early. If the observed ORR assessed by central independent assessment is ≤ 25% there may be a consideration to stop the enrollment into the HGG cohort due to insufficient efficacy. The final decision on whether to stop enrollment into this cohort will also take into account all available study information at the IA cut-off including safety data and all efficacy endpoints. Any decision to halt further enrollment into the HGG cohort will not impact the treatment options for patients already enrolled into this cohort. HGG patients deriving benefit as per investigator discretion may continue receiving dabrafenib plus trametinib treatment on study.<br><br>In addition, an additional interim analysis of key safety and PK data of the adolescent patients in the HGG cohort may be performed to support a health authority request for data in adolescent patients.<br><br>**Sample size for HGG cohort:**<br>Approximately 40 patients will be enrolled in HGG cohort if the study is not stopped for futility at the time of IA. |

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| | With a total of 40 patients and with 16 patients included in the futility interim analysis and when the true ORR is ≤ 20%:<br>• the probability of meeting the futility consideration criteria at IA is > 79%,<br>• the probability of the 95% CI excluding 20% at the primary analysis is < 1.6%,<br>• and the probabilities of the 95% CI and the 80% CI excluding 32% at the primary analysis are both < 0.1% respectively.<br>With a total of 40 patients and with 16 patients included in the futility interim analysis and if the true ORR is 55% or higher, then:<br>• the probability of meeting the futility consideration criteria at IA is < 2%,<br>• the probabilities of the 95% CI excluding 20% and the 80% CI excluding 32% at the primary analysis are both > 90% respectively,<br>• and the probability that the 95% CI excludes 32% is > 78%.<br>**Sample size for LGG cohort:**<br>For LGG cohort, to detect a 30% improvement in ORR based on central independent assessment response of 50% in the dabrafenib in combination with trametinib arm vs 20% in the carboplatin plus vincristine arm with at least 80% power, 102 patients are required to be randomized in the two treatment arms in a 2:1 ratio using a Maentel-Haenszel chi-squared test, and one-sided alpha = 2.5%. |
| **Key words** | High grade glioma, HGG, Low grade glioma, LGG, *BRAF*, DRB436, dabrafenib, TMT212, trametinib, carboplatin and vincristine, children, adolescent |

[redacted]

## Amendment 5 (26-Nov-2019)

As of 26-Nov-2019, twenty six (26) patients have been enrolled and treated in the HGG cohort of CDRB436G2201 and forty four (44) patients have been randomized in the LGG cohort of CDRB436G2201.

### Amendment Rationale

The main purpose of this amendment is (1) to add dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which have been reported during treatment with dabrafenib in combination with trametinib outside this clinical study, and (2) to change the duration of male and female contraception following the last dose of dabrafenib from 4 weeks to 2 weeks and following the last dose of trametinib from 6 months to 16 weeks.

These changes were made in order to align with updated information available in dabrafenib and trametinib Investigator's Brochure Edition 11.

Further, inclusion criterion 3 was clarified as local histological diagnosis of HGG is sufficient for the study entry and criteria for patients with Gilbert's syndrome were established for inclusion criterion 11.

Other clarifications and corrections are also applied throughout the protocol.

### Changes to the protocol

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

Updated Section 4.1.2.2: Section has been corrected to clarify that for LGG patient, Day 1 of crossover therapy must occur within 90 days from the date of the first centrally confirmed progression.

Updated Section 5.2: Inclusion criterion 3 has been clarified by removing mention of central confirmation of histopathology as this is not required for eligibility, inclusion criterion 11 has been modified to allow specific laboratory criteria for enrollment of patientswith Gilbert's syndrome. Exclusion criteria 14 and 17 have been modified to reflect the modified contraception requirements.

Updated Section 6.3.1.11: Management of severe skin cutaneous adverse reactions has been modified in line with DRB436 Investigator Brochure 11 and provide guidance on SCAR event management.

Section 8.4: wording regarding the duration of reporting period for pregnancy after patient discontinued treatment has been modified to 16 weeks after stopping treatment with trametinib monotherapy or dabrafenib in combination with trametinib, and 2 weeks after stopping treatment with dabrafenib monotherapy, whichever is longer.

[redacted]

### Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB)

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

The changes described in this amended protocol require IRB/IEC/REB 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.

### Summary of previous amendment

## Amendment 4 (11-Mar-2019)

As of 28-Feb-2019, fifteen (15) patients have been enrolled and treated in the HGG cohort of CDRB436G2201 and fourteen (14) patients have been randomized in the LGG cohort of CDRB436G2201.

### Amendment rationale

The purpose of this amendment is to add an additional interim analysis of key safety and pharmacokinetics (PK) data of the adolescent patients (ages ≥12 to <18 years) in the HGG cohort to support a health authority request in the1st half of 2019 for data in adolescent patients.

In addition, exclusion criteria #18 was added to exclude patients with history or current evidence of retinal vein occlusion and central serous retinopathy. This exclusion criteria is standard language for all studies with trametinib and was inadvertently omitted from previous versions of CDRB436G2201.

Also, optional cerebrospinal fluid (CSF) collection was removed. Based on experience to date, CSF samples are expected to be very limited (1/30 patients provide a sample). Hence, the value of the analyses is limited.

Other clarifications and corrections are also applied throughout the protocol.

### Changes to the protocol

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

- Updated protocol summary table to match changes throughout protocol
- Updated Table 3-1 to remove optional CSF sample collection
- Updated Figures 4-1 and 4-2 to reflect that trametinib dosing is age and weight based
- Updated Section 4.1.2 to reference Visit Evaluation Schedule Table 7-3 created for the chemotherapy arm
- Updated Section 4.2 to include an additional interim analysis in the HGG cohort to support a health authority request

[redacted]

- Updated Section 5.2
  - Inclusion criterion #5: Removed CLIA-approved laboratory (US only) or local equivalent, removed requirement for molecular testing for *BRAF* V600 confirmation
- Updated Section 5.3
  - Added Exclusion criterion #18: To exclude patients with history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy
  - Exclusion criterion #14: Added the option to use hormonal IUD or IUS in addition to non-hormonal IUD or IUS as a form of birth control. Removed the term "Hormonal-based methods" from the note.
- Updated Table 6-16 for pyrexia dose modifications to indicate that patients and parents should be re-educated about pyrexia syndrome
- Changed "renal toxicity" to nephrotoxicity in Section 6.1.2.1 to be consistent with language in Section 6.3.1.16
- Corrected reference to RPED dose modiciation table in Table 6-19
- Clarified in Section 6.3.1.16 that the induction cycle of chemotherapy should only be modified in the event of grade 3 neurotoxicity, grade 2 nephrotoxicity, grade 4 hematologic toxicity, or disease progression.
- Updated Section 6.4.2.1 to clarify that anti-cancer surgery is allowed in HGG patients once investigator has declared progressive disease.
- Updated Section 6.4.3 to remove the reference to dabrafenib concentrations as the prohibited concomitant therapy is for vincristine.
- Updated Tables 7-1 and 7-2 to remove optional CSF sample collection, remove reference to chemotherapy patients as this was moved to Tablet 7-3 for clarity
- Added Table 7-3 in Section 7.1 for LGG chemotherapy patients. Updated protocol throughout with Table 7-3 reference.
- Updated table number throughout Section 7
- Updated Section 7.1.2 to remove exclusion of immunohistochemistry testing for local testing for *BRAF* V600 confirmation.
- [redacted].
- Updated Table 7-7 and Section 7.2.4.3 to remove the optional CSF sample collection
- Updated Section 8.1.3 to combine Cutaneous squamous cell carcinoma (cuSCC), keratoacanthomas, noncutaneous treatment emergent malignancies (excluding cuSCC keratoacanthomas and BCC) and new primary malignant melanoma into one Adverse Event of Special Interest of "New primary/secondary malignancy"
- Updated Section 10.5.3.1 to remove optional CSF sample collection
- Updated Section 10.7.1 to include an additional interim analysis in the HGG cohort to support a health authority request
- Updated Table 14-2 to remove oxcarbazepine from list of prohibited medications during study treatment

[redacted]

## Amendment 3 (07-Aug-2018)

Protocol amendment 3 changed the age range of patients eligible to enroll in the study from ≥6 to <18 years of age to ≥12 months to <18 years of age. This change was possible as the recommended dose for the combination of dabrafenib with trametinib for patients between 12 months and 6 years of age has been determined.

The inclusion and exclusion criteria were also updated to clarify the eligible population for the LGG cohort as patients with *BRAF* V600 mutant LGG, who either have progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression. Further, the exclusion criteria specified that LGG patients who have had any prior systemic anticancer therapy or antitumor radiotherapy are excluded.

In addition, the primary endpoint for the High Grade Glioma cohort was changed from investigator assessment of Overall Response Rate (ORR) to central independent review of ORR. This change may lessen the potential for bias that may be introduced due to investigator assessment in a single arm trial. Investigator assessment of ORR has therefore been added as a secondary endpoint.

## Amendment 2 (23-Feb-2018)

Protocol amendment 2 added a new cohort of *BRAF* V600 mutant Low Grade Glioma children and adolescent patients whose tumor is unresectable and require systemic treatment. Additionally the amendment also added a pediatric formulation of dabrafenib as a dispersible tablet.

The LGG cohort was added to enroll approximately 102 pediatric patients with *BRAF* V600 mutant low grade glioma, randomized 2:1 dabrafenib with trametinib versus carboplatin plus vincristine, with overall response rate (PR+CR) as primary endpoint.

In addition, taste questionnaires for trametinib and dabrafenib pediatric formulations were implemented for all patients who receive the trametinib oral solution and/or dabrafenib oral suspension. The PROMIS Patient Reported Outcome questionnaire was added for the LGG cohort of patients. Sparse PK collection was included for a subset of LGG patients. The specific RANO criteria for LGG were added into Appendix 2.

## Amendment 1 (07-Jun-2017)

Protocol amendment 1 revised the investigational treatment regimen from dabrafenib monotherapy to include trametinib with dabrafenib for children and adolescents with *BRAF* V600 mutation positive relapsed or refractory HGG. Guidance provided to the sponsor by the FDA and CHMP, in addition to updated efficacy data from the ongoing dabrafenib monotherapy study [BRF116013, CDRB436A2102] supported the use of combination treatment in pediatric glioma clinical studies. Safety related changes were also implemented to include:

- Requirement to obtain informed consent/assent for patients who continue treatment beyond progression per RANO criteria.
- Added ophthalmic examinations to follow any visual changes in patients receiving trametinib and dabrafenib combination therapy.

[redacted]

- Updated dose modification guidance for combination treatment.
- Revised cardiac toxicity monitoring and the conditions for re-starting study treatment per FDA advice.
- [redacted]
- Updated the adverse events of special interest pertaining to dabrafenib and trametinib

[redacted]

# 1 Background

## 1.1 Overview of disease pathogenesis, epidemiology and current treatment

### 1.1.1 Pathogenesis

High grade glioma (HGG) typically arises from cells within the glial lineage and are classified by the World Health Organization (WHO) as either grade III or IV meaning that they are highly aggressive tumors with characteristic pathological findings (Louis 2007). HGG include a variety of heterogeneous lesions with differing histologies, the most common being anaplastic astrocytoma (WHO Grade III) and glioblastoma multiforme (GBM; WHO grade IV). There are also less frequently occurring pediatric HGGs of grade III (anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, anaplastic pleomorphic xanthoastrocytoma, and anaplastic pilocytic astrocytoma) and grade IV (giant cell glioblastoma, epitheloid glioblastoma and gliosarcoma).

Low grade glioma (LGG) also represents a diverse group of histologically distinct tumor types, including pilocytic astrocytoma, ganglioglioma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma and others. They are distinguished historically from HGG generally by their lower apparent mitotic rates (Louis 2016, Lassaletta 2017).

### 1.1.2 Epidemiology

HGGs are rare tumors in the pediatric population, and comprise approximately 8–12% of all primary, pediatric central nervous system (CNS) tumors (Bondy 2008; Broniscer 2006). Among patients 0–19 years old in the USA, the overall total incidence of HGGs (including anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, mixed glioma, and malignant glioma) was approximately 0.85 per 100,000 (CBTRUS 2012). Similar incidence estimates for pediatric HGG have been reported from the German Childhood Cancer Registry (Kaatsch 2001). Thus, approximately 350-400 new cases of pediatric HGG are diagnosed in Europe yearly (EMA 2011). Grade III tumors are believed to have a more favorable natural history than grade IV tumors but the impact of tumor grade on prognosis is relatively minor. Thus for the purposes of clinical trials there has been expert consensus that grade III and IV tumors should be studied together (EMA 2011).

Although LGGs are also rare pediatric tumor types, they are approximately 2 times as common (incidence 1.68 cases per 100,000) as HGG (CBTRUS 2015). This is a heterogeneous group of tumors in children with different locations, histologic subtypes, ages at presentation, and clinical behavior. Pilocytic astrocytoma is the most common histologic subtype. Evolving molecular characterization of this group of tumors reveals most will have only a small number of mutations, and these mutations often converge on the activation of the RAS/MAPK pathway (Lassaletta 2017).

[redacted]

### 1.1.3 Current Treatments and Unmet Medical Need

#### 1.1.3.1 High Grade Glioma

Current therapies for children with HGGs are limited. The current standard of care for newly diagnosed children is gross total surgical resection, followed by focal irradiation to the tumor bed plus additional chemotherapy (MacDonald 2011). Independent of other known prognostic factors such as age, tumor location and histology, the extent of surgical resection is one of the strongest predictors of survival in children with HGG (Finlay 1995; Jones 2012). Given the infiltrative nature of HGGs, there is high likelihood of local recurrence. Thus for older children (>3 years of age), adjuvant radiotherapy to the tumor bed and surrounding margin has become a standard. Multi-agent chemotherapy is routinely used in conjunction with radiotherapy to treat children with newly diagnosed HGGs. However, while a number of trials have explored the use of varying agents and schedules, the toxicity is burdensome, results are contradictory and the exact role of chemotherapy and the true survival benefit are disputed (Fangusaro 2012; Broniscer 2004; Finlay 2005; EMA 2011). Among younger patients (<3 years of age), radiotherapy is generally not used due to its substantial neurocognitive toxicity. These patients are often treated with radiation sparing approaches such as chemotherapy alone (Broniscer 2004). Multiple trials have also been conducted in pediatric patients with HGGs utilizing biologic agents in combination with focal radiotherapy, but none have demonstrated a benefit in overall survival (OS) (MacDonald 2011).

Long-term outcomes for patients with pediatric HGGs are poor despite aggressive multimodality therapy and improvements in neurosurgery, radiotherapy, and chemotherapy. After a new diagnosis of HGG, the median duration of survival is approximately 18-24 months in children (Qaddoumi 2009; EMA 2011). Five-year survival outcomes range from 10 to 35% with the large majority of children ultimately succumbing to their disease (Broniscer 2004; Finlay 2005; Broniscer 2006; Cohen 2011; Wolff 2010). The majority of patients do develop recurrent disease and in these cases the therapeutic options are limited, with very few treatment options providing clinically meaningful responses. Temozolomide is most often used in the recurrent disease setting. However, in 5 trials evaluating temozolomide monotherapy or temozolomide-based combinations, the RR in recurrent or refractory, pediatric HGG ranged from 0-12% (Lashford 2002; Nicholson 2007; Ruggiero 2006; Warren 2012; Hummel 2013). A variety of targeted agents have also been evaluated in this patient population and response rates have been noted to be less than 10%. Given the lack of clinically meaningful activity, there have been no targeted agents that have been approved for patients with pediatric HGG. Due to the lack of an efficacious standard of care, participation in clinical trials is highly encouraged for these patients.

One approach to recurrent disease has been the use of high dose chemotherapy followed by autologous hematopoietic stem cell rescue. This is still considered very controversial, but there may be a role for this strategy in a specific group of children (Guruangan 1998; Finlay 2008; Massimino 2010). The limitations of this strategy are significant treatment-related morbidity, and the fact that despite these risks, a minority of patients with HGG have long term survival. Studies of rational chemotherapy combinations and targeted agents in this disease setting have also failed to show clinical activity in pediatric HGG patients and emphasise the poor outcomes for this patient population. Given that refractory or recurrent pediatric HGG is a rare tumor type,

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there is no robust and reliable prospective study to describe the natural history in a large population.

A comprehensive literature review was performed by GSK/Novartis for trials that treated a minimum of 5 pediatric patients with recurrent or refractory HGG (Table 1-1). Trials that included myeloablative therapy with stem cell rescue were excluded from this review. Trials that did not specify low vs. high grade glioma were also excluded. Limitations of all the trials were limited sample size, non-randomized design, limited efficacy endpoints (response but no duration of response or time to event endpoint data) and a likely selection bias. It is also unclear how these results apply to pediatric HGG patients harbouring a *BRAF* V600 mutation as the predictive and prognostic effect of this mutation in this particular disease is unknown. These data demonstrate that for both chemotherapy and/or targeted agents, the response rate to second line therapy is typically <10%. To supplement the limited data available in the literature, GSK has sought the insight of clinicians with expertise in pediatric neuro-oncology. These consultants estimate that pediatric HGG patients who have failed frontline therapy have response rate of 10-12% to second line temozolomide therapy. Given the low response rates, they felt that there is no true standard of care in this setting.

**Table 1-1 Efficacy Outcomes in Trials for Relapsed, Refractory Pediatric HGG**

| Agent | n | RR (%) | mPFS (m) | 6m PFS (%) | OS (m) | Reference |
|---|---|---|---|---|---|---|
| Irinotecan | 5[e] | 3 (60) | NR | NR | NR | Turner 2002 |
| Paclitaxel | 13[e] | 1 (8) | NR | NR | NR | Hurwitz 2001 |
| Carboplatin | 15[e] | 0 (0) | NR | NR | NR | Gaynon 1990 |
| Etoposide | 14[e] | 3 (21) | NR | NR | NR | Chamberlain 1997 |
| Erlotinib | 29 | 0 (0) | 1.5 | 34 | 4.1 | Geoerger 2011 |
| Nimotuzumab | 46 | 4 (9) | NR | NR | 4.4 | Bode 2007 |
| Imatinib | 40 | 0 (0) | NR | 17.9-18.2[b] | NR | Pollack 2007 |
| Bevacizumab + Irinotecan | 15 | 0 (0) | 4.2 | 41.8 | | Guruangan 2010 |
| Cilengitide | 24 | 0 (0) | 0.92[c] | NR | NR | MacDonald 2013 |
| Temsirolimus | 6 | 0 (0) | 2[a] | 38%[a,d] | NR | Geoerger 2012 |
| Tipifarnib | 31 | 1 (3) | NR | NR | NR | Fouladi 2007 |
| Temozolomide | 25 | 3 (12) | NR | NR | 4.7 | Lashford 2002 |
| Temozolomide | 23 | 1 (4) | NR | NR | NR | Nicholson 2007 |
| Temozolomide | 24 | 0 (0) | 3 | NR | NR | Ruggiero 2006 |
| O6-Benzylguanine +Temozolomide | 25 | 1 (4) | 1.7 | 16 | NR | Warren 2012 |
| Temozolomide +Vorinostat | 7 | 0 (0) | NR | NR | NR | Hummel 2013 |
| Lobradimil + carboplatin | 9 | 0 (0) | 2.6[c] | NR | NR | Warren 2006 |
| Poly-ICLC | 12 | 1 (8) | NR | NR | NR | Hartman 2014 |

a. Includes patients with HGG and diffuse pontine intrinsic glioma
b. Six month event free survival
c. Median time to progression
d. mPFS at 12 weeks
e. Trial accrued patients with refractory brain tumors of various types. The results reported are those for recurrent, pediatric HGG

[redacted]

The European Medicines Agency (EMA) hosted a pediatric research expert meeting in 2011 that focused on current pediatric HGG treatment modalities and research. The outcomes highlighted the inadequacy of current treatment options, and suggested that pediatric patients with relapsed, refractory, and or resistant HGGs should consider experimental treatments available in clinical trials. The committee minutes indicate agreement that outcomes in pediatric patients with HGG are generally very unfavourable with the different multi-agent chemotherapy regimens in current use, often with burdensome toxicity and limited benefit. For children, only one anticancer substance, temozolomide, is currently authorized in some jurisdictions (i.e. European Union, EU) specifically for HGG (for use in relapsed or progressive disease). Although it is used in children based on adult efficacy data, its benefit in children is considered modest at best. Overall, the treatment of children with HGG reflects a significant unmet need, with almost no improvement in survival outcomes in recent years (EMA 2011).

The role of *BRAF* V600 mutation in the clinical behaviour of pediatric HGG has been studied in a large retrospective analysis of patients with available tumor tissue and known clinical course (Korsunov 2015). Of the 202 patients with histological classification of pediatric HGG, 21 of the tumors were *BRAF* V600 mutant. Using the pattern of DNA methylation to further characterize these tumors, forty of the 202 tumors were identified to have a 'low grade glioma' methylation signature and an improved clinical outcome (PFS, OS). Seventeen of the 21 *BRAF* V600 mutant tumors were also classified as 'low grade glioma methylation signature' and thus associated with a more favourable prognosis. A univariate evaluation of the patient specific data from this report reveals no apparent difference in PFS for tumors with *BRAF* V600 mutation relative to *BRAF* wildtype, while the OS of patients with the mutation appears favourable. The public data from this analysis does not include information on response to standard treatment in the second line setting. Nonetheless, the data do suggest that pediatric patients with *BRAF* V600 mutant HGG may be more likely respond to conventional therapy in the second line setting, as their time to first progression is similar to patients with *BRAF* V600 wild type tumors, yet their OS is distinctly longer. In a recent analysis of anaplastic ganglioglioma, a subtype of HGG, in both pediatric and adult patients, the *BRAF* V600 mutation does not appear to have prognostic significance, while other histologic and molecular features were identified with potential prognostic significance (Zanello 2016). The *BRAF* V600 mutation was detected in 4 of 5 (80%) of the pediatric tumor specimens and 9 of 18 adult tumor specimens (50%).

This study will evaluate the ORR (CR+PR) in patients with relapsed or refractory *BRAF* V600 mutant HGG.

#### 1.1.3.2 Low Grade Glioma

Unlike patients with HGG, patients with LGG typically have a more protracted natural history. For unselected pediatric patients with LGG who could not be cured by surgical resection and enrolled into studies of cytotoxic chemotherapy, the 5 year PFS was 46% and OS was 89% (Gnekow 2017). Treatment goals generally are to prolong overall and progression free survival while minimizing morbidity of treatment. Surgical removal, when practical, is often the treatment of choice. The extent of resection is predictive of progression free interval. Most patients will eventually experience progression of their disease and require post-surgical therapy. Because of the typical young age of pediatric LGG patients, and the potential for long term neurocognitive effects of radiotherapy, post-surgical therapy often includes chemotherapy

[redacted]

with carboplatin and vincristine. In one large study, the ORR (CR+PR) by central review was 35% (Ater 2012) in unselected patients with LGG requiring post-operative systemic therapy with carboplatin and vincristine.

The *BRAF* V600 mutation is identified in about 17% of pediatric LGG tumors (Lassaletta 2017). The role of *BRAF* V600 mutation in the clinical course of pediatric LGG has recently been described. First, patients with LGG who have progressed to secondary HGG (sHGG) are more likely to have had *BRAF* V600 mutation in their LGG at initial diagnosis (Mistry 2015), and thus suggestive of a poor prognosis. More recently, the molecular profile of archived diagnostic tumor tissues has been coupled with clinical outcomes of patients treated with standard of care. This analysis revealed that those patients whose tumor harbored the *BRAF* V600 mutation had worse PFS and OS (Lassaleta 2017) than those with tumors with wild type sequence at *BRAF* V600. This research also revealed a lower ORR for these patients when treated with chemotherapy with apparent 11% PR+CR rate. In both analyses, there was evidence of poorer outcomes when deletion of CDKN2A was coupled with the *BRAF* V600 mutation (Mistry 2015, Lassaletta 2017, Jones 2017)).

Pediatric patients with LGG harboring a *BRAF* V600 mutation have a poorer prognosis than those without this mutation, and require improved treatment options.

## 1.2 Introduction to investigational treatment(s) and other study treatment(s)

### 1.2.1 Overview of Dabrafenib

Dabrafenib is a potent and selective inhibitor of *BRAF* kinase (a member of the RAF kinases) with a mode of action consistent with adenosine triphosphate-competitive inhibition. Dabrafenib suppresses ERK [pERK] that is downstream of *BRAF* in the MAPK pathway and demonstrated anti-proliferative activity against multiple *BRAF* V600 mutation-positive tumor cell lines, and tumor regression in *BRAF* mutation positive xenograft models, and has demonstrated significant anti-tumor efficacy in *BRAF* V600-mutation positive tumors, including melanoma, and non-small cell lung cancer.

Dabrafenib (Tafinlar®) was first approved by the FDA on 29 May 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with the *BRAF* V600E mutation. Tafinlar® is currently also approved in the, EU, Switzerland, Canada, Australia and multiple other countries for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation. Prior to initiation of dabrafenib patients must have confirmation of tumor *BRAF* V600 mutation. These approvals include the following limitation of use: dabrafenib is not indicated for the treatment of wild-type *BRAF* melanoma. The recommended dose of dabrafenib is 150 mg (two 75 mg capsules) BID (corresponding to a total daily dose of 300 mg). Dabrafenib in combination with trametinib is also approved in the US and EU for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a *BRAF* V600 mutation.

#### 1.2.1.1 Non-clinical experience

The toxicologic effects following administration of dabrafenib to rats, mice and/or dogs were noted in skin, heart, vasculature, testes, epithelium, hematologic/lymphoid tissues, liver,

[redacted]

gastrointestinal and respiratory tract. The principal dose-limiting toxicity in animals was adverse gastrointestinal effects, which can be clinically monitored. Aside from mild to moderate increases in heart rate, there were no significant findings in safety pharmacology studies in animals evaluating the cardiovascular and respiratory systems and in a general behavioral study conducted with dabrafenib. In a dabrafenib and trametinib 4-week combination study in dogs, there were no significant new findings or exacerbations of toxicities previously observed with either agent alone. Details of non-clinical experience can be found in the [Dabrafenib Investigators Brochure].

In support of clinical development in pediatric cancer patients, toxicity studies in juvenile rats with dabrafenib were conducted. These studies included an oral tolerability/dose range juvenile toxicity study, a GLP juvenile toxicity study, and an oral investigative renal study. Key findings from these studies are presented below. No further nonclinical studies are planned.

### Renal Effects

Renal toxicity was observed primarily in pre-weaning juvenile rats (PND 7-21) which was not previously observed in adult rats, dogs or mice. Renal findings were partially reversible following a 6-week off-drug period and were consistent with an obstructive nephropathy characterised by tubular deposits, increased incidence of cortical cysts and tubular basophilia with reversible increases in serum urea and/or creatinine concentrations. The renal tubular deposits were found to contain calcium, phosphate, potassium and lipids; dabrafenib-related material was not present in the deposits. These effects were seen in juvenile rats at a renal functional maturity stage similar to a 6 to 12 month old human, suggesting a higher risk for tubular injury for human infants <1 years of age. Monitoring for potential renal effects will be performed in pediatric patients by monitoring of serum creatinine evaluations and urinalysis. Patients in clinical studies [BRF116013, CDRB436A2102] (Phase I/IIa) and [BRF116536, CDRB436G2201] (Phase II) must be ≥1 year old to participate.

### Constitutional and Developmental Effects

In juvenile rat toxicity studies of dabrafenib monotherapy, there were dose-dependent decreases in body weight and/or gain, food consumption and long bone growth. These changes in bone growth were likely related to overall growth of the animal and not due to a bone specific effect of dabrafenib. Pediatric patients will be monitored for potential effects on body weight and growth through physical examination including routine monitoring of height and weight.

### Fertility In testes

Testicular toxicity in the seminiferous tubules was observed with evidence of partial recovery after a 12-week recovery period in rats, suggesting a potential human risk for impaired spermatogenesis, which may be irreversible.

### Non-clinical pharmacokinetics and metabolism

Dabrafenib induces CYP3A4- and CYP2C9- mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19 and UDP glucuronosyltransferases (UGT). Dabrafenib may also induce transporters (e.g. P-glycoprotein (P-gp)). In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to

[redacted]

32 times the control levels and was shown to be an inducer of CYP3A4 and CYP2C9 *in vivo*. Human liver microsome studies suggest that CYP2C8 and CYP3A4 are the primary CYP enzymes involved in the oxidative metabolism of dabrafenib *in vitro* while its metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates.

Dabrafenib is a highly permeable molecule which distributes widely into tissues and is mostly eliminated by 3 days post administration. No brain penetration of drug-related material was observed after a single dose in rats and pigs (repeat dose studies were not conducted in these species); however, following repeat dosing in mice, low levels of dabrafenib may reside in the cerebro spinal fluid.

For more details please refer to the latest [Dabrafenib Investigator Brochure].

#### 1.2.1.2 Clinical experience

As of 22 June 2017, approximately 10,000 patients, primarily with *BRAF* V600-mutated cancer, have received dabrafenib alone or in combination with trametinib across the clinical development program. Cumulative postmarketing exposure to dabrafenib through 31 March 2015 is estimated to be 3,546.16 patient-years. The estimated exposure from June 2015 to June 2016 was approximately 5204.45 patient-years [Dabrafenib Investigator Brochure].

Updated safety data from an integrated safety population (N=586) receiving 150 mg BID showed that 97% had experienced AEs, the most common (≥20%) being hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, alopecia, skin papilloma, and rash. A total of 174 (30%) patients experienced serious adverse events (SAE), and 114 (19%) patients had treatment-related SAEs. The proportion of patients who experienced AEs leading to discontinuation of study treatment was low (3%).

In the pivotal Phase III study [BRF113683, BREAK-3, CDRB436A2301], dabrafenib was associated with a 70% reduction in the risk of progression or death compared with dacarbazine with a hazard ratio (HR) of 0.30 (95% CI: 0.18, 0.51; p<0.0001) in patients with *BRAF* V600E mutation positive melanoma and no brain metastases (Hauschild 2012). Dabrafenib provided a clear and meaningful benefit in patients with *BRAF* V600E mutation-positive melanoma with brain metastases as demonstrated by overall intracranial response rate (OIRR) over 30% and median OS exceeding 7 months in study [BRF113929, BREAK-MB]. Patients with *BRAF* V600E mutation positive melanoma also benefit from dabrafenib treatment, with a confirmed response rate of 13% and the median duration of response of 5.3 months [BRF113710, BREAK-2, CDRB436A2201]. For the latest summarized efficacy results for these studies, please refer to the Dabrafenib approved local prescribing information and [Dabrafenib Investigator Brochure].

##### 1.2.1.2.1 Dabrafenib pediatric experience

A Phase I clinical trial of dabrafenib is ongoing in children with *BRAF* V600 mutant solid tumors [BRF116013, CDRB436A2102].

Eighty patients have been enrolled into study [BRF116013, CDRB436A2102] beginning in April 2013 through the interim data cut off 12-Sept-2017; 27 into part 1 dose finding across 4 dose levels, and 53 into part 2 (disease specific cohort expansions) at the recommended phase 2 dose. Thirty-two patients with relapsed refractory LGG, 31 with relapsed refractory HGG,

[redacted]

13 with advanced Langerhans Cell Histiocytosis (LCH) and 4 other solid tumor patients were enrolled into the various parts of the study.

Part 1 patients had a median age of 8 years, while part 2 patients had a median age of 11 years. All were previously treated for their tumor. Similar to the experience in adults, a maximally tolerated dose was not identified in this study. Based on the doses in part 1 that achieved target exposures (median AUCs 0-12 hours > 4000 ng*hr/mL, parent molecule), there are currently separate phase II dose recommendations for those under 12 years of age (5.25mg/kg/day), and those 12 and older (4.5mg/kg/day).

At the time of interim data cutoff, 45 of the 80 patients remained on study (56%), with 35 still on protocol therapy (44%).

Efficacy for glioma patients was determined using RANO criteria by investigators, as well as by an independent pediatric neuro-radiologist. Independent expert histopathology review of tumor specimens from the patients enrolled with presumed HGG was performed in all cases where tissue was available. Safety monitoring included standard clinical trial methods, as well as routine echocardiograms and dermatologic exams.

### Efficacy Results

### High Grade Glioma

Of the 31 enrolled HGG patients, 10 (32%) had investigator confirmed responses (CR + PR) following dabrafenib monotherapy. Independent radiologic determination of RANO response identified 14 patients (45%) with confirmed responses (CR+PR). Median duration of treatment was 24 weeks, and median duration of response was 33 weeks. Independent histopathology revealed that 7 of the 31 patients (23%) had grade 1 or 2 gliomas in the submitted tumor specimen. Four additional patients did not have sufficient tissue submitted to make any determination of glioma grade. The therapy has been generally well tolerated and adverse events easily managed.

### Low Grade Glioma

At the time of interim analysis, 32 pediatric patients with relapsed, refractory or progressive LGG with *BRAF* V600 mutations were enrolled into [BRF116013, CDRB436A2102]. Of these, there was one independently confirmed CR, and 13 PRs for an ORR of 14/32 or 44%. In addition, 11 patients had independently confirmed SD. Median duration of treatment was 24 months. Median duration of independently confirmed response was 110 weeks.

### Langerhans Cell Histiocytosis

At the time of interim analysis, 13 pediatric patients with previously treated severe LCH and *BRAF* V600 mutations were enrolled into [BRF116013, CDRB436A2102]. Investigator assessed responses were 5 complete resolutions, and 5 regressions. Median duration of treatment was 76 weeks. Nine patients remain in response.

### Other solid tumors

Four patients with other solid tumors and *BRAF* V600 mutations were enrolled; three discontinued within 16 weeks of enrollment (2 with Neuroblastoma, another with a sarcoma).

[redacted]

One patient with *BRAF* V600 mutant papillary thyroid cancer has stable disease and continues therapy at almost 4 years.

## Safety Results

### Adverse events

The four most common AEs occurring in pediatric patients with advanced *BRAF* V600 mutation positive solid tumors treated with dabrafenib were pyrexia, vomiting, fatigue and rash.

### Serious Adverse Events

As of the clinical cut-off date for [BRF116013, CDRB436A2102], a single fatal SAE of depressed level of consciousness was reported in one subject at 5.25 mg/kg/day dose in Part 1. This event was associated with disease progression, and was considered not related to study drug.

At the time of the interim analysis, 31 of the 80 enrolled patients (39%) were reported to have SAEs. The most common SAEs were pyrexia (11), pneumonia (4) and headache (4); all other SAEs occurred in one or two patients.

### Dose limiting toxicity

There was one patient with LGG (10 years old at 4.5 mg/kg/d dose) who experienced a dose limiting toxicity (DLT) of Grade 3 maculopapular rash with onset on day 1 of dosing. After protocol specified dose interruption, the patient was able to resume treatment at 3.75 mg/kg/day and continues on treatment beyond one year, with tolerable skin toxicity of grade ≤2.

### Dose modifications

Forty four of the 80 patients (55%) had at least one dose interruption due to AEs while on study.

### Discontinuations for toxicity

At the time of interim analysis, 6 patients had been withdrawn from study for toxicity.

### Safety Conclusions

Based on the interim analysis of the dabrafenib monotherapy study, the toxicity profile observed in pediatric patients is generally similar to that observed in the adult patient experience. Both populations experienced frequent rash, pyrexia, fatigue, arthralgia and headache. The frequency of rash and related adverse events may be higher in this pediatric population than in adults. There were three patients (4%) with grade 3 rash in the pediatric study, while there were no patients with Grade ≥3 rash in the integrated safety population (n=586) in adults. Rash management guidelines suggested in the protocol were followed for patients with rash as they remained on therapy. There were no cases of cutaneous SCC observed in these pediatric patients. The most common AEs according to the system organ class was skin. Adequate exposures were obtained without reaching a maximally tolerated dose.

[redacted]

### 1.2.1.3 Pharmacokinetics - Dabrafenib

In adults following oral administration of dabrafenib HPMC capsules, the plasma concentrations of dabrafenib peaked approximately 2 hours post-dose and decreased thereafter following a bi-exponential decline. The terminal half-life (t1/2) is 8.4 hours, mainly due to a prolonged terminal phase after oral administration. The t1/2 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, the AUC on Day 18 was 27% lower than on Day 1. Following administration of 150 mg BID (HPMC capsules), the geometric mean Cmax, AUC(0-τ) and predose concentration (Cτ) were 1478 ng/mL, 4341 ng*hr/mL and 26.1 ng/mL, respectively. Interpatient variability was 37- 38% for Cmax and AUC(0-τ) and 119% for Cτ. Administration of dabrafenib with food reduced the bioavailability ($C_{max}$ and AUC decreased by 51 % and 31 % respectively) and delayed the absorption of dabrafenib capsules when compared to the fasted state. Dabrafenib should be taken either at least one hour before, or at least two hours after a meal.

The relative bioavailability of single dose dabrafenib was slightly lower (AUC decreased by 20%) when administered as an oral suspension (dispersible tablets) compared to HPMC capsules. 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.

Results of a population pharmacokinetic analysis in adults 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 patients 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 patient 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 patient. 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 exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely to be significant.

[redacted]

Preliminary pharmacokinetic results from study BRF116013 (CDRB436A2102) in pediatric patients are summarized in Table 1-2 as doses of 3, 3.75, 4.5 and 5.25 mg/kg/day (divided into two daily doses) based on the data cut-off date of 7 March 2015.

Results from Table 1-2 show that median plasma AUC achieved its target (between 95%CI: 3599, 5235 ng*h/mL, which is from the adult Phase III study BRF113683) in older pediatric patients (> 12 years) at 4.5 mg/kg/day dose level. In younger patients (≤ 12 years), target median was achieved at 5.25 mg/kg/day, while the median observed at 4.5 mg/kg/day was below the target. These results were used to determine the recommended part 2 dose (s) in BRF116013.

Since Part 2 dose selection, an interim analysis was performed based on a data cut-off of 01-April-2016. Results from Table 1-3 show that for patients 6 years and greater after administration of the dosing regimen selected in Part 1: the geometric mean AUC(0-tau) in Part 2 are within the exposure range associated with efficacy in adults when given as monotherapy (BRF113683) and in combination therapy with trametinib (BRF113220 and MEK115306).

**Table 1-2 Median Steady-State Dabrafenib AUC (ng*h/mL) (day 15) by Dose and Age Cohorts**

| | Dabrafenib dose cohort (total daily dose) | | | |
|---|---|---|---|---|
| **Age cohort** | **3 mg/kg/day** | **3.75 mg/kg/day** | **4.5 mg/kg/day** | **5.25 mg/kg/day** |
| All AUC, ng*h/mL (n) | 2911 (3) | 3389 (10) | 3903 (9) | 4384 (5) |
| ≤ 12 years | 2269 (2) | 2928 (4) | 3592 (6) | 4384 (5) |
| >12 years | 6604 (1) | 3850 (6) | 5285 (3) | NA |

**Table 1-3 Geometric mean Steady-State Dabrafenib AUC(ng*h/mL) (day 15) by Age groups for Part 2**

| Age Range | Dose | N | AUC(0-tau)* (ng*hr/mL) |
|---|---|---|---|
| 12-17 years | 4.5 mg/kg/day | 15 | 3979 |
| 6-<12 years | 5.25 mg/kg/day | 8 | 3972 |

In study [MEK116540, CTMT212X2101], four pediatric patients were dosed with the recommended dabrafenib doses from study BRF116013 and the recommended dose for trametinib (from Part A MEK116540) in combination. Preliminary PK was available in 3 subjects; dabrafenib Day 15 AUC(0-tau) values (3490, 4339, 3570 ng*hr/mL) were within the range observed in the pediatric patients from the dabrafenib monotherapy study BRF116013.

### 1.2.2 Overview of Trametinib

Trametinib (GSK1120212/TMT212) is a MEK1 and MEK2 inhibitor with selective anti-proliferative activity towards *BRAF* and RAS mutant cancer cell lines and hematopoietic cancer cells from acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) origins. Trametinib inhibited the proliferation of most *BRAF* mutant melanoma cell lines tested (22 of 25) and it effectively inhibited the growth of *BRAF* mutant melanoma xenografts in vivo alone or in combination with dabrafenib. Trametinib inhibits ERK phosphorylation leading to G1 cell cycle arrest and tumor xenograft growth inhibition in vivo following oral dosing. The effects of trametinib in combination with dabrafenib and other anticancer agents have also been studied in a variety of human cancer cell lines and in vivo models.

[redacted]

Trametinib is being developed for the treatment of a variety of cancers and is currently approved:

- In the United States, EU, and other countries as a monotherapy and in combination with dabrafenib for the treatment of subjects with unresectable or metastatic melanoma with a BRAF V600 mutation
- In the United States and other countries in combination with dabrafenib for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection
- In the United States, and EU in combination with dabrafenib for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation
- In the United States in combination with dabrafenib for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation and with no satisfactory locoregional treatment options

Please refer to local labeling for further details on approved indications.

#### 1.2.2.1 Non-clinical experience

The nonclinical toxicology findings associated with trametinib administration to mice, rats and dogs are consistent with pharmacologically mediated changes as a result of MEK1/MEK2 inhibition and disruption of mitogen-activated protein kinase (MAPK) signaling pathways. Trametinib caused adverse effects in a variety of tissues and systems (skin, gastrointestinal tract, phosphate homeostasis, liver, ovary, bone and hematological tissues). The majority of the findings in mice and dogs appeared to be related to effects within the gastrointestinal tract. In rats, tolerability was more dependent on changes occurring in skin over time and its effect on impaired barrier function. These findings may be related to those seen in the clinic in the form of skin rashes and diarrhea. Rats were more sensitive to trametinib, with liver, phosphate homeostasis, soft tissue mineralization, bone, hematopoietic and ovary effects. In a dabrafenib and trametinib 4 week combination study in dogs, there were no significant new findings or exacerbations of toxicities previously observed with either agent alone.

Trametinib may impair female fertility based on the reduction of corpora lutea in rats. There were no effects on male reproductive organs in toxicology studies in rats or dogs, indicating that trametinib is unlikely to affect male fertility. In embryo fetal development studies, maternal toxicity and developmental toxicity, including total loss of pregnancy and post-implantation loss, were observed in rats and/or rabbits.

The principal effects of trametinib in juvenile rats were on growth (bodyweight and long bone length) and in bone, phosphate homeostasis, eye, skin, liver, heart and female reproductive system effects, consisting of a delay in a physical landmark of sexual maturity and mammary gland development, lower corpora lutea and lower ovarian weights. With the exception of corneal mineralization/dystrophy and increased heart weight, similar effects have been observed in adult animals given trametinib.

The genotoxicity assessments conducted indicate that trametinib does not present a genotoxic hazard to humans.

Trametinib was phototoxic in the in vitro mouse fibroblast 3T3-Neutral Red Uptake (3T3-NRU) assay at significantly higher concentrations than clinical exposures.

[redacted]

The principal dose limiting nonclinical toxicology findings associated with trametinib treatment were either directly or indirectly associated with its pharmacologic activity. Administration of trametinib to mice, rats and dogs produced dose-dependent effects related to inhibition of cell proliferation in tissues with high proliferative rates including hematopoietic, gastrointestinal and integument systems. These findings are associated with inhibitory pharmacology due to the role of the MAPK pathway in cellular proliferation (Sebolt-Leopold 2000). In mice, rats and dogs, these effects generally occurred at or below the exposures achieved at the oral therapeutic dose of 2 mg/day in cancer patients. Other findings include effects on phosphate homeostasis and soft tissue mineralization, liver, bone, ovary and the developing embryo or fetus.

#### 1.2.2.2 Clinical experience

As of 22-Jun-2017, approximately 1632 patients have been treated with trametinib monotherapy across 25 clinical studies.

Data from a Phase I, II and III studies indicate substantial clinical activity of trametinib in unresectable, *BRAF* mutation positive melanoma. Efficacy results from the pivotal Phase III study MEK114267 (CTMT212A2301) (melanoma) study and the supporting studies MEK113583 (melanoma), MEK111054 (solid tumors or lymphoma), and MEK114653 (NSCLC) indicated:

- Substantial evidence of effectiveness in unresectable *BRAF* V600 mutation positive melanoma as evidenced by prolongation of progression-free survival (PFS) and overall survival (OS). Updated long term results from MEK114267 (CTMT212A2301) study also consolidated the OS benefit of trametinib treatment over chemotherapy in this patient population.
- The clinical activity of trametinib observed in melanoma subjects whose tumors harbor *BRAF* V600K mutations is comparable to the activity seen in *BRAF* V600E mutations.
- The efficacy of trametinib in melanoma was evident across all demographic (i.e., age, gender) and prognostic factors (i.e., tumor stage, Eastern Cooperative Oncology Group Performance Status [ECOG PS], lactate dehydrogenase (LDH) levels, history of brain metastases).

In the 11 monotherapy studies of trametinib for which data are available, 50% to 100% of all subjects in any dose group had at least 1 AE, and 0% to 70% of all subjects in any dose group had at least 1 serious adverse event (SAE). Of the studies with discontinuations or withdrawals, 3% to 26% of subjects receiving trametinib permanently discontinued study treatment or withdrew due to AEs.

In the 2.0 mg dose group across all completed monotherapy studies with AEs, the most common AEs were rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin.

For more details please refer to the latest [Trametinib Investigator Brochure].

##### 1.2.2.2.1 Trametinib pediatric experience

Study [MEK116540, CTMT212X2101] is an ongoing study of trametinib monotherapy, including dose finding, age specific cohort expansions, disease specific cohort expansions, as

[redacted]

well as combination dabrafenib and trametinib dose finding and disease specific cohort expansions.

The recommended phase 2 dose (RP2D) for trametinib monotherapy is 0.025 mg/kg/day (not to exceed adult dose) for patients 6 years old and above and is equivalent to the 2 mg/day dose for an average 80 kg adult. This dose was the highest tolerated dose tested in this age group, with 0.04mg/kg/day dosing resulting in unacceptable skin toxicity across each age category. Twelve patients under 6 years of age were treated with an intermediate dose of 0.032 mg/kg/day to determine tolerability and in an effort to achieve suitable exposures in this age group. Preliminary data are available. During the 28 day dose limiting toxicity (DLT) period, there were no DLTs, no dose adjustments, and no SAEs. Interruption of dosing due to adverse events occurred in 2 patients, each after about 25 weeks of treatment.

The RP2D for the combination of dabrafenib with trametinib is 100% of dabrafenib with 100% of trametinib. Evaluation of the combination in patients under 6 years of age (N=3, July 2018) reveals that 100% of each monotherapy dose is tolerated, with no DLTs, dose adjustments, nor SAEs reported in this group.

Results from an interim analysis with data cutoff date of 19-Sept-2017 are available. From January 2015 to the data cutoff date, 90 patients have enrolled into this multipart study. Forty patients enrolled into part A across 4 trametinib monotherapy dose levels. Thirty eight patients enrolled into part B disease specific cohorts (Part B1, Neuroblastoma; part B2, LGG with fusion; Part B3, NF1 with plexiform neurofibromas (NF1 with PN); and part B4, solid tumors with *BRAF* V600 mutation – all of which had LGG) and were treated with the RP2D of trametinib monotherapy. In addition, 12 patients were enrolled into two dose level cohorts of combination therapy, dabrafenib (50% of RP2D (n=3) or 100% of RP2D (n=9)) combined with trametinib (100% of RP2D). Across parts A and B, there were 26 patients with NF1 and PN, 23 patients known to have LGG with *BRAF* fusion, 12 known to have LGG with *BRAF* V600 mutation, and 9 with neuroblastoma. All were previously treated for their tumor. At the time of interim data cutoff, 55 of the 90 patients (61%) were still on protocol therapy.

Efficacy for glioma patients was determined using RANO criteria by investigators, as well as by an independent pediatric neuro-radiologist. Efficacy for NF1 patients with PN was reported by investigators as RECIST, the volumetric approach, or both. Independent determination of efficacy using the volumetric approach was also reported. Safety monitoring included standard clinical trial methods, as well as routine echocardiograms, ophthalmologic exams, and dermatologic exams.

### Neurofibromatosis 1 with plexiform neurofibromas (NF1 with PN)

There were 26 patients with NF1 with PN enrolled into several dose levels in part A and at RP2D in part B. Independent response determination using the volumetric approach yielded 12 partial responses (46%), 9 SD and 1 PD, and 4 unknown or too soon to determine. At the time of data cutoff, 20 of 27 patients remained on treatment with a median duration of 61 weeks.

### Low Grade Glioma with *BRAF* fusion

There were 23 patients with LGG and a known fusion involving the *BRAF* gene, across parts A and B. At data cutoff, 15 (65%) patients remained on treatment with minimum follow up of at

[redacted]

least one year. Independent response determination was performed using RANO. One patient (4%) had confirmed PR as best response, 18 (78%) had stable disease and four were not evaluable. None had a best response of progressive disease.

### Low Grade Glioma with *BRAF* V600 mutation

There were 12 patients with LGG and known *BRAF* V600 mutation, across parts A and B. Independent response determination was performed using RANO. Two patients (17%) had confirmed PR as best response, 6 (50%) had SD, while 4 (33%) had PD within 16 weeks' time.

### Neuroblastoma

There were 9 patients with neuroblastoma enrolled. One has remained on treatment beyond one year; the others have withdrawn from treatment within three months' time.

### Trametinib monotherapy

Adverse events occurring at the RP2D can be described among the 38 patients from part B disease cohort expansion. The median duration of treatment is 55 weeks with 26 (68%) still on treatment. The most common AEs experienced with trametinib monotherapy from part B on this study have been diarrhea 53%, dry skin 42%, pyrexia 40%, anemia (37%), vomiting (34%), alopecia (32%), and paronychia (32%). Treatment related AEs leading to discontinuation occurred in 5 (13%) patients; 14 (37%) patients required some dose adjustment or interruption for AEs. Five patients experienced at least one treatment related serious adverse event, with no event reported more than once. There were no on-study deaths. Adverse events of special interest were collected, regardless of study drug relationship. Thirty-one (82%) patients had skin related toxicity, 20 (53%) had diarrhea, 15 (40%) had pyrexia, 13 (34%) had hepatic events, 12 (32%) had hypersensitivity, and 11 (29%) had bleeding events. 4 (11%) patients had ocular events. All but 2 events were grade 2 or less (one each of hepatic disorder, hypersensitivity).

### Safety conclusions

The safety of trametinib monotherapy has previously been described in the adult population, and in pediatric patients in the ongoing study [MEK116540, CTMT212X2101]. Most patients experienced skin related toxicity, as well as diarrhea, pyrexia, anemia, vomiting, and alopecia. Thirty-seven percent required some form of dose adjustment or interruption due to toxicity. Most patients remain on treatment more than one year since starting therapy. Treatment with trametinib monotherapy is manageable following protocol described treatment and dose modification for toxicity.

## 1.2.2.3 Pharmacokinetics - Trametinib

Trametinib pharmacokinetic (PK) parameters in adults were determined after single and repeat dose oral administration. Trametinib was absorbed rapidly, requiring 1.5 hr to reach the maximum concentration (Tmax) after single oral administration under fasting conditions [MEK113709]. The absolute oral bioavailability of a single trametinib 2 mg tablet is moderate to high (72%) relative to a co-administered intravenous microdose [MEK116540, CTMT212X2101]. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in maximum observed concentration (Cmax) and a 10% decrease in

[redacted]

area under the concentration-time curve from time zero (pre-dose) extrapolated to infinity [AUC(0-∞)] compared to fasted conditions [MEK113709].

Following repeat-dosing, the mean area under the concentration-time curve over the dosing interval (AUC0-∞) and Cmax increased in a dose proportional manner. Trametinib accumulates with repeat dosing, with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97. Terminal half-life is 5.3 days, determined after single dose administration. Steady state is achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (Cτ), Cmax and AUC from time zero (pre-dose) to 24 hr AUC(0-24h) between Day 15 and Day 21. In adults receiving trametinib 2 mg daily for 15 days (n=13) the geometric mean AUC(0-24h) (coefficient of variation [CV] %) was 370 (22%) ng*hr/mL, Cmax 22.2 (28%) ng/mL, Tmax 1.75 hr (range 1-3 hr), and Cτ12.1 (19%) ng/mL (Infante, 2012).

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

A population PK model was developed with data (n=493) combined from the FTIH study [MEK111054], and the Phase II and III studies in subjects with *BRAF* V600 mutation positive melanoma [MEK113583] and [MEK114267, CTMT212A2301]. Trametinib CL/F was estimated as 5.07 L/hr and was dependent on gender and weight. Although smaller female subjects will tend to have higher exposure than heavier male subjects, no dosage adjustment is warranted in this population.

In adults, administration of trametinib and dabrafenib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib relative to single agent administration.

Preliminary trametinib PK results for the selected dose of 0.025 mg/kg/day from study [MEK116540, CTMT212X2101] are summarized in Table 1-4. The summary includes 6 patients with available Day 15 PK who received the combination treatment. For patients aged 6 to 17 years, the median trametinib average concentration (Cavg) value was similar to that achieved in adults with melanoma that were treated with 150 mg dabrafenib BID in combination with trametinib 2mg QD (BRF113220 median= 13.4 ng/ml). Median Ctrough was also consistent between patients aged 6 to 17 years and adults in [BRF113220] (10.1 ng/mL). In study [BRF113220], an increase in confirmed response rate was noted in subjects that received dabrafenib in combination with 2mg trametinib as compared to combination with 1 mg trametinib.

Preliminary trametinib PK results for the selected dose of 0.032 mg/kg/day for subjects less than 6 years old from study [MEK116540, CTMT212X2101] are summarized in Table 1-4. The summary includes 3 patients with available Day 15 PK who received the combination treatment. Cavg for this age group was similar to that achieved in adults with melanoma at the recommended combination regimen [BRF113220].

**Table 1-4 Median trametinib PK (day 15) by age groups**

| Age Range | Dose (mg/kg/day) | N | Ctrough (ng/mL) | Cavg (ng/mL) |
|---|---|---|---|---|
| 12-17 years | 0.025 | 14 | 9.9 | 13.5 |

[redacted]

| Age Range | Dose (mg/kg/day) | N | Ctrough (ng/mL) | Cavg (ng/mL) |
|---|---|---|---|---|
| 6-<12 years | 0.025 | 16 | 12.0 | 16.3 |
| 6-17 years | 0.025 | 30 | 11.7 | 16.3 |
| < 6 years | 0.032 | 3 | 7.91 | 12.5 |

### 1.2.3 Overview of dabrafenib and trametinib combination therapy

The safety of dabrafenib and trametinib combination therapy has been evaluated in multiple studies of adults treated with dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily. The most common adverse reactions (>20%) for dabrafenib and trametinib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, arthralgia, hypertension, vomiting and cough. Increased risks of intracranial and gastrointestinal hemorrhage are notable concerns for the combination treatment compared to dabrafenib monotherapy; confounding factors in these cases include brain metastasis and anticoagulant therapy. The safety profile of the combination of dabrafenib and trametinib in adults generally reflects the safety profiles of the individual agents, with adverse events that are manageable with appropriate intervention. Pyrexia remains the most common AE for the combination and hyperproliferative skin lesions including cuSCC are reduced for the combination when compared to dabrafenib monotherapy.

Based on efficacy data for adults with *BRAF* V600 mutant metastatic melanoma or *BRAF* V600 mutant NSCLC, the concomitant and more complete inhibition of the MAPK pathway at the level of the *BRAF*- and MEK- kinases provides greater anti-tumor effect than administration of dabrafenib alone. Additionally the combination prevents the paradoxical activation of the MAPK pathway in *BRAF* wild-type cells resulting in lower incidence of cuSCC.

Preliminary data from [MEK116540, CTMT212X2101] are available for pediatric patients treated with the combination of dabrafenib and trametinib. The combination was tolerated when dosed at 100% of recommended pediatric phase 2 dose of each agent.

#### 1.2.3.1 Safety of dabrafenib with trametinib

Twelve patients were treated in part C dose exploration for combination therapy of dabrafenib with trametinib, 3 at 50% dabrafenib, and 9 at full dose dabrafenib. Each received full dose trametinib.

All twelve patients had *BRAF* V600 mutant LGG. Two (17%) had independently confirmed PR as best response, 8 (67%) had SD, and 2 (17%) had PD as best response. Eight (67%) remain on treatment, with median treatment duration at 41 weeks at the time of interim analysis.

The most common AEs reported, regardless of causal relationship were rash (67%), pyrexia (58%), diarrhea, fatigue, headache, and vomiting (each 42%). Two patients had a total of 5 possibly related SAEs, both with ejection fraction decrease (17%) and one each with nausea, vomiting, and pyrexia (8%). Dose interruptions for toxicity were required for 8 (67%) patients. There have been no deaths in this group.

No dose limiting toxicities were observed. Evaluation of combination therapy in patients under 6 years of age also demonstrates tolerability at the 100% dose of trametinib (0.032 mg/kg/day) together with 100% dabrafenib dose (5.25 mg/kg/day divided into two equal doses per day).

[redacted]

### 1.2.4 Overview of carboplatin and vincristine chemotherapy

The carboplatin with vincristine chemotherapy regimen has been employed in the systemic treatment of pediatric patients with LGG for several decades, and continues to serve as the standard of care treatment in several large studies (Ater 2012, Gnekow 2017).

There are multiple treatment schedules or regimens for administering carboplatin with vincristine in this setting of first systemic therapy for patients with LGG. The most widely utilized are those employed in the COGA9952 protocol (Ater 2012) and the SIOP-LGG-2004 protocol (Gnekow 2017). For CDRB436G2201, the treatment regimen from COGA9952 will be used for those patients assigned to chemotherapy treatment in the LGG cohort.

The treatment regimen is described in detail in Section 6.1.2, and consists of 10 weeks of induction therapy, followed by 8 cycles of maintenance therapy.

# 2 Rationale

## 2.1 Study rationale and purpose

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by alterations in specific proteins, including *BRAF*, which phosphorylates MEK on two regulatory serine residues.

Dabrafenib is a potent and selective inhibitor of *BRAF* kinase activity. Excluding RAF enzymes, dabrafenib demonstrated IC50 values <100 nM against only 8 kinases from ~300 protein and lipid kinases tested. In addition, dabrafenib suppresses phosphorylated ERK [pERK]) that is downstream of *BRAF* in the MAPK pathway and demonstrated anti-proliferative activity against multiple *BRAF* mutation positive tumor cell lines, and tumor regression in *BRAF* mutation positive xenograft models.

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 tumor progression 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 >10% of patients with certain types of gliomas (both low- and high-grade tumors) (Dougherty 2010; MacConaill 2009; Schiffman 2010; Janeway 2013; Jones 2012).

Relapsed, refractory or resistant pediatric HGG lacks a standard of care. *BRAF* V600 mutant, recurrent or refractory, pediatric HGG is a rare tumor type with a dismal prognosis. Multiple chemotherapies and targeted agents have been studied in this setting but none have demonstrated clinical activity. Temozolomide has demonstrated poor expected ORR in this setting. The most relevant historical efficacy data for pediatric patients with relapsed, refractory, or progressed HGG may come from the literature (Lashford 2002). The observed response rate of 12% (4 PRs in 33 temozolomide treated pediatric patients) is low and is generally consistent with other similar studies. A more recent study of bevacizumab and irinotecan, conducted based on demonstrated efficacy in treating adults with recurrent HGG, failed to show efficacy in pediatric patients with second line HGG (Gururangan 2010). Other targeted agents have also been studied in this disease setting but have shown a lack of efficacy (Jones 2012). Preliminary

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results from [BRF116013, CDRB436A2102] showed that 6 of 19 patients (31.5%) with relapsed or refractory *BRAF* V600 mutant HGG and measurable disease had investigator confirmed responses (CRs+PRs) following dabrafenib monotherapy. These results indicate that dabrafenib may offer improvement in treatment outcome for these patients.

The prognostic role of *BRAF* V600 mutation in pediatric HGG is unclear, but available data suggest that *BRAF* V600 mutation may be prognostically favourable in pediatric HGG. For this reason, the historical RR in *BRAF* V600 mutant pediatric relapsed refractory HGG may be higher than that observed in unselected populations, where the RR is less than 12%. The combination of dabrafenib with trametinib in adults with *BRAF* V600 mutant melanoma, NSCLC and other tumors have resulted in improved efficacy over dabrafenib monotherapy and suggests that greater efficacy may also be seen in the pediatric setting such as patients with relapsed refractory *BRAF* V600 mutant HGG. Given the high unmet medical need in pediatric HGG, the encouraging efficacy of dabrafenib monotherapy in pediatric patients with *BRAF* V600 mutant HGG, and the improved efficacy seen in adult cancer studies upon the addition of trametinib to dabrafenib, the HGG cohort portion of this study aims to demonstrate the effectiveness of dabrafenib with trametinib in pediatric patients with *BRAF* V600 mutant relapsed refractory HGG.

Recent analysis of tumor tissue and clinical outcomes has revealed that patients with *BRAF* V600 mutant LGG represent a subgroup of patients with LGG who have a significantly worse prognosis, with lower ORR, shorter PFS and shorter OS (Lassaletta 2017). While unselected patients with LGG requiring systemic therapy typically are adequately treated with standard of care chemotherapy, this group of patients with *BRAF* V600 mutant LGG has a need for improved treatment options over standard cytotoxic chemotherapy. The observed activity of dabrafenib monotherapy in patients with *BRAF* V600 mutant LGG that had failed their first systemic anticancer therapy (CR+PR 44%) [BRF11603, CDRB436A2102] exceeds historical expectations (11%) (Lassaletta 2017) for this subgroup of patients, and suggests a role for dabrafenib treatment in this disease.

The LGG cohort portion of this trial will compare the relative clinical benefit of combination targeted therapy of dabrafenib and trametinib to carboplatin with vincristine chemotherapy.

The decision to use systemic therapy for pediatric patients with LGG can be complex. Treatment is reserved for those patients who are deemed to require therapy for their disease, having had optimal surgical resection, where further surgical treatment would result in unacceptable neurologic toxicity and who will have further neurologic deterioration due to their disease.

Carboplatin with vincristine chemotherapy has been employed in the systemic treatment of pediatric patients with LGG for several decades, and has served as the standard of care treatment in several large studies. Toxicity in treatment with carboplatin and vincristine includes hematologic suppression, peripheral neurotoxicity, and significant hypersensitivity reactions. Median progression free survival in unselected patients undergoing their first systemic chemotherapy with carboplatin with vincristine was about 5 years (Ater 2012).Response rate (CR+PR) at the end of chemotherapy was 35% in this study.

[redacted]

## 2.2 Rationale for the study design

CDRB436G2201 combines two pediatric glioma cohorts into a single multi-center, open-label, phase II study.

The HGG cohort is a single arm study that will evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation positive relapsed or refractory HGG tumors. Eligible patients must have received at least one prior standard therapy. Approximately 40 patients will be enrolled and treatment will continue until disease progression or patients are no longer receiving clinical benefit in the opinion of the investigator, death, or unacceptable toxicity. Patients will be followed from the first dose of study treatment for both efficacy and safety. Patients must have local and centrally confirmed measurable disease for enrolment, and efficacy will be determined using the RANO criteria by independent expert pediatric neuro-radiologists. After discontinuation of the study treatment, patients will remain on the study for follow-up assessments and collection of information on subsequent anti-cancer treatments and survival.

A single arm design is used in the HGG cohort for the following reasons:

1. There is no standard of care comparator available in this patient population.
2. There is no non-standard therapy available that would offer equipoise to dabrafenib or dabrafenib in combination with trametinib in this setting.
3. A non-randomized approach is suitable as the study aims to demonstrate a large treatment effect.
4. It is infeasible to conduct a larger statistically robust randomized controlled trial in such a rare tumor population.

Eligible patients must have tumors harboring the *BRAF* V600 mutation, as the antitumor effect of dabrafenib is limited to tumors with this mutation. Approximately 10% of pediatric HGGs will have this mutation. This enrichment of the trial population limits the participation of patients with *BRAF* V600 wild type tumors who would not be expected to respond to dabrafenib therapy and thus allows those patients to promptly seek alternative treatments that might be more beneficial to them.

Tumor response is the primary endpoint, representing an objective measurement of clinically relevant antitumor effect that can be ascertained in a uniform and reliable fashion. Response assessment will be performed using the RANO criteria. ORR is a direct measure of therapeutic effect and is not affected by disease natural history. ORR can also be determined relatively rapidly and thus early futility declared. There are extensive historical ORR data for a variety of salvage therapies in this patient population, including cytotoxic chemotherapies and targeted agents. These studies can serve as indirect comparators for the proposed study.

*BRAF* V600 mutation status, tumor histopathology and grade III/IV will be centrally confirmed for all enrolled patients. ORR will be determined by investigator and also be assessed through independent central review. Independent assessment of ORR will be the primary endpoint. Central review of tumor histopathology is intended to assure consistent application of the WHO 2016 glioma classification scale. Together, these measures should allow for more reliable comparison to historical studies conducted to similarly rigorous standards.

[redacted]

Trametinib is added to dabrafenib in this setting in an effort to further improve the response rates, as well as the duration of responses that might result from targeted therapy in this population. Formulations of both dabrafenib and trametinib to be used in this study will be those already commercially available or very similar to formulations intended to be marketed in the future, pending successful clinical results.

The LGG cohort is a randomized comparison of dabrafenib with trametinib versus chemotherapy in the treatment of chemotherapy naïve patients with *BRAF* V600 mutant LGG whose tumor is unresectable and who require treatment. Eligible patients will have locally determined *BRAF* V600 mutant LGG with both local and centrally confirmed measurable disease. Approximately 102 patients will be randomized in a 2:1 ratio to either dabrafenib with trametinib or carboplatin with vincristine chemotherapy. Treatment with carboplatin plus vincristine will continue until completion of the prescribed chemotherapy regimen. Treatment with dabrafenib plus trametinib will continue until disease progression or patients are no longer receiving clinical benefit in the opinion of the investigator, death, or unacceptable toxicity. After discontinuation of the study treatment, patients will remain on the study for follow-up assessments and collection of information on subsequent anti-cancer treatments and survival.

A randomized comparison of the safety and efficacy of experimental targeted therapy to that of cytotoxic chemotherapy will provide substantial evidence upon which to base future treatment recommendations for this and closely related patient populations. Safety and efficacy data are becoming available from ongoing non-randomized clinical studies using dabrafenib with trametinib in pediatric patients with *BRAF* V600 mutant tumors. While these data are valuable, the interpretation of results obtained from a non-randomized study in a molecularly defined subset of patients can be significantly constrained by the lack of available robust historical datasets upon which to compare. For example, the assumptions of relative clinical efficacy used to design the LGG cohort of this study are taken from a relatively small number of patients with molecularly selected tumors who were treated with targeted therapy for the experimental arm, and taken from a retrospective analysis of clinical outcomes database where there was also sufficient clinical tumor material available to allow molecular profiling (Lassaletta 2017) for the chemotherapy arm. While the data are encouraging and supportive of further exploration of targeted therapy in this patient subset, the data may not be sufficient to establish future treatment recommendations for this and closely related patient populations. Through the use of a randomized comparison, the LGG cohort portion of this trial aims to prove the relative clinical benefit of combination targeted therapy of dabrafenib with trametinib as compared to standard of care cytotoxic chemotherapy.

The primary endpoint for the LGG cohort of this study is ORR by RANO criteria as determined by blinded independent expert pediatric neuroradiologist central review. This independent reviewer will not have access to clinical data prior to making radiologic determination of response. This approach reduces the potential for bias regarding the treatment assignment to interfere with objective determination of response.

To avoid introduction of bias into the determination of progression free survival, frequent tumor assessments are scheduled during the first 12 months.

The study design assures a determination of clinical activity for the LGG cohort in a reasonable time frame. The overall sample size is sufficient to demonstrate the superiority of the

[redacted]

experimental arm over the standard chemotherapeutic arm under the assumptions of this trial using the response rate (CR+PR) as the primary endpoint. Additionally, the study design will allow for a description of the important endpoint of progression free survival in this indolent disease at a later time point, to supplement the ORR results. Randomization will be in a 2:1 ratio, favoring targeted therapy, reducing the number of patients assigned to cytotoxic chemotherapy. Patients randomized to the chemotherapy arm will have the opportunity to receive experimental therapy of dabrafenib in combination with trametinib at the time of centrally confirmed progression of their disease on study.

It is not feasible to blind this study for multiple reasons. The two treatment arms are very distinct in the route of administration, the schedule for administration, and the clinically obvious toxicity profiles. The necessary supportive care will also vary depending on treatment assignment.

## 2.3 Rationale for dose and regimen selection

The combination dose regimen rationale for this study was based on safety, tolerability and PK.

In Study [BRF116013, CDRB436A2102] the recommended dabrafenib monotherapy doses were determined based on PK as an MTD was not determined. Dabrafenib exposure associated with efficacy in adult studies has been well demonstrated, while an MTD has not been determined. The geometric mean (95% CI) dabrafenib AUC(0-12) after administration of 150 mg BID in the Phase III study [BRF113683, CDRB436A2301] (patients with *BRAF* mutant metastatic melanoma) was 4341 (3599, 5235) ng*h/mL. Therefore the exposure target range of ~4000-5500 ng*h/mL was applied in the dose-escalation part of the pediatric Phase I study [BRF116013, CDRB436A2102].

Based on the preliminary PK data, the following doses were determined:

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

In Study [MEK116540, CTMT212X2101], three dose levels were initially tested for trametinib: 0.0125, 0.025 and 0.04 mg/kg/day. Since the dose regimen of 0.04 mg/kg/day resulted in dose limiting toxicities, 0.025 mg/kg/day was selected as the recommended trametinib dose for patients 6 years of age and older, based on safety and tolerability. An intermediate dose of 0.032 mg/kg/day trametinib was studied in patients under 6 years of age and was well tolerated and is the recommended trametinib dose for patients under 6 years of age.

In Part C of MEK114560 the combination regimen was tested using a dose escalation scheme for dabrafenib: trametinib 0.025 mg/kg/day with half the recommended dabrafenib dose from study [BRF116013, CDRB436A2102] (dose level 1) and with 100% of the recommended dabrafenib dose from [BRF116013, CDRB436A2102] (dose level 2). The combination regimen was safe and tolerated at both dose levels. For patients under 6 years of age a higher dose of 0.032 mg/kg/day for trametinib in combination with 5.25 mg/kg/day dabrafenib was evaluated with the aim of achieving higher exposure levels than those observed at the trametinib 0.025 mg/kg/day dose in this age group.This higher dose was safe and tolerated based on data from three patients in Part C that received the combination regimen.

[redacted]

Based on PK data from [BRF116013, CDRB436A2102] and [MEK116540, CTMT212X2101] at the recommended dabrafenib doses for patients ≥6 years; dabrafenib AUC(0-tau) on Day 15 was within the exposure values associated with efficacy in adults (Section 1.2.2.1).

Based on preliminary PK data from [MEK116540, CTMT212X2101] at the recommended trametinib dose (0.025 mg/kg/day) for patients ≥6 years: the trametinib Cavg was greater than 10 ng/mL for 90% of patients and at the recommended dose (0.032 mg/kg/day) for patients < 6 years: the trametinib Cavg was greater than 10 ng/mL for 2 out of 3 patients (Section 1.2.2.3). This target concentration has been associated with higher response rate in adults receiving combination therapy.

Overall the PK of dabrafenib and trametinib are within the exposure ranges associated with efficacy in adults and the combination regimen has a manageable safety profile. Collectively these data support the selected dabrafenib and trametinib dose(s) for children and adolescents.

The recommended combination dosing regimen for children and adolescents are:

- Trametinib
  - < 6 years old: 0.032 mg/kg/day
  - ≥6 years old: 0.025 mg/kg/day
- Dabrafenib
  - < 12 years old: 5.25 mg/kg/day, divided into two equal doses
  - ≥12 years old: 4.5 mg/kg/day, divided into two equal doses

Patients enrolled in this study will receive dabrafenib twice daily and trametinib once daily. The total daily dose of dabrafenib will not exceed 300 mg (150 mg BID) and for trametinib will not exceed 2 mg. Treatment will continue until disease progression or patients are no longer receiving clinical benefit as determined by the investigator, death or unacceptable toxicity.

## 2.4 Rationale for choice of combination drugs

Not applicable.

## 2.5 Rationale for choice of comparators drugs

Carboplatin with vincristine chemotherapy has been employed in the systemic treatment of pediatric patients with LGG for several decades, and has served as the standard of care treatment in several large studies (Ater 2012, Gnekow 2017)

There are multiple treatment schedules or regimens for administering carboplatin with vincristine in this setting of first systemic therapy for patients with LGG. The most widely utilized are those employed in the COGA9952 protocol (Ater 2012) and the SIOP-LGG-2004 protocol (Gnekow 2017). For this current study, the treatment regimen from COGA9952 will be used for those patients assigned to chemotherapy in the LGG cohort. The treatment regimen includes 10 weeks of induction therapy, followed by 8 cycles of consolidation therapy.

There have been no randomized comparisons of these regimens, but they are considered comparable in overall outcomes. The chosen regimen is slightly shorter in duration. This schedule was selected with guidance from the protocol steering committee as one that is well recognized and has a good benefit risk profile for this patient population.

[redacted]

## 2.6 Risks and benefits

### Potential Risks

Based on the interim analysis of the 65 pediatric patients enrolled across four dose levels [BRF113773, CDRB436A2101], the toxicity profile of dabrafenib is generally similar to that observed in the adult patient experience. Both populations experienced frequent rash, pyrexia, fatigue, arthralgia and headache. The frequency of rash and similar adverse events may be higher in this pediatric population than in adults. In contrast, there were no cases of cutaneous SCC observed in these pediatric patients. The most common adverse events (AEs) were in the Skin body system. Adequate exposures were obtained without reaching a maximally tolerated dose.

Results from the ongoing [MEK116540, CTMT212X2101] study are preliminary. Dose limiting toxicity was predominantly skin toxicity (rash, folliculitis). In adults in the 2.0 mg dose group across all completed monotherapy trametinib studies, the most common AEs were rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin.

The combination treatment of pediatric patients at full recommended monotherapy dose of dabrafenib and trametinib was tested in a small (less than 10) number of patients. No DLTs were observed. In adults, the safety of dabrafenib and trametinib combination therapy has been evaluated in multiple studies of adults treated with dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily. The most common adverse reactions (>20%) for dabrafenib and trametinib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting and cough. The safety profile of the combination of dabrafenib and trametinib in adults generally reflects the safety profiles of the individual agents, with adverse events that are manageable with appropriate intervention. Pyrexia remains the most common AE for the combination and hyperproliferative skin lesions including cuSCC are reduced for the combination therapy when compared to dabrafenib monotherapy.

The safety experience in the pediatric population is described in more detail in the latest [Investigator Brochure].

### Potential Benefits

Relapsed or refractory pediatric HGG is associated with very unfortunate outcomes using conventional therapy, with expectations of less than 12% RR and a median survival of 5 months for unselected patients. Interim analysis of [BRF116013, CDRB436A2102] includes independently confirmed response rate of 45% (10/22) and manageable safety profile for dabrafenib monotherapy. The combination of dabrafenib with trametinib has been studied in adult patients with *BRAF* V600 mutant metastatic melanoma or NSCLC and has shown greater efficacy than with dabrafenib alone.

Pediatric patients with *BRAF* V600 mutant LGG who progress following optimal surgical resection often require systemic treatment. The standard of care in this setting has been a regimen of carboplatin and vincristine. Recent analysis of paired tumor molecular profiles and patient outcomes reveals that this standard of care may not be as effective as previously noted in patients whose tumor carries the *BRAF* V600 mutation, with lower response rate, PFS and

[redacted]

OS than those without this mutation. Furthermore, in patients with *BRAF* V600 mutant LGG who have failed prior systemic chemotherapy, independently confirmed response rate (RANO, CR+PR) of dabrafenib monotherapy (44%) [BFR116013, CDRB436A2102] exceeds historical expectations (11%) (Lassaletta 2017) for this subgroup of patients. Thus, it is possible that this apparent improved outcome in relapsed or refractory LGG may also be seen in patients with *BRAF* V600 mutant LGG experiencing their first post-surgical progression. For the reasons stated previously, the addition of trametinib to dabrafenib is predicted to further improve the outcomes for LGG patients. Patients randomized to the chemotherapy treatment arm of the LGG cohort will benefit from the treatment approach that has been utilized for many years, but will also have the opportunity to cross over to the experimental therapy upon reaching the centrally confirmed progression of disease endpoint. Patients with LGG often receive substantial benefit from subsequent treatments, suggesting that those patients who do cross over as part of their study treatment, may experience benefit from that therapy.

### Overall Conclusion

Overall, these results suggest that dabrafenib monotherapy represents a potentially favorable benefit risk to pediatric patients with *BRAF* V600 mutant relapsed refractory or progressive HGG and LGG, and that the addition of trametinib to this treatment may result in even greater response rates, with possible longer duration of responses, while maintaining a tolerable risk profile. For patients in the LGG cohort, a recognized standard of care treatment regimen of carboplatin and vincristine (Ater, 2012) will be utilized, together with the option to cross over to treatment with dabrafenib plus trametinib at the time of centrally confirmed disease progression on study. The study is designed in such a way as to reduce the overall sample size, including the number of patients randomized into the chemotherapy treatment arm of the LGG cohort, while providing a reasonable expectation of meaningful results to guide future treatment decisions in this molecularly selected patient populations. Risks will also be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring, and interim analysis to determine early stopping for futility if sufficient clinical activity is not demonstrated for the HGG cohort. An independent Data Monitoring Committee (DMC) will be constituted and will be responsible for monitoring and reviewing clinical data for safety during the study. Recommended guidelines for prophylactic or supportive management of study drug induced adverse events are provided in Section 6.3. There may be unforeseen risks which could be serious. Refer to the latest [Investigator's Brochure].

# 3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

**Table 3-1 Objectives and related endpoints**

| Objective | Endpoint | Analysis |
|---|---|---|
| **Primary** | | Refer to Section 10.4 |
| **HGG Cohort:**<br>Evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria. | ORR, proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) by independent assessment per RANO criteria. | |
| **LGG Cohort:**<br>Compare the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria. | ORR, proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) by blinded independent review per RANO criteria. | |
| **Secondary** | | Refer to Section 10.5.1 |
| **HGG Cohort:**<br>1. Evaluate ORR by investigator assessment<br>2. Evaluate duration of response (DOR) by investigator and central independent assessment<br>3. Evaluate progression free survival (PFS) by investigator and central independent assessment<br>4. Evaluate time to response (TTR) by investigator and central independent assessment<br>5. Evaluate clinical benefit rate (CBR) by investigator and central independent assessment<br>6. Evaluate overall survival (OS)<br>7. Evaluate the safety and tolerability profile of dabrafenib in combination with trametinib in children and adolescents<br>8. Evaluate the palatability of dabrafenib oral suspension and trametinib oral solution<br>9. Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population | 1. ORR by investigator assessment per RANO criteria<br>2. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.<br>3. PFS, defined as time from first dose of study treatment to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria<br>4. TTR, calculated as the time from the start date of study treatment to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria<br>5. CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria. | |

[redacted]

| Objective | Endpoint | Analysis |
|---|---|---|
| | 6. OS, defined as the time from first dose of study treatment to death due to any cause<br>7. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO.<br>8. Palatability questionnaire data<br>9. Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters | |
| **Secondary** | | Refer to Section 10.5.1 |
| **LGG Cohort:**<br>10. Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator assessment.<br>11. Evaluate the DOR of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and central independent assessment.<br>12. Evaluate PFS of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment.<br>13. Evaluate TTR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment.<br>14. Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment<br>15. Evaluate OS of dabrafenib in combination with trametinib versus carboplatin with vincristine.<br>16. Evaluate 2-year OS estimate of dabrafenib in combination with trametinib versus carboplatin with vincristine.<br>17. Evaluate the safety and tolerability of dabrafenib in combination with trametinib versus carboplatin with vincristine =.<br>18. Evaluate the palatability of dabrafenib and trametinib<br>19. Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population | 10. ORR by investigator assessment per RANO criteria.<br>11. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.<br>12. PFS, defined as time from date of randomization to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria<br>13. TTR, calculated as the time from the date of randomization to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria<br>14. CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria.<br>15. OS, defined as the time from date of randomization to death due to any cause.<br>16. 2-year OS estimate<br>17. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO.<br>18. Palatability questionnaire data | |

[redacted]

| Objective | Endpoint | Analysis |
|---|---|---|
| 20. Assess patient reported outcomes of dabrafenib in combination with trametinib versus carboplatin with vincristine | 19. Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters<br>20. Change from baseline in PROMIS Parent Proxy scale - Global Health 7+2 | |

[redacted]

[redacted]

# 4 Study design

## 4.1 Description of study design

### High Grade Glioma (HGG) Cohort

The HGG cohort is a multi-center, single arm, open-label part of this phase II study conducted in children and adolescent patients with *BRAF* mutation positive, refractory or relapsed HGG tumors after having received at least one previous standard therapy.

Approximately 40 patients will be enrolled to receive dabrafenib and trametinib.

The primary objective is to evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by ORR to study treatment by central independent assessment using RANO criteria in the Full Analysis Set (FAS) population. ORR as assessed by investigator, DOR, PFS, TTR, and CBR assessed by investigator and independent central review, OS, palatability and the safety and tolerability profile of dabrafenib and trametinib are secondary endpoints.

A Steering Committee (SC) will be established, composed of investigators and Novartis personnel participating in the trial, to ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 8.7.

A Data Monitoring Committee (DMC) will also be established for the study. The DMC will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be responsible to review study data from the HGG and LGG cohorts approximately every 6 months during the conduct of the study as outlined in Section 8.6.

Patients in the HGG cohort may continue to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study termination by the sponsor.

HGG patients who have disease progression by RANO criteria may continue study treatment if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study treatment may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study treatment and sign the Informed Consent for treatment beyond progression. The decision to continue study treatment after PD must be documented in the patient records and eCRF after every tumor evaluation. In this case, the patient will continue assessments as defined in Section 7. An End of Treatment visit will be performed when patients permanently discontinue study treatment.

Patients who discontinue the study treatment without disease progression by RANO criteria will continue tumor assessment and safety evaluation as part of the post treatment follow-up outlined in Section 7, until central independently confirmed disease progression by RANO criteria or death irrespective of start of new anti-neoplastic therapy.

[redacted]

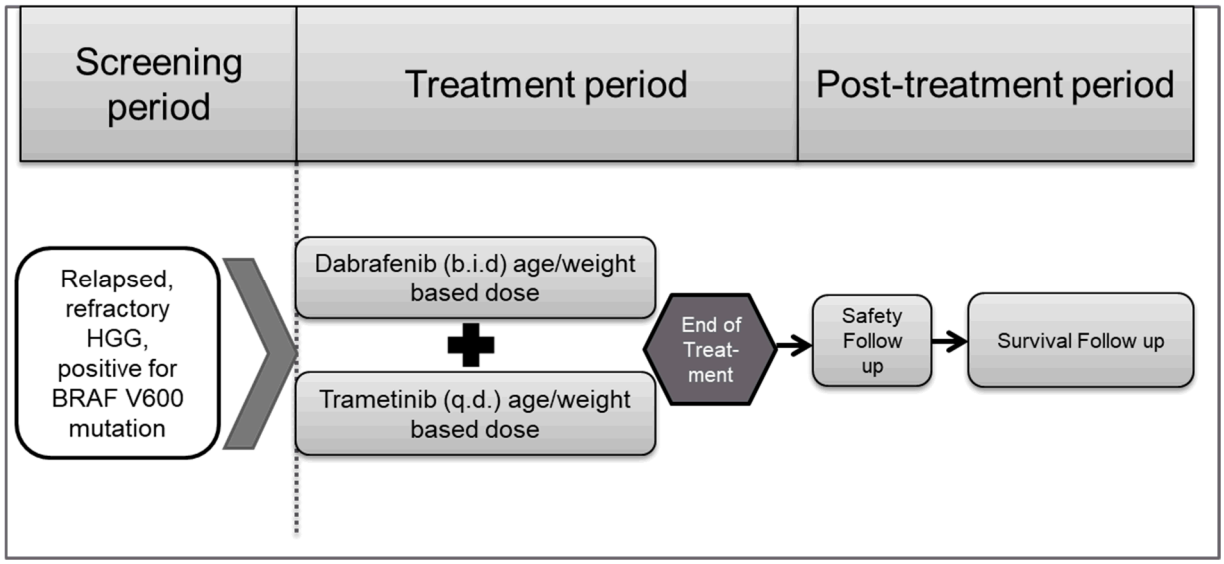
Patients who discontinue study treatment and efficacy follow-up, and have completed the post-treatment skin examination will enter the post treatment survival follow-up during which survival data is collected every 3 months. During the survival follow-up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected.

All patients will be followed for survival for at least 2 years after the last patient first study treatment (except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation).

An interim analysis for futility will be implemented to allow possible termination of recruitment of the HGG cohort in the event that there is insufficient efficacy. The patients for inclusion in the formal interim analysis for futility will be determined shortly after 16 HGG patients in the FAS have been enrolled. The interim analysis will be conducted when this initial group of patients in the HGG cohort included in the analysis have all had at least 20 weeks of follow-up or have withdrawn early. If the observed ORR in the HGG cohort assessed by central independent reviewer is ≤ 25%, there may be a consideration to stop the HGG cohort due to insufficient efficacy. The final decision on whether to stop enrollment in the HGG cohort will take into account all available study information at the IA cut-off including safety data and all efficacy endpoints. Any decision to halt further enrollment into the HGG cohort will not impact the treatment options for patients already enrolled into this cohort. HGG patients deriving benefit as per investigator discretion may continue receiving dabrafenib plus trametinib treatment on study.

The primary analysis of the HGG cohort will be conducted based on the all treated patients when all HGG patients have either completed at least 32 weeks of treatment or have discontinued earlier. In order to evaluate response against the efficacy seen in existing Standard of Care (SOC) and to provide evidence that trametinib contributes to the effect of the combination therapy for the HGG cohort, the point estimate and exact binomial confidence intervals (CIs) of ORR will be provided. The lower bound of the CIs will be used to provide evidence that the true ORR is greater than a certain specific response rate.

**Figure 4-1 Study Design for HGG Cohort**



### Low Grade Glioma (LGG) Cohort

The LGG cohort is a multi-center, randomized, open-label part of this phase II study conducted in children and adolescent patients with *BRAF* mutation positive, with progressing LGG whose tumor is unresectable and who require treatment.

Approximately 102 patients will be randomized in a 2:1 ratio to either dabrafenib plus trametinib or carboplatin with vincristine.

The primary objective is to compare the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by ORR by central independent assessment using RANO criteria in the Full Analysis Set (FAS) population. Secondary endpoints include ORR as assessed through investigator assessment, DOR, PFS, TTR, and CBR assessed by both investigator and independent central review and OS. Patient reported outcomes from the PROMIS questionnaire, palatability, and the safety and tolerability profile of dabrafenib and trametinib are additional secondary endpoints.

A Steering Committee (SC) composed of investigators and Novartis personnel participating in the trial will ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 8.7.

A Data Monitoring Committee (DMC) will be established for the study. The DMC will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be responsible to review data from the HGG and LGG cohorts approximately every 6 months during the conduct of the study as outlined in Section 8.6.

LGG patients receiving carboplatin with vincristine treatment will follow the regimen in Section 6.1.2 in conjunction with institutional practice. Duration of treatment should continue for the prescribed number of cycles as tolerated, or until unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, study termination by the sponsor, or until disease progression. See Section 6.3.1.16 for dose modifications and management guidelines or carboplatin with vincristine. Patients randomized to the carboplatin with vincristine treatment arm will only be allowed to cross over to receive dabrafenib in combination with trametinib after centrally confirmed RANO-defined disease progression. Crossover will be allowed during the treatment period or the post-treatment period.

LGG patients on dabrafenib with trametinib treatment may continue to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study termination by the sponsor.

LGG patients receiving dabrafenib with trametinib who have disease progression by RANO criteria may continue study treatment if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study treatment may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study treatment and sign the Informed Consent for treatment beyond progression. The decision to continue study treatment after PD must be documented in the patient records and eCRF after every tumor

evaluation. In this case, the patient will continue assessments as defined in Section 7. An End of Treatment visit will be performed when patients permanently discontinue study treatment.

Patients who discontinue dabrafenib with trametinib treatment or complete carboplatin with vincristine treatment without disease progression by RANO criteria will continue tumor assessment as part of the post treatment follow-up outlined in Section 7 until central independently confirmed disease progression by RANO criteria or death irrespective of start of new anti-neoplastic therapy.

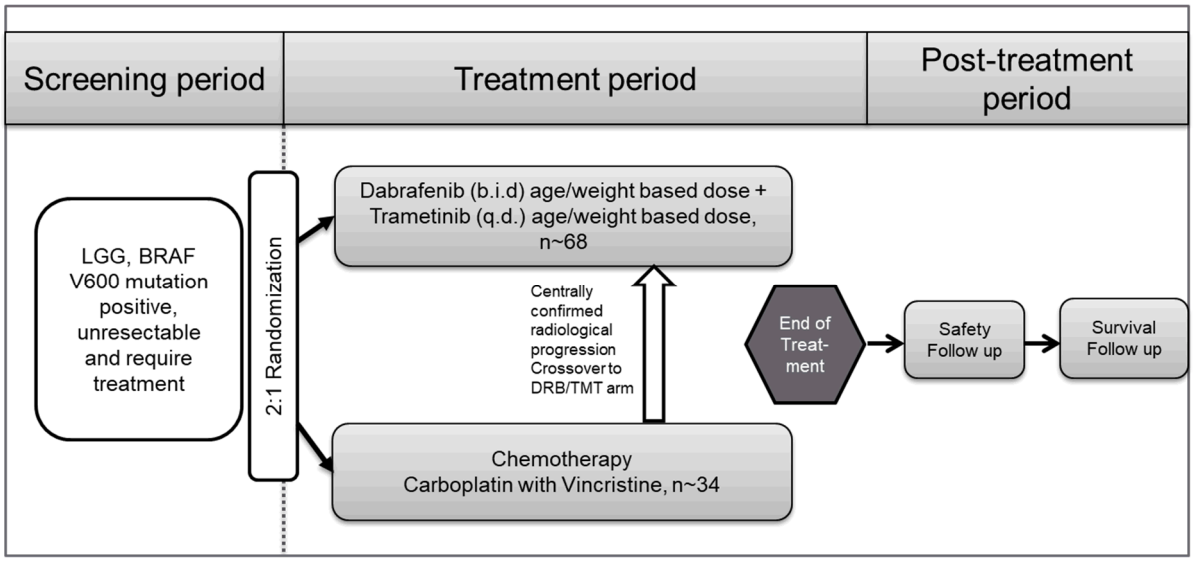
Patients who discontinue study treatment and efficacy follow-up, and have completed the post-treatment skin examination will enter the post treatment follow-up period during which survival will be collected every 3 months. During the survival follow-up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation and response to those treatments will be collected.

All patients will be followed for survival for at least 2 years after the last patient first study treatment (except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation).

No formal interim analysis is planned for the LGG cohort.

The primary analysis will be conducted based on all treated patients when all patients have either completed at least 32 weeks of treatment or have discontinued earlier.

**Figure 4-2 Study Design for LGG Cohort**




### 4.1.1 Screening

Pediatric patients for both cohorts will be screened for eligibility during the 28 days immediately prior to starting study treatment on Day 1. During this time, the inclusion and exclusion criteria will be assessed and all screening procedures will be performed. Results of all screening evaluations must be reviewed by the investigator or his/her designee prior to enrollment of each patient into the study to ensure all criteria have been met.

Eligible patients may only be included in the study after the patient or parental/legal guardian provides written (witnessed, where required by law or regulation) informed consent. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

As part of the screening, all patients must have available tumor samples (either formalin-fixed, paraffin-embedded [FFPE] blocks or slides) for central confirmation of *BRAF* V600 mutation (HGG and LGG), and for patients enrolled into the HGG cohort, for independent confirmation of HGG histopathology by an independent neuropathologist. The sample should be the best representation of the tumor and submitted for central confirmation approximately within one month of enrollment onto the study. Eligibility will be assessed based on local results of histology and *BRAF* V600 mutation.

Central confirmation of baseline measurable disease by an independent radiologist will be required before enrollment.

Following the completion of screening procedures and verifying patient eligibility based on assessments, the patient will be enrolled via the Interactive Response Technology (IRT) system. Please refer to and comply with detailed guidelines in the IRT manual. IRT systems will confirm the inclusion of eligible patients.

### 4.1.2 Treatment

The study treatment phase begins on Day 1 with the first administration of study treatment. In the HGG cohort, all patients will receive dabrafenib in combination with trametinib. In the LGG cohort, patients will be randomized 2:1 to receive dabrafenib in combination with trametinib or carboplatin with vincristine.

All patients who receive dabrafenib with trametinib will take dabrafenib twice daily and trametinib once daily until no longer receiving clinical benefit as determined by the investigator, disease progression, death, unacceptable toxicity that precludes further treatment, start of new anticancer therapy, or study is terminated by Sponsor.

Patients enrolled into the LGG cohort and randomized in the control arm will be administered carboplatin with vincristine, according to the regimen defined in Section 6.1.2. Treatment should continue for the prescribed number of cycles, as tolerated, or until unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, study is terminated by the sponsor or until disease progression. Patients randomized to the control arm are expected to follow protocol specified evaluations according to Table 7-3, including efficacy and safety assessments.

Patients in both cohorts will be assessed at screening (within 28 days before initiation of study treatment) and every 8 weeks for the first year on treatment, and every 16 weeks thereafter for efficacy using RANO criteria. All radiological scans will be collected for independent central review.

In the HGG cohort, clinical response will be monitored during the study to enable early stopping for futility if sufficient clinical activity is not demonstrated. After the first 16 patients have been

[redacted]

enrolled, have completed at least 20 weeks of treatment or have discontinued treatment earlier, an interim analysis will be conducted in order to determine whether the futility criteria have been met.

Safety assessments (collection of AEs, concomitant medications, laboratory parameters, dermatologic skin evaluations, and ophthalmologic exams) will be conducted on a continuous basis during the treatment phase according to Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3. [redacted]

#### 4.1.2.1 Treatment after Progression of Disease

Patients receiving dabrafenib with trametinib are permitted to continue treatment beyond investigator-assessed, RANO-defined PD, as long as they meet the following criteria:

- Investigator assessed clear evidence of clinical benefit
- Tolerance of study treatment
- Continuation of study treatment is in the best interest of the patient as determined by the Investigator
- Patient/legal guardian is willing to continue on the study and sign Informed Consent for treatment beyond progression

If the Principal Investigator determines that all above criteria are met, the patient may continue dabrafenib with trametinib treatment on study and follow all study related procedures, including tumor assessments, as scheduled in Table 7-1. After each tumor assessment, the Principal investigator must confirm if the patient is still benefitting from study treatment, and document this in patient medical records and the eCRF.

#### 4.1.2.2 Crossover and Continuation of Treatment (LGG Cohort)

For the LGG cohort, patients randomized to the carboplatin with vincristine treatment arm will be allowed to crossover to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression. Patients who cross over are expected to continue to undergo protocol specified evaluations according to Table 7-2, including efficacy and safety assessments.

LGG patients who crossover to receive dabrafenib in combination with trametinib must continue to meet the inclusion criteria for cardiac function, be willing to follow all contraception guidance, and cannot meet the exclusion criteria for allergy to dabrafenib, trametinib, or their excipients. Measurable disease is not mandatory but a new baseline tumor evaluation must be established within 28 days of starting dabrafenib in combination with trametinib crossover treatment. Day 1 of crossover therapy must occur within 90 days from the date of the first centrally confirmed progression. After the final PFS analysis and assuming significant favorable ORR and favorable PFS for the experimental therapy, patients randomized to carboplatin plus vincristine arm with persistent stable disease and deemed suitable for further systemic therapy for their disease may be allowed to crossover to receive dabrafenib in combination with trametinib.

[redacted]

PRO, taste questionnaires and pharmacokinetic samples will not be obtained on those patients who cross over to receive dabrafenib plus trametinib therapy.

### 4.1.3 Post Treatment Follow up

After discontinuation of study treatment, all patients will be followed for safety for at least 30 days after the last dose of study treatment except in the case of death, loss to follow-up or withdrawal of consent. All patients who discontinue study treatment for reasons other than disease progression, death, lost to follow up, or withdrawal of consent will move into Post Treatment Follow Up phase.

Tumor evaluations during this period will continue as per Table 7-1, Table 7-2 or Table 7-3 until central independently confirmed disease progression by RANO criteria, withdrawal of consent by patient or a parental/legal guardian to tumor status follow-up, or lost to follow-up. Patients who start a new anti-cancer therapy prior to disease progression will continue tumor evaluations following the same above schedule until radiographic evidence of disease progression is centrally confirmed.

Skin examinations should be performed at 3 and 6 months after the last dose of study treatment or until the start of a new anti-cancer therapy. Safety assessments including physical exams and growth/developmental follow up will continue according to Table 7-1, Table 7-2 or Table 7-3 and Section 7.1.6.

Patients who discontinue study treatment due to disease progression by RANO criteria that has been confirmed by central independent assessment, and begin new anti-cancer therapy at EOT will enter Survival follow-up outlined in Section 4.1.4.

### 4.1.4 Survival follow-up

All patients will be followed for survival once they discontinue study treatment and complete protocol required efficacy assessments, and the required skin evaluation per Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3. Survival follow-up assessments will be done every 12 weeks or earlier if a survival update is required to meet safety or regulatory needs. Survival information can be obtained by clinical visits or telephone calls until death, the patient is lost to follow-up, the patient/legal guardian withdraws consent or study discontinuation.

## 4.2 Timing of interim analyses and design adaptations

An interim analysis for futility will be implemented to allow possible termination of recruitment in the HGG cohort in the event that there is insufficient efficacy. The patients for inclusion in the formal interim analysis for futility will be made shortly after 16 patients in the FAS have been enrolled. The interim analysis will be conducted when this initial group of patients to be included in the analysis have all had at least 20 weeks of follow-up or have withdrawn early. If the observed ORR assessed by central independent reviewer is $\leq$ 25%, there may be a consideration to stop the HGG cohort due to insufficient efficacy. The final decision on whether to stop the HGG cohort will also take into account all available study information at the IA cut-off including safety data and all efficacy endpoints. If enrollment into the HGG cohort is stopped early, patients on study continuing to derive benefit from dabrafenib plus trametinib

[redacted]

may continue to receive treatment on this study or may be transferred to another study where drug will be provided.

The statistical considerations for the interim analysis can be found in Section 10.7.

In addition, an interim analysis of key safety and PK data of the adolescent patients in the HGG cohort may be performed to support a health authority request for data in adolescent patients. There is no intent to declare efficacy or futility based on this interim analysis.

No formal interim analysis is planned for the LGG cohort.

### 4.3 Definition of end of study

The end of study will occur when all patients have had at least two years of follow-up i.e. 2 years after last patient first treatment, or if the study is terminated early. At the end of the study, patients continuing to derive benefit from dabrafenib plus trametinib study treatment may be transferred to another clinical study where study drug will be provided to ongoing patients. Long term effects on patients who have received dabrafenib and trametinib may be assessed in a separate protocol.

### 4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patients should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 and Section 7.1.5 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

If the study is terminated early for any reason, patients continuing to derive benefit from dabrafenib plus trametinib treatment may be transferred to another study where study drug will be provided.

## 5 Population

### 5.1 Patient population

This study will be conducted in two cohorts: HGG and LGG pediatric patient cohorts.

For the HGG cohort, the patient population is children and adolescent patients with *BRAF* V600 mutation positive, refractory or relapsed HGG tumors after having received at least one previous standard therapy.

For the LGG cohort, the patient population is children and adolescent patients with *BRAF* V600 mutant LGG with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

[redacted]

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

## 5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Male or female between ≥12 months and <18 years of age at the time of signing the informed consent form. Patients under 6 years old must weigh at least 7 kg at the time of enrollment. Patients over 6 years old must weigh at least 10 kg at the time of enrollment.
2. **For HGG cohort only:** Relapsed, progressed, or failed to respond to frontline therapy. Frontline therapy is presumed to be optimal surgical approach (biopsy or resection) with radiation and/or chemotherapy.

   **For LGG cohort only:** Patients with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression.
3. Locally determined HGG or LGG as defined by WHO histological classification system, revised 2016 (Appendix 4). **For HGG cohort only:** Locally confirmed histologic diagnosis of High Grade Glioma (Grade III or IV glioma), including anaplastic pleomorphic xanthoastrocytoma (aPXA) and anaplastic gangliogliomas.

   **For LGG cohort only**: Locally confirmed histologic diagnosis of Low Grade Glioma (Grade I or II)
4. Locally determined and centrally confirmed measurable disease with minimal bi-perpendicular diameter that must be at least twice the imaging slice thickness to be used for efficacy assessments. (Both local and centrally confirmed results must show measurable disease to meet eligibility)
5. *BRAF* V600 mutation-positive tumor as assessed locally, or at a Novartis designated central reference laboratory if local *BRAF* V600 testing is unavailable.
6. Tumor tissue must be available and subsequently provided to Novartis for central confirmatory testing of *BRAF* mutational status (HGG and LGG cohort), and for HGG histopathology (HGG cohort).
7. Performance score of ≥50% according to the Karnofsky/Lansky performance status scale.
8. Females of child-bearing potential must be willing to practice acceptable methods of birth control. Additionally, females of childbearing potential must have a negative serum pregnancy test within 28 days prior to day 1.
9. Must have adequate bone marrow function per central or local lab in the absence of growth factor support and is defined as:
   - Absolute neutrophil count (ANC) ≥1000/µL;
   - Platelets ≥75,000/µL and transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to meeting this enrollment criteria. **Note for LGG patients only**, platelets ≥ 100,000/µL prior to Day 1 dosing.
   - Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions)
10. Adequate renal function defined as:
    - Calculated eGFR (Schwartz formula) or radioisotope GFR ≥90 mL/min/1.73 $m^2$; or

[redacted]

- A serum creatinine within the testing lab reference range (for age/gender, if available)

11. Adequate liver function defined as:
    - Total Bilirubin (sum of direct and indirect) ≤ 1.5 x upper limit of normal (ULN) for age except for subjects with Gilbertsyndrome who may only be included if the total bilirubin is ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
    - AST and ALT ≤2.5 x ULN
12. Adequate cardiac function defined as:
    - LVEF greater than or equal to institutional LLN by ECHO (while not receiving medications for cardiac function)
    - Corrected QT (QTcF) interval ≤480 msecs.
13. If receiving glucocorticoids, patient must be on a stable or weaning dose for at least **7** days prior to the first dose of study treatment.
14. Written informed consent/assent must be obtained prior to any protocol specific screening procedures being performed.

## 5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Malignancy OTHER than *BRAF* V600 mutant HGG or LGG.
2. Previous treatment with dabrafenib or another RAF inhibitor, trametinib or another MEK inhibitor, or ERK inhibitor.
3. HGG patients: Cancer therapy (chemotherapy with delayed toxicity, immunotherapy, biologic therapy, vaccine therapy) or investigational drugs within 3 weeks preceding the first dose of study treatment. LGG patients: Any systemic anticancer therapy (chemotherapy, immunotherapy, biologic therapy, or vaccine therapy) or investigational drugs prior to enrollment.
4. HGG patients: Radiotherapy to CNS glioma lesions within 3 months prior to first dose of study treatment, unless there is clear evidence of radiologic progression outside of the field of radiation. LGG patients: Radiotherapy to CNS glioma lesions at any point prior to enrollment.
5. History of malignancy with confirmed activating RAS mutation or with *BRAF* fusion such as BRF-KIAA1549 or with known diagnosis of NF1. Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.
6. Current use of a prohibited medication or herbal preparation or requires any of these medications during the study. See Section 6.4 for details.
7. Unresolved toxicity greater than NCI CTCAE v 4.03 grade 2 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 the study treatment (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy).
8. History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib, trametinib and their excipients. For LGG patients only: history

[redacted]

of allergic reactions or contraindications to the use of carboplatin or vincristine (refer to local product label or SmPC).

9. Autologous or allogeneic stem cell transplant within 3 months prior to the first dose of study treatment [NOTE: patients with evidence of active graft versus host disease are excluded regardless of elapsed time].
10. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
    - recent myocardial infarction (within last 6 months),
    - uncontrolled congestive heart failure,
    - unstable angina (within last 6 months),
    - clinically significant (symptomatic) or known, uncontrolled cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker) except sinus arrhythmia within the past 24 weeks prior to the first dose of study treatment
    - coronary angioplasty or stenting (within last 6 months)
    - intra-cardiac defibrillators
    - abnormal cardiac valve morphology (≥ grade 2) documented by echocardiogram (patients with grade 1 abnormalities [i.e. mild regurgitation/stenosis] can be enrolled on study. Patients with moderate valvular thickening should NOT be enrolled.
11. 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
12. 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.
13. A history of Hepatitis B Virus, or Hepatitis C Virus infection (patients with laboratory evidence of cleared Hepatitis B Virus and/or Hepatitis C Virus may be enrolled).
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (e.g. are menstruating), unless they are using highly effective methods of contraception during dosing of study treatment and for 16 weeks after stopping study medication with trametinib monotherapy or dabrafenib in combination with trametinib, and 2 weeks after stopping treatment with dabrafenib monotherapy, whichever is longer. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation or tubal occlusion 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 is she considered not of child bearing potential.

[redacted]

- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- 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.

**Note:** Oral contraceptives are not permitted as a method of contraception due to potential drug-drug interactions with dabrafenib.

15. Pregnant females as determined by positive human chorionic gonadotropin (hCG) test at screening or prior to dosing.
16. Lactating females who are actively breast feeding.
17. Sexually active males (including those that have had a vasectomy) unless they use a condom during intercourse while on study and for 16 weeks after stopping study treatment, and agree not to father a child during this period.
18. A history or current evidence of retina vein occlusion (RVO) or central serous retinopathy.

# 6 Treatment

## 6.1 Study treatment

In this study, the term "study treatment or drug" refers to Novartis study drug dabrafenib (DRB436) with trametinib (TMT212) or carboplatin and vincristine.

Refer to Section 6.1.1.1 for dabrafenib (DRB436) and trametinib (TMT212) dosing instructions. Refer to Section 6.1.2 for carboplatin and vincristine dosing instructions.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

### 6.1.1 Dabrafenib and Trametinib Dosing regimen

Dabrafenib (DRB436) will be administered orally, twice daily based on weight, age and the appropriate dose level. Trametinib (TMT212) will be administered orally, once daily in combination with the first daily dose of dabrafenib based on weight. A dosing nomogram based on weight and/or age will be used to prescribe dabrafenib (DRB436) and trametinib (TMT212) to minimize inter-patient dosing variability. Dabrafenib is available as capsules and as dispersible tablets for oral suspension (Table 6-1, Table 6-2, Table 6-3 and Table 6-4) and trametinib is available as tablets and as a powder in bottle for oral solution (Table 6-5, Table 6-6, Table 6-7 and Table 6-8).

**Dabrafenib Dosing Tables**

- Patients <12 years old and ≥16 kg may be administered either the dabrafenib capsules (Table 6-1) or dabrafenib dispersible tablets for oral suspension (Table 6-3)
- Patients ≥12 years old and ≥19 kg may be administered either the dabrafenib capsules (Table 6-2) or dabrafenib dispersible tablets for oral suspension (Table 6-4)
- Patients <12 years old and <16 kg **must** be administered dabrafenib dispersible tablets for oral suspension (Table 6-3)

[redacted]

- Patients ≥12 years old and <19 kg **must** be administered dabrafenib dispersible tablets for oral suspension (Table 6-4)

**Table 6-1 Dose and treatment schedule for dabrafenib (DRB436) capsules for patients less than 12 years of age (5.25 mg/kg/day)**

| Weight | Dose | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|
| 16-23.5 kg | 50 mg | b.i.d | 100 mg | Capsules for oral administration |
| 23.6-33.5 kg | 75 mg | b.i.d | 150 mg | Capsules for oral administration |
| 33.6-42.5 kg | 100 mg | b.i.d | 200 mg | Capsules for oral administration |
| 42.6-52.5 kg | 125 mg | b.i.d | 250 mg | Capsules for oral administration |
| ≥52.6 kg | 150 mg | b.i.d | 300 mg | Capsules for oral administration |

**Table 6-2 Dose and treatment schedule for dabrafenib (DRB436) capsules for patients greater or equal 12 years of age (4.5 mg/kg/day)**

| Weight | Dose | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|
| 19-27.5 kg | 50 mg | b.i.d | 100 mg | Capsules for oral administration |
| 27.6-38.5 kg | 75 mg | b.i.d | 150 mg | Capsules for oral administration |
| 38.6-50.5 kg | 100 mg | b.i.d | 200 mg | Capsules for oral administration |
| 50.6-61.5 kg | 125 mg | b.i.d | 250 mg | Capsules for oral administration |
| ≥61.6 kg | 150 mg | b.i.d | 300 mg | Capsules for oral administration |

**Table 6-3 Dose and treatment schedule for dabrafenib (DRB436) dispersible tablets for patients less than 12 years of age (5.25mg/kg/day)**

| Weight (kg) | Dose | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|
| 7-9.5 | 20 mg | b.i.d | 40 mg | Dispersible tablet for oral suspension |
| 9.6-13.5 | 30 mg | b.i.d | 60 mg | Dispersible tablet for oral suspension |
| 13.6-17.5 | 40 mg | b.i.d | 80 mg | Dispersible tablet for oral suspension |
| 17.6-20.5 | 50 mg | b.i.d | 100 mg | Dispersible tablet for oral suspension |
| 20.6-24.5 | 60 mg | b.i.d | 120 mg | Dispersible tablet for oral suspension |
| 24.6-28.5 | 70 mg | b.i.d | 140 mg | Dispersible tablet for oral suspension |
| 28.6-32.5 | 80 mg | b.i.d | 160 mg | Dispersible tablet for oral suspension |
| 32.6-36.5 | 90 mg | b.i.d | 180 mg | Dispersible tablet for oral suspension |
| 36.6-40.5 | 100 mg | b.i.d. | 200 mg | Dispersible tablet for oral suspension |
| 40.6-43.5 | 110 mg | b.i.d | 220 mg | Dispersible tablet for oral suspension |
| 43.6-47.5 | 120 mg | b.i.d | 240 mg | Dispersible tablet for oral suspension |
| 47.6-51.5 | 130 mg | b.i.d | 260 mg | Dispersible tablet for oral suspension |
| 51.6-55.5 | 140 mg | b.i.d. | 280 mg | Dispersible tablet for oral suspension |
| ≥55.6 kg | 150 mg | b.i.d | 300 mg | Dispersible tablet for oral suspension |

[redacted]

**Table 6-4 Dose and treatment schedule for dabrafenib (DRB436) dispersible tablet for patients greater than or equal 12 years of age (4.5 mg/kg/day)**

| Weight (kg) | Dose | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|
| 10-11.5 | 20 mg | b.i.d | 40 mg | Dispersible tablet for oral suspension |
| 11.6-17.5 | 30 mg | b.i.d | 60 mg | Dispersible tablet for oral suspension |
| 17.6-20.5 | 40 mg | b.i.d | 80 mg | Dispersible tablet for oral suspension |
| 20.6-24.5 | 50 mg | b.i.d | 100 mg | Dispersible tablet for oral suspension |
| 24.6-28.5 | 60 mg | b.i.d | 120 mg | Dispersible tablet for oral suspension |
| 28.6-32.5 | 70 mg | b.i.d | 140 mg | Dispersible tablet for oral suspension |
| 32.6-36.5 | 80 mg | b.i.d | 160 mg | Dispersible tablet for oral suspension |
| 36.6-40.5 | 90 mg | b.i.d | 180 mg | Dispersible tablet for oral suspension |
| 40.6-43.5 | 100 mg | b.i.d | 200 mg | Dispersible tablet for oral suspension |
| 43.6-47.5 | 110 mg | b.i.d | 220 mg | Dispersible tablet for oral suspension |
| 47.6-51.5 | 120 mg | b.i.d | 240 mg | Dispersible tablet for oral suspension |
| 51.6-55.5 | 130 mg | b.i.d | 260 mg | Dispersible tablet for oral suspension |
| 55.6-64.5 | 140 mg | b.i.d | 280 mg | Dispersible tablet for oral suspension |
| ≥64.6 | 150 mg | b.i.d | 300 mg | Dispersible tablet for oral suspension |

### Trametinib Dosing Tables

- Patients <6 years old and <26 kg **must** be administered the trametinib oral solution (Table 6-5)
- Patients <6 years old and ≥26 kg may be administered either the trametinib oral solution (Table 6-5) or trametinib tablets (Table 6-7)
- Patients ≥6 years old and ≥10 kg < 33 kg **must** be administered the trametinib oral solution (Table 6-6)
- Patients ≥6 years old and ≥33 kg may be administered either the trametinib oral solution (Table 6-6) or the trametinib tablets (Table 6-8)

**Table 6-5 Dose and treatment schedule for trametinib (TMT212) oral solution for patients less than 6 years old (0.032 mg/kg/day)**

| Weight (kg) | Dose | | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|---|
| | mL | mg | | | |
| 7-9.9 | 5 | 0.25 | q.d | 0.25 | Solution for oral administration |
| 10-12.5 | 7.5 | 0.375 | q.d | 0.375 | Solution for oral administration |
| 12.6-16.5 | 10 | 0.5 | q.d | 0.5 | Solution for oral administration |
| 16.6-24.5 | 12.5 | 0.625 | q.d | 0.625 | Solution for oral administration |
| 24.6-35 | 17.5 | 0.875 | q.d | 0.875 | Solution for oral administration |
| 35.1-45 | 25 | 1.25 | q.d | 1.25 | Solution for oral administration |
| 45.1-55 | 30 | 1.5 | q.d | 1.5 | Solution for oral administration |
| ≥55.1 | 40 | 2 | q.d | 2 | Solution for oral administration |

[redacted]

**Table 6-6 Dose and treatment schedule for trametinib (TMT212) oral solution for patients greater or equal to 6 years old (0.025 mg/kg/day)**

| Weight (kg) | Dose | | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|---|
| | mL | mg | | | |
| 10-12.5 | 5 | 0.25 | q.d | 0.25 | Solution for oral administration |
| 12.6-16.5 | 7.5 | 0.375 | q.d | 0.375 | Solution for oral administration |
| 16.6-24.5 | 10 | 0.5 | q.d | 0.5 | Solution for oral administration |
| 24.6-35 | 15 | 0.75 | q.d | 0.75 | Solution for oral administration |
| 35.1-45 | 20 | 1.0 | q.d | 1.0 | Solution for oral administration |
| 45.1-55 | 25 | 1.25 | q.d | 1.25 | Solution for oral administration |
| 55.1-68 | 30 | 1.5 | q.d | 1.5 | Solution for oral administration |
| 68.1-72 | 35 | 1.75 | q.d | 1.75 | Solution for oral administration |
| >72 | 40 | 2 | q.d | 2 | Solution for oral administration |

**Table 6-7 Dose and treatment schedule for trametinib (TMT212) tablets for patients less than 6 years and weight greater or equal 26kg (0.032 mg/kg/day)**

| Weight | Dose | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|
| 26-39.5 | 2 X 0.5 mg | q.d | 1 mg | Tablets for oral administration |
| 39.6-54.5 kg | 3 X 0.5 mg | q.d | 1.5 mg | Tablets for oral administration |
| ≥54.6 kg | 1 X 2 mg | q.d | 2 mg | Tablets for oral administration |

**Table 6-8 Dose and treatment schedule for trametinib (TMT212) tablets for patients greater or equal to 6 and weight greater or equal 33kg (0.025 mg/kg/day)**

| Weight | Dose | Frequency and/or Regimen | Total Daily Dose | Pharmaceutical form and route of administration |
|---|---|---|---|---|
| 33-49.5 kg | 2 X 0.5 mg | q.d | 1 mg | Tablets for oral administration |
| 49.6-69.5 kg | 3 X 0.5 mg | q.d | 1.5 mg | Tablets for oral administration |
| ≥69.6 kg | 1 X 2 mg | q.d | 2 mg | Tablets for oral administration |

The investigator or responsible site personnel should instruct the patient and guardians to take the study drug as per protocol (promote compliance).

If a patient's weight changes by more than the allowed institutional standard (or 10% if no institutional standard), the patient's administered dose may be adjusted based on the current weight of the patient using protocol Table 6-1 through Table 6-8.

If a patient has increased in weight and is tolerating the current dose administered, the protocol dosing Table 6-1 through Table 6-8 should be consulted to determine if a higher dose should be given. Otherwise, it is optional to consider if a higher dose should be administered.

If the patient has decreased in weight, they may continue on the current administered dose if it is tolerated. However, if the current administered dose is not tolerated, then the protocol dosing Table 6-1 through Table 6-8 should be consulted to determine if a lower dose should be given. Otherwise, it is optional to consider if a lower dose should be administered.

[redacted]

If a patient's weight should fall below the lowest weight specified in Table 6-1 through Table 6-8, and per investigator the patient requires a lower administered dose (i.e., not tolerating current dose) then the dose specified in dose modification Table 6-12 through Table 6-15 should be utilized.

#### 6.1.1.1 Dabrafenib (DRB436) and trametinib (TMT212) dosing

Study medications should be taken as follows:

- Dabrafenib will be administered twice daily per the dosing regimen shown in Table 6-1, Table 6-2, Table 6-3 and Table 6-4.
- Trametinib will be administered once daily per the dosing regimen shown in Table 6-5, Table 6-6, Table 6-7 and Table 6-8.
- Trametinib should be taken in combination with dabrafenib once daily, preferably in the morning.
- Dabrafenib capsules and trametinib tablets should be taken with approximately 120-240 mL of water.
- Trametinib pediatric oral solution formulation will be administered with a graduated syringe. Please refer to the trametinib oral solution Instructions for Use.
- Dabrafenib pediatric oral suspension formulation administration will be administered using dosing cup and/or graduated syringe. Please refer to dabrafenib oral suspension Instructions for Use.
- Refer to the dabrafenib and trametinib Instructions for Use documents if enteral feeding tubes are required for administering pediatric oral solutions.
- Patients less than 12 years of age who weigh less than 16 kg must be administered the dabrafenib dispersible tablets for oral suspension.
- Patients equal to or greater than 12 years of age who weigh less than 19 kg must be administered the dabrafenib dispersible tablets for oral suspension.
- Patients less than 6 years old who weigh less than 26 kg must be administered the trametinib oral solution.
- Patients older than 6 years old must weigh at least 33 kg to be administered the trametinib tablets.
- Patients should be encouraged to take dabrafenib at approximately 12 hour intervals and at similar times each day.
- Study treatment should be administered under fasting conditions, at least 1 hour before or 2 hours after a meal.
- If it is not possible for a patient to tolerate the fasting conditions noted above, study treatment may be administered with a small non-fat meal (e.g. small amount of apple juice/sauce, a piece of dry toast). Patients and their guardians should be advised to avoid administering study drug with milk or high-fat, high-calorie foods.
- Patients who are being breastfed may continue to be breastfed on demand. If the patient is breastfed during collection of PK samples the time of breastfeeding should be recorded as a meal.

[redacted]

- If a patient vomits after taking study drug, the patient should be instructed not to retake the dose and wait for the next scheduled dose.
- If a patient misses a dabrafenib dose, they should be instructed not to double the next regularly scheduled dose. However, patients may take the missed dose immediately if the next scheduled dose is at least 6 hours later. Patients may then take the next dose at the scheduled time.
- If a patient misses a trametinib dose, they should be instructed not to double the next regularly scheduled dose. However, patients may take the missed dose immediately if the next scheduled dose is at least 12 hours later. Patients may then take the next dose at the scheduled time.
- The total daily dose of dabrafenib will not exceed 300 mg (150 mg BID).
- The total daily dose of trametinib will not exceed 2 mg.

#### 6.1.1.2 Additional dosing guidelines for pharmacokinetic sampling/chemistry panel collection

PK samples will be collected on all HGG patients and LGG patients randomized to receive dabrafenib with trametinib treatment. PK samples will not be collected from the LGG patients randomized to receive carboplatin with vincristine, even after crossover from carboplatin with vincristine to dabrafenib plus trametinib.

On days with PK, the following additional guidelines must be followed:

- On protocol visit days when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days, patients may take dabrafenib and trametinib at home.
- Post-dose PK samples should be collected after dosing of the study treatment in the morning (AM). PK sample collection will be performed according to Table 7-5 and Table 7-6.

### 6.1.2 Carboplatin and Vincristine Dosing Regimen

Carboplatin and vincristine will be supplied locally as commercially available and labelled accordingly to comply with legal requirements of each country. Carboplatin and vincristine will be administered as one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy. Each maintenance cycle is 6 weeks. Maintenance cycles are only given following sufficient recovery of hematologic parameters.

Chemotherapy administration should follow the guidelines below and as per local product labels or SmPC. Please consult local product labels and institutional standards for duration of infusion and flush requirements when administering carboplatin and vincristine.

Local safety laboratory testing to confirm hematologic parameters may be conducted per institutional practice during induction and maintenance phases of chemotherapy prior to dosing when central labs are not scheduled per protocol or when central lab results will not be available prior to dosing. Results will be collected in the eCRF.

[redacted]

### 6.1.2.1 Induction Therapy

Prior to induction, central or local lab results must be assessed to confirm ANC ≥1000/µL and platelet count ≥100,000/µL.

Induction will consist of 10 weeks of therapy followed by 2 weeks without chemotherapy. Induction should only be interrupted in the event of grade 3 neurotoxicity, grade 2 nephrotoxicity, grade 4 hematologic toxicity, or disease progression. See Section 6.3.1.16 for dose modification guidelines.

Carboplatin (CBDCA): 175 mg/m$^2$ as weekly IV infusion over 60 minutes on weeks 1 to 4, and on weeks 7 to 10, on the same day as VCR dosing

Vincristine (VCR): 1.5 mg/m$^2$ as weekly IV bolus infusion (0.05 mg/kg if child is <12 kg) (maximum dose of 2.0 mg) for 10 weeks.

**Table 6-9 Induction therapy**

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VCR CBDCA | VCR CBDCA | VCR CBDCA | VCR CBDCA | VCR | VCR | VCR CBDCA | VCR CBDCA | VCR CBDCA | VCR CBDCA | Rest | Rest |

### 6.1.2.2 Maintenance Therapy

Following induction therapy and two weeks of rest, maintenance therapy should begin if peripheral counts recover to ANC ≥1,000/µL and platelet count ≥100,000/µL. Repeat blood counts every 7 days until counts are adequate. Recovery of peripheral counts is required prior to starting each maintenance cycle. Local laboratory results may be used prior to dosing if a central lab is not scheduled per protocol or when central lab results will not available in time for a scheduled cycle. Results will be collected in the eCRF.

Each maintenance cycle will be 6 weeks in duration and consists of 4 weekly doses of carboplatin, and three weekly doses of vincristine given concomitantly with the first 3 weeks of carboplatin, followed by two weeks of rest. Maintenance will continue for a total of 8 cycles. See Section 6.3.1.16 for dose modification guidelines.

Carboplatin (CBDCA): 175 mg/m$^2$ as weekly IV infusion over 60 minutes on weeks 1 to 4 of each cycle.

Vincristine (VCR): 1.5 mg/m$^2$ as weekly IV bolus infusion (0.05 mg/kg if child is <12 kg) (maximum dose of 2.0 mg) on weeks 1 to 3 of each cycle, on the same day as CBDCA dosing.

**Table 6-10 Maintenance therapy**

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|---|---|---|---|---|---|
| VCR CBDCA | VCR CBDCA | VCR CBDCA | CBDCA | Rest | Rest |

### 6.1.3 Ancillary treatments

Not applicable

[redacted]

### 6.1.4 Rescue medication

Not applicable

### 6.1.5 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.3.

### 6.1.6 Treatment duration

**Dabrafenib with trametinib:**

Patients will receive dabrafenib in combination with trametinib until disease progression or loss of clinical benefit as determined by the investigator, death, unacceptable toxicity, withdrawal of consent or if the investigator judges that further therapy is no longer in the best interest of the patient, or early termination of the study by the sponsor.

Patients who have disease progression (as defined by RANO) may continue on study treatment if the investigator determines that the patient has clear evidence of clinical benefit from study treatment, continuing study drug may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study drug and sign Informed Consent for treatment beyond progression. If the patient is continuing on study treatment, then all study procedures including tumor assessments must be followed as scheduled (Table 7-1 or Table 7-2). In addition, after each tumor assessment, the investigator must confirm and document in patient medical records and the eCRF that the patient is still benefitting from study treatment and therefore can continue receiving study treatment.

**Carboplatin with vincristine for LGG Cohort only:**

Duration of treatment should continue for the prescribed number of cycles, as tolerated or until unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, study is terminated by the sponsor or until disease progression.

Carboplatin should always be given in a setting with rapid access to pediatric advanced life-supporting support capability. See Section 6.3.1.16.5 for additional guidelines for the management of allergic reactions. Patients who develop an intolerable allergic reaction to carboplatin should be managed per institutional standards. Only after centrally confirmed RANO-defined disease progression will patients randomized to carboplatin with vincristine treatment will be allowed to crossover to receive dabrafenib in combination with trametinib treatment.

## 6.2 Dose escalation guidelines

Not applicable.

[redacted]

## 6.3 Dose modifications

### 6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dosing interruptions or modifications are mandated in order to allow patients to continue the study treatment.

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and for which specific guidelines do not apply are provided in Table 6-11. 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. Refer to Section 6.3.1.16 for general guidelines for dose modifications for carboplatin and vincristine.

**Table 6-11 General guidelines for dose modification for adverse events considered related to dabrafenib and trametinib combination treatment**

| Grade | Recommended adverse event management guidelines | Mandatory dose modification requirements |
|---|---|---|
| Grade 1 or Grade 2 tolerable | • Monitor closely.<br>• Provide supportive care according to institutional standards. | • Continue dabrafenib and trametinib at the same dose level. |
| Grade 2 intolerable or Grade 3 | • Monitor closely.<br>• Provide supportive care according to institutional standards. | • Interrupt dabrafenib and trametinib (except for cuSCC, keratoacanthoma, new primary melanoma, and basal cell carcinoma).<br>- When toxicity resolves to ≤ Grade 1 or baseline, restart dabrafenib and trametinib reduced by one dose level.<br>• If the Grade 2 (intolerable) or Grade 3 toxicity recurs, interrupt dabrafenib and trametinib.<br>- When toxicity resolves to Grade 1 or baseline, restart dabrafenib and trametinib reduced by another dose level. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met. |
| Grade 4 | • Monitor closely.<br>• Provide supportive care according to institutional standards. | • Interrupt dabrafenib and trametinib.<br>• Restart with dabrafenib and trametinib reduced by one dose level once toxicity resolves to ≤ Grade 1 or baseline or permanently discontinue dabrafenib and trametinib at the discretion of investigator. |

These are general guidelines and investigators should always use clinical judgment in adverse event management 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

[redacted]

related toxicity is a possibility. All dose modifications are based on the worst preceding toxicity using Common Terminology Criteria for Adverse Events (CTCAE) Version v4.03.

If treatment related toxicities occur that are specific to combination treatment of dabrafenib and trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exception shown below:

Exception where dose modifications are necessary for **only dabrafenib**:

- Uncomplicated pyrexia (Table 6-16)
- Uveitis (Table 6-21)

Exception where dose modifications are necessary for **only trametinib**:

- Retinal vein occlusions (RVO) (Table 6-19) and retinal pigment epithelial detachment (RPED) Table 6-20)
- Left ventricular ejection fraction (LVEF) reduction (Table 6-23)

If the patient requires a dose interruption of > 28 days (greater than 6 weeks for uveitis, iritis, see Table 6-21) from the previous dose for persistent grade 2 or greater dabrafenib and/or trametinib treatment related toxicity, then the patient must be discontinued from study treatment. Up to two dose reductions will be allowed.

Dose reductions will occur in increments of 50 mg from the total daily dose for dabrafenib capsules and in increments of 0.5 mg from the total daily dose for trametinib tablets. If a patient is receiving trametinib 0.05 mg/mL oral solution, dose modification guidelines in Table 6-12 and Table 6-13 should be followed. If patient is receiving dabrafenib dispersible tablet, dose modification guidelines in Table 6-14 and Table 6-15 should be followed. If more than two dose reductions are needed, the patient must be discontinued from study treatment. Patients who discontinue study treatment due to adverse event will be followed until resolution or stabilization of the event. All dose changes and the reason for dose interruption must be recorded on the Dosage Administration Record eCRF.

**Table 6-12 Dose Modification for trametinib (TMT212) oral solution for patients greater or equal to 6 years old**

| Weight (kg) | Dose | | Dose Reduction Level 1 | | Dose reduction Level 2 | |
|---|---|---|---|---|---|---|
| | mL | mg | mL | mg | mL | mg |
| 10-12.5 | 5 | 0.25 | 3.5 | 0.175 | 2.5 | 0.1225 |
| 12.6-16.5 | 7.5 | 0.375 | 5 | 0.25 | 3.5 | 0.175 |
| 16.6-24.5 | 10 | 0.5 | 7 | 0.35 | 5 | 0.25 |
| 24.6-35 | 15 | 0.75 | 10 | 0.5 | 7 | 0.35 |
| 35.1-45 | 20 | 1.0 | 14 | 0.7 | 10 | 0.5 |
| 45.1-55 | 25 | 1.25 | 17.5 | 0.875 | 12 | 0.6 |
| 55.1-68 | 30 | 1.5 | 20 | 1 | 14 | 0.7 |
| 68.1-72 | 35 | 1.75 | 25 | 1.25 | 17.5 | 0.875 |
| >72 | 40 | 2 | 28 | 1.4 | 20 | 1 |

Dose: 0.025 mg/kg/day
Dose Level 1: ~30% reduction
Dose Level 2: ~30% reduction

[redacted]

**Table 6-13 Dose Modification for trametinib (TMT212) for oral solution for patients less than 6 years old**

| Weight (kg) | Dose | | Dose Reduction Level 1 | | Dose reduction Level 2 | |
|---|---|---|---|---|---|---|
| | mL | mg | mL | mg | mL | mg |
| 7-9.9 | 5 | 0.25 | 3.5 | 0.175 | 2.5 | 0.1225 |
| 10-12.5 | 7.5 | 0.375 | 5 | 0.25 | 3.5 | 0.175 |
| 12.6-16.5 | 10 | 0.5 | 7.5 | 0.375 | 5 | 0.25 |
| 16.6-24.5 | 12.5 | 0.625 | 10 | 0.5 | 7 | 0.35 |
| 24.6-35 | 17.5 | 0.875 | 15 | 0.75 | 10 | 0.5 |
| 35.1-45 | 25 | 1.25 | 20 | 1 | 14 | 0.7 |
| 45.1-55 | 30 | 1.5 | 25 | 1.25 | 17.5 | 0.875 |
| ≥55.1 | 40 | 2 | 30 | 1.5 | 20 | 1 |

Dose: 0.032 mg/kg/day
Dose Level 1: ~0.025 mg/kg/day
Dose Level 2: ~ 30% reduction

**Table 6-14 Dose Modification for dabrafenib (DRB436) dispersible tablet for patients less than 12 years of age**

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

**Table 6-15 Dose Modification for dabrafenib (DRB436) dispersible tablet for patients greater or equal 12 years of age**

| Weight | Dose (b.i.d) | Dose Reduction Level 1 (b.i.d) | Dose Reduction Level 2 (b.i.d) |
|---|---|---|---|
| 10-11.5 | 20 mg | 10 mg | 0 mg |
| 11.6-17.5 | 30 mg | 20 mg | 10 mg |
| 17.6-20.5 | 40 mg | 30 mg | 20 mg |
| 20.6-24.5 | 50 mg | 40 mg | 30 mg |

[redacted]

| | | | |
|---|---|---|---|
| 24.6-28.5 | 60 mg | 50 mg | 40 mg |
| 28.6-32.5 | 70 mg | 60 mg | 50 mg |
| 32.6-36.5 | 80 mg | 70 mg | 50 mg |
| 36.6-40.5 | 90 mg | 80 mg | 60 mg |
| 40.6-43.5 | 100 mg | 90 mg | 60 mg |
| 43.6-47.5 | 110 mg | 100 mg | 70 mg |
| 47.6-51.5 | 120 mg | 110 mg | 80 mg |
| 51.6-55.5 | 130 mg | 120 mg | 80 mg |
| 55.6-64.5 | 140 mg | 130 mg | 100 mg |
| ≥64.6 | 150 mg | 140 mg | 110 mg |
| Dose: 4.5 mg/kg/day<br>Dose level 1: 3.75 mg/kg/day<br>Dose level 2: 3.00 mg/kg/day | | | |

If a patient's dose of dabrafenib and trametinib has been reduced per the dose modification instructions, dose re-escalation may be considered provided the following criteria are met:

- A period of 4 weeks of treatment have passed since restarting dosing at the lower dose level and treatment has been well tolerated
- Patient is deriving clinical benefit

Dose re-escalation follows the same dosing steps as de-escalation, in increments of 50 mg from the total daily dose for dabrafenib capsules and in increments of 0.5 mg from the total daily dose for trametinib tablets. Patients receiving trametinib 0.05 mg/mL oral solution are to follow Table 6-12 and Table 6-13 for dose re-escalation. Patients receiving dabrafenib dispersible tablet are to follow Table 6-14 and Table 6-15 for dose re-escalation. The dabrafenib dose must not exceed 150 mg twice daily (300 mg total daily dose). The trametinib dose must not exceed 2 mg once daily.

The following sections address the specific instructions for mandatory dose modifications and recommended management for AEs considered suspected to be related to study treatment.

#### 6.3.1.1 Pyrexia

Episodes of pyrexia syndrome have been observed in patients receiving dabrafenib monotherapy or in combination with trametinib. The pyrexia syndrome is defined as treatment-related fever (≥38°C) or chills/rigors/night sweats or flu-like symptoms. In a minority of cases pyrexia was accompanied by symptoms such as severe chills/rigors, dehydration, and hypotension, dizziness or weakness and required hospitalization. The incidence and severity of pyrexia syndrome are increased when dabrafenib is used in combination with trametinib compared to dabrafenib monotherapy.

Patients and guardians must be instructed on the importance of immediately reporting febrile episodes. Dabrafenib and trametinib must be interrupted promptly and anti-pyretics (acetominophen, ibuprofen, similar) started at the very first symptom of pyrexia or its associated prodrome (chills or rigors or night sweats or flu-like symptoms). Adequate hydration status should be maintained. Dabrafenib and trametinib should be restarted upon improvement of symptoms of at least 24 hours, and at the same dose.

[redacted]

In the event of recurring pyrexia events despite the use of antipyretics and drug interruption, the use of oral corticosteroids may be considered when restarting dabrafenib and trametinib. In patients experiencing pyrexia associated with rigors, severe chills, dehydration or hypotension, serum creatinine increase and other evidence of renal function decrease 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 are to be reported as a SAE.

Guidelines for dose modification and management for pyrexia syndrome considered to be related to dabrafenib are provided in Table 6-16.

**Table 6-16 Mandatory dose modification and recommended clinical management for pyrexia syndrome suspected to be related to dabrafenib and/or trametinib treatment**

| **Pyrexia** | | |
|---|---|---|
| **Occurrence** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| **1st occurrence and subsequent occurrences** | • Re-educate patient/family about pyrexia syndrome and immediately interrupt dabrafenib and trametinib at the very first symptom of pyrexia or its associated prodrome (chills or rigors or night sweats or flu-like symptoms).<br>• Clinical evaluation for infection and hypersensitivity[a]<br>• Laboratory work-up[a]<br>• Administer anti-pyretic treatment with non-steroidal anti-inflammatory drugs (NSAID) and/or paracetamol[b]<br>• Oral hydration should be encouraged in patients without evidence of dehydration. Intravenous hydration is recommended in patients experiencing pyrexia complicated by dehydration/hypotension.<br>• For recurring pyrexia events despite the use of anti-pyretics and dose interruption, consider oral corticosteroids (i.e. prednisone 10mg or pediatric equivalent, or more) for at least 5 days or as clinically indicated.<br>• Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia | • Dabrafenib and trametinib must be interrupted promptly at the very first symptom of pyrexia or its associated prodrome (chills, rigors, night sweats or flu-like symptoms) Adequate hydration status should be maintained. Dabrafenib and trametinib should be restarted upon improvement of symptoms of at least 24 hours, at the same dose<br>• If pyrexia cannot be managed with interruption, dose reduction must be considered if clinically indicated. |

a. For patients experiencing pyrexia, a clinical evaluation and laboratory work-up is mandatory for each event; thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver transaminases, blood culture, and urine culture.

b. Anti- pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment is recommended to be discontinued after three days in the absence of pyrexia.

[redacted]

### 6.3.1.2 Renal Insufficiency

Cases of renal insufficiency have occurred in adult patients receiving dabrafenib and the combination of dabrafenib and trametinib. 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 Table 6-17.

**Table 6-17 Mandatory dose modifications and recommended clinical management guidelines for renal function alterations**

| **NCI-CTCAE v4.03** | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| Grade 1 (Creatinine > ULN to ≤ 1.5× ULN) | • Monitor creatinine weekly<br>• If creatinine return to baseline resume routine creatinine monitoring per protocol<br>• Promote hydration and cessation of nephrotoxic drugs. | • Continue dabrafenib and trametinib at the same dose. |
| Grade 2 (Creatinine > 1.5× to ≤ 3× ULN | • Monitor creatinine every 2 to 3 days<br>• Consult with specialist and consider renal biopsy<br>• Promote hydration and cessation of nephrotoxic drugs. | **1st occurrence**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reinstate dabrafenib and trametinib at the same dose.<br>**2nd occurrence:**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**3rd occurrence:**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**4th occurrence**<br>• Permanently discontinue dabrafenib and trametinib. |
| Grade 3 (Creatinine > 3.0 to < 6×ULN) | • Monitor creatinine every 1 to 2 days.<br>• Consult with nephrologist.<br>• Promote hydration and cessation of nephrotoxic drugs. | **1st occurrence:**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower. Re-escalation of the |

[redacted]

| NCI-CTCAE v4.03 | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| | | patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**2nd occurrence:**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose. Re-escalation of the subject's dose is recommended if criteria in Section 6.3.1 are met.<br>**3rd occurrence:**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose, if available as dose level -2. If already at dose level -2 at time of occurrence, permanently discontinue dabrafenib and trametinib. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**4th occurrence:**<br>• Permanently discontinue dabrafenib and trametinib. |
| Grade 4: Creatinine > 6× ULN | • Monitor creatinine daily.<br>• Consult with specialist and recommend renal biopsy.<br>• Promote hydration and cessation of nephrotoxic drugs. | • Permanently discontinue dabrafenib and trametinib. |

### 6.3.1.3 Pneumonitis

Pneumonitis has been observed in patients receiving trametinib in combination with dabrafenib. Guidelines for dose modification and management of pneumonitis considered to be related to study treatment by the investigator are provided in Table 6-18.

[redacted]

**Table 6-18 Mandatory dose modifications and recommended clinical management guidelines for pneumonitis**

| **Pneumonitis (NCI-CTCAE v4.03)** | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| Grade 1: Radiographic changes only- Asymptomatic | • CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks<br>• Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection<br>• Monitoring of oxygenation via pulse oximetry recommended<br>• Consultation of pulmonologist recommended. | • Continue dabrafenib and trametinib at the same dose. |
| Grade 2: Symptomatic medical intervention indicated; limits instrumental Activities of Daily Living (ADLs) | • CT scan (high-resolution with lung windows)<br>• Monitor symptoms daily, consider hospitalization<br>• Clinical evaluation and laboratory work up for infection<br>• Consult pulmonologist<br>• Pulmonary function tests if normal at baseline, repeat every 8 weeks<br>• Bronchoscopy with biopsy and/or bronchoscopic alveolar lavage (BAL) recommended<br>• Symptomatic therapy including corticosteroids if clinically indicated (systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated). | **1st occurrence:**<br>• Interrupt trametinib until recovery to ≤ Grade 1 or baseline. Dabrafenib may continue at the same dose.<br>  • Once recovered, reduce trametinib to the next lower dose. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>  • If no recovery to ≤ Grade 1 within 4 weeks, permanently discontinue trametinib. Dabrafenib may continue.<br>  • If worsens treat as Grade 3 or 4. |
| Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated | • CT scan (high-resolution with lung windows)<br>• Clinical evaluation and laboratory work-up for infection<br>• Consult pulmonologist<br>• Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal<br>• Bronchoscopy with biopsy and/or BAL if possible<br>• Treat with intravenous steroids (methylprednisolone 125 mg or equivalent) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg/day or dexamethasone 4 mg every 4 hours or equivalent). | • Interrupt trametinib until recovery to Grade ≤1 or baseline. Dabrafenib may continue.<br>  • Once recovered, trametinib may be restarted at the next lower dose. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>  • If no recovery to Grade ≤ 1 or baseline within 4 weeks, permanently discontinue trametinib. Dabrafenib may continue. |

[redacted]

| Pneumonitis (NCI-CTCAE v4.03) | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| | • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication | |
| Grade 4: Life- threatening respiratory compromise | • Same as Grade 3 | • Same as Grade 3 |

#### 6.3.1.4 Dose modification and management guideline for visual changes suspected to be related to dabrafenib and/or trametinib treatment

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

Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO). Treatment emergent cases of RVO and RPED are to be reported as SAEs.

Guidelines for dose modifications and management for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in Table 6-19 and Table 6-20.

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. Guidelines for dose modifications and management for uveitis, including iritis considered to be related to study treatment are provided in Table 6-21.

**Table 6-19 Mandatory dose modification and recommended clinical management for visual changes and/or ophthalmic examination findings suspected to be related to trametinib treatment**

| Visual changes (Eye disorders – Other, CTCAE Version 4.03, retinal, and similar) | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| Grade 1<br><br>If visual changes are clearly unrelated to study treatment (e.g. allergic conjunctivitis), monitor closely but ophthalmic examination is not required | Initiate local therapy and consult ophthalmologist within 7 days of onset. | • If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. Continue dabrafenib.<br><br>If RPED and RVO excluded, continue (or restart) trametinib at same dose level<br><br>• If RPED suspected or diagnosed: see RPED dose modification Table 6-20; report as SAE if diagnosed.<br>• If RVO diagnosed: Permanently discontinue trametinib and report as SAE. |

[redacted]

| Visual changes (Eye disorders – Other, CTCAE Version 4.03, retinal, and similar) | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| Grade 2 and Grade 3 | • Initiate local therapy and consult ophthalmologist immediately | Interrupt trametinib. Dabrafenib may be continued at the current dose.<br>• If RPED and RVO excluded, restart trametinib at same dose level.<br>• If RPED diagnosed, see RPED dose modification in Table 6-20; report as SAE.<br>• If RVO diagnosed: Permanently discontinue trametinib and report as SAE. |
| Grade 4 | • Initiate local therapy and consult ophthalmologist immediately | • Interrupt trametinib. Dabrafenib may be continued at the same dose.<br>• If RPED and RVO excluded, consider restarting trametinib at the same or reduced dose level.<br>• **If RVO diagnosed, permanently discontinue trametinib and report as SAE.** |

**Table 6-20 Mandatory dose modification and recommended clinical management for retinal pigment epithelial detachments (RPED) suspected to be related to trametinib treatment**

| Retinal pigment epithelial detachments (RPED) | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| • Grade 1 (Asymptomatic; clinical or diagnostic observations only) | • If RPED worsens follow instructions below. | • Continue treatment with retinal evaluation monthly until resolution. |
| • Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity). | • Retinal evaluation monthly. | • Interrupt trametinib.<br>• If improved to ≤ Grade 1, restart trametinib at a lower dose. |

**Table 6-21 Mandatory dose modification and recommended clinical management for uveitis, including iritis suspected to be related to dabrafenib treatment**

| Grade | Recommended adverse event management guidelines | Mandatory dose modification requirements |
|---|---|---|
| Grade 1 | Initiate local therapy and consult ophthalmologist immediately | • Continue dabrafenib and trametinib<br>• If no response to local treatment within 7 days, interrupt dabrafenib. Once uveitis resolves, restart dabrafenib<br>• Continue trametinib |
| Grade 2, 3 or 4 | Initiate local therapy and consult ophthalmologist immediately | • Interrupt dabrafenib<br>• If ≥ grade 2 uveitis (including iritis and iridocylitis) lasts >6 weeks on local treatment and dabrafenib has not been restarted, permanently discontinue dabrafenib<br>• Continue trametinib |

[redacted]

#### 6.3.1.5 Dose modification and management guideline for new malignancies suspected to be related to dabrafenib and/or trametinib treatment

**New Malignancies: Cutaneous and Non-cutaneous**

##### 6.3.1.5.1 Cutaneous malignancies

Cutaneous squamous cell carcinoma (CuSCC), keratoacanthomas (KA) and new primary melanomas have been observed in patients treated with dabrafenib and dabrafenib/trametinib combination therapy. These treatment-related lesions should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC, KA, or new primary melanoma, however cuSCC and new primary melanoma are to be reported as a SAE. In addition, a biopsy of the lesion should be taken, where possible, and submitted for further analyses and a summary of the results submitted to Novartis. Patients should be instructed to immediately inform their physician if new lesions develop. Skin examinations are to be performed prior to initiation of study treatment and throughout therapy as detailed in the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). Monitoring will occur at 3 and 6 months following discontinuation of study treatment or until initiation of another anti-neoplastic therapy. Monitoring of the skin can be performed by a qualified local physician at the discretion of the investigator during non-clinic visits. If possible, the same local physician should perform each exam throughout the study to ensure consistency between evaluations.

##### 6.3.1.5.2 Non-Cutaneous Malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling 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. Consider the benefits and risks before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

New non-cutaneous malignancies are to be reported as a SAE. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses including RAS mutation status with the results provided to Novartis. [redacted]

Patients should be monitored for secondary malignancy as clinically appropriate. This may include review of signs and symptoms and physical exam. If there is clinical concern or possible increased risk for the development of an occult secondary malignancy, additional imaging such as whole-body MRI may be 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.

[redacted]

#### 6.3.1.6 Dose modification and management guideline for 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 patients 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.

#### 6.3.1.7 Guidelines for prolonged QTc

Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided in Table 6-22.

If ECG results demonstrate a prolonged QT interval (QTcF ≥501 msec), obtain two or more additional ECGs over a brief period, and then use the average QTc values of the three ECGs to determine if study treatment should be interrupted or discontinued. If the QTc prolongation resolves to Grade 1 or baseline, the patient may resume study treatment if the investigator determines that the patient may benefit from further treatment. This determination must be documented by the investigator in the patient's medical record.

**Table 6-22 Withholding and Stopping Criteria for QTc-Prolongation**

| **QTc Prolongation** | **Action and Dose Modifications** |
|---|---|
| QTcF ≥501 msec<br>Based on average QTc value of triplicate ECGs | • Assess the quality of the ECG recording and the QT value and repeat if needed<br>• Interrupt dabrafenib and trametinib (study treatments) until QTcF prolongation resolves to Grade 1 or baseline<br>• Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits.<br>• Review concomitant medication associated with QT prolongation, including drugs with a "known", "possible" or "conditional risk of Torsade de pointes" and drugs with the potential to increase the risk of study drug exposure related to QT prolongation<br>• If event resolves to grade 1 or baseline, patient may restart study treatments at current dose level if patient may benefit from further treatment<br>• If event does not resolve within 28 days, permanently discontinue study treatments. Consider evaluation with cardiologist.<br>• If event recurs, permanently discontinue study treatments. Consider evaluation with cardiologist. |
| Abbreviations: ECG = electrocardiogram; msec = milliseconds; QTcF = QT duration corrected for heart rate by Fredericia formula. | |

#### 6.3.1.8 Left Ventricular Ejection Fraction Stopping Criteria

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in patients receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients, Table 7-3). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-23. ECHO to be performed at baseline and at follow up visit(s).

[redacted]

**Table 6-23 Mandatory dose modification and recommended clinical management for LVEF suspected to be related to dabrafenib and/or trametinib treatment**

| Left Ventricular Ejection Fraction decrease (NCI-CTCAE v4.03) | | |
|---|---|---|
| **LVEF-drop (%) & clinical symptoms** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| **Asymptomatic:**<br>Absolute decrease of >10% in LVEF compared to baseline **and** ejection fraction below the institution's LLN | • Closely monitoring LVEF via ECHO, repeat ECHO within 2 weeks*.<br>• If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN **and** absolute decrease ≤10% compared to baseline)<br>  • Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter.<br>• If repeat LVEF does not recover within 4 weeks.<br>  • Consult with cardiologist<br>  • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution | • **Report as SAE.**<br>• Interrupt trametinib.<br>• If the LVEF recovers, restart trametinib reduced by one dose level and continue dabrafenib at the same dose level.<br>• More than two occurrence, permanently discontinue trametinib.<br>• Permanently discontinue trametinib if repeat LVEF does not recover within 4 weeks. |
| **Symptomatic:**<br>Resting LVEF 39-20%<br>or >20% absolute reduction from baseline<br>resting LVEF <20% | • Consult with cardiologist.<br>• Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution. | • **Report as SAE.**<br>• Permanently discontinue trametinib.<br>• Interrupt dabrafenib<br>• Restart dabrafenib if LVEF recovers including resolution of symptoms. |

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

### 6.3.1.9 Cardiac valvular toxicity stopping criteria

**Grade 2:** Patients who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity) should temporarily discontinue dabrafenib and trametinib 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, the patient may be restarted at a reduced dose(s). For such patients, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after re-challenge, 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 patient should permanently discontinue dabrafenib and trametinib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

**Grade 3:** Patients with a Grade 3 valvular toxicity (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) must discontinue dabrafenib and trametinib. 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 and the patient is receiving unequivocal clinical benefit from the study treatment

[redacted]

as per documented investigator assessment, the patient may restart dabrafenib and trametinib at a reduced dose.

**Grade 4:** Patients with a Grade 4 valvular toxicity [life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)] must **permanently discontinue** dabrafenib and trametinib.

#### 6.3.1.10 Dose modification and management guideline for skin rash

Guidelines for dose modification and management of skin rash considered to be related to study treatment by the investigator are provided in Table 6-24.

**Table 6-24 Mandatory dose modifications and recommended clinical management guidelines for rash**

| **Rash Events (NCI-CTCAE v4.03)** | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| Grade 1: Rash covering < 10% body surface area | • Initiate prophylactic and symptomatic treatment measures.<br>• Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream)<br>• Reassess after 2 weeks | • Continue dabrafenib and trametinib at the same dose. |
| Grade 2: 10-30% of body surface area | • If tolerable, as per Grade 1<br>• If intolerable, initiate systemic steroids (0.5 to 1 mg/kg/day prednisone or equivalents)<br>• If symptoms persist or recur consider skin biopsy. | • If tolerable, continue dabrafenib and trametinib at the same dose.<br>• If intolerable:<br>**1st occurrence**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1, and reduce dabrafenib and trametinib to the next dose level. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met. |
| Grade 3: More than 30% of body surface area | • Obtain a skin biopsy and dermatology consult.<br>• Initiate therapy with high dose steroids (1 to 2 mg/kg/day prednisone or equivalents) | **1st occurrence**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1, and reduce dabrafenib and trametinib to the next dose level. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**2nd occurrence**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the |

[redacted]

| Rash Events (NCI-CTCAE v4.03) | | |
|---|---|---|
| **Grade** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| | | patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**3rd occurrence**<br>• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level, if available as dose level -2. If already at dose level -2 at time of occurrence, permanently discontinue dabrafenib and trametinib. Re-escalation of the patient's dose is recommended if criteria in Section 6.3.1 are met.<br>**4th occurrence**<br>• Permanently discontinue dabrafenib and trametinib. |
| Grade 4: Life-threatening | • Same as Grade 3 | • Permanently discontinue dabrafenib and trametinib. |

### 6.3.1.11 Management of Severe cutaneous adverse reactions (SCAR)

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

### 6.3.1.12 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 (refer to Table 6-9)
- **Pancreatitis** – In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis. If pancreatitis is suspected, dabrafenib should be held until recovery. Trametinib dosing

[redacted]

may continue. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis

#### 6.3.1.13 Dose modification and management guideline for hypertension suspected to be related to dabrafenib and/or trametinib treatment

Increases in blood pressure have been observed in patients receiving trametinib. For adequate monitoring and management of hypertension, all blood pressure assessments should be performed under the following optimal conditions:

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

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

Persistent hypertension is defined as an increase of systolic or diastolic blood pressure (SBP, DBP) > 95th percentile for age in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the protocol visits outlined in Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3. Ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP or DBP >95$^{th}$ percentile in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension.

For patients experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for dose modifications and management of hypertension are described below in Table 6-25.

**Table 6-25 Mandatory dose modification and recommended clinical management for hypertension**

| **Hypertension (NCI-CTCAE 4.03)** | | |
|---|---|---|
| **Severity** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| (Scenario A)<br>• Asymptomatic and persistent[a] increase of SBP or DBP >95$^{th}$ percentile<br>• Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg). | • Adjust current or initiate new antihypertensive medication.<br>• Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP<br>• If BP is not well controlled within 2 weeks, recommended to refer to a specialist and go to scenario (B). | • Continue dabrafenib and trametinib at the same dose. |

[redacted]

| Hypertension (NCI-CTCAE 4.03) | | |
|---|---|---|
| **Severity** | **Recommended adverse event management guidelines** | **Mandatory dose modification requirements** |
| (Scenario B)<br>• Asymptomatic increase of SBP or DBP >99th percentile, or<br>Failure to achieve well-controlled BP within 2 weeks in Scenario A | • Adjust current or initiate new antihypertensive medication(s).<br>• Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP. | • Interrupt dabrafenib and trametinib if clinically indicated.<br>• Once BP is well controlled, restart dabrafenib and trametinib reduced by one dose level. |
| • Symptomatic[c] hypertension or<br>• Persistent increase in SBP or DBP >99th percentile, despite antihypertensive medication and dose reduction of study treatment. | • Adjust current or initiate new antihypertensive medication(s)<br>• Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP.<br>• Referral to a specialist for further evaluation and follow-up is recommended. | • Interrupt dabrafenib and trametinib.<br>• Once BP is well controlled, restart dabrafenib and trametinib reduced by one dose level. |
| • Refractory hypertension unresponsive to above interventions or hypertensive crisis. | • Continue follow-up per protocol. | • Permanently discontinue dabrafenib and trametinib. |

a. Hypertension detected in two separate readings during up to three consecutive visits.
b. Well-controlled blood pressure defined as SBP and DBP ≤ 95th percentile in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

#### 6.3.1.14 Dose modification and management guideline for hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur when dabrafenib is administered with trametinib. Permanently discontinue dabrafenib and trametinib for all Grade 4 hemorrhagic events and for any persistent Grade 3 hemorrhagic events. Withhold dabrafenib and trametinib for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

#### 6.3.1.15 Dose modification and management guideline for thromboembolic events

Advise patients to immediately seek medical care if they develop symptoms of DVT or pulmonary embolism (PE), such as shortness of breath, chest pain, or arm or leg swelling. If any signs or symptoms of venous thromboembolism are present, the patient will undergo specific laboratory and medical imaging assessments to confirm. The medical imaging assessment(s) selected will depend on the anatomic site or organ of involvement. If the diagnosis is confirmed, appropriate medical care according to standard local clinical practice should be initiated immediately.

Permanently discontinue trametinib for life threatening PE. Withhold trametinib for uncomplicated venous thromboembolism for up to 3 weeks; if improved, trametinib may be resumed at a lower dose level. Dabrafenib dosing may continue.

[redacted]

#### 6.3.1.16 Dose modification and management guidelines for carboplatin with vincristine treatment

The induction cycle should only be interrupted in the event of grade 3 neurotoxicity, grade 2 nephrotoxicity, grade 4 hematologic toxicity, or disease progression.

##### 6.3.1.16.1 Myelosuppression

To begin induction or each cycle of maintenance chemotherapy:

- ANC should be ≥1000/μL and platelet count ≥100,000/μL

If ANC <1,000/μL or platelet count <100,000/μL:

- hold administration and repeat counts every 7 days.

Each cycle of induction or maintenance chemotherapy should begin at full dose, unless delays have been required because of myelosuppression during the previous two successive cycles. If this has occurred, then begin the next cycle with 75% of full dose carboplatin.

During induction or maintenance:

- If ANC falls <500/μL and/or platelet count <50,000/μL, hold chemotherapy administration and repeat counts every 7 days until they recover to an ANC of ≥1000/μL and platelet count of ≥100,000/μL.
- Resume at 75% of full dose carboplatin when these levels are reached. The 75% reduced dose should continue for the remainder of Induction or Maintenance.

However, if a patient is dose reduced during Induction, they can start the first maintenance cycle at 100% dosing. Those patients who are dose reduced during maintenance, should continue at the dose reduction throughout the remainder of all maintenance cycles.

Once induction or maintenance has started, vincristine should not be held due to Myelosuppression.

##### 6.3.1.16.2 Nephrotoxicity

If creatinine is greater than upper limit of normal for the patient's age, a creatinine clearance or GFR must be determined. If the creatinine clearance is <75% of normal for the patient's age, then the carboplatin dose should be held until creatinine clearance recovers to 75% of normal. Carboplatin dose should then be reduced by 25%.

##### 6.3.1.16.3 Hepatotoxicity

If Grade 3-4 hepatotoxicity develops during maintenance, hold chemotherapy until toxicity is less than Grade 2. If the etiology of the toxicity is unexplained, then the dose of vincristine and carboplatin should be reduced by 25%.

[redacted]

#### 6.3.1.16.4 Neurotoxicity

**Seizures**

For seizure due to vincristine, hold one dose, then resume at 1.0 mg/m$^2$ (1.5 mg max) while on anticonvulsants. If seizures do not recur, escalate to full dose. For seizures not associated with vincristine, place patient on anticonvulsants after appropriate neurological evaluations, and proceed with chemotherapy at full doses.

**Encephalopathy**

Neither carboplatin nor vincristine commonly cause encephalopathy. Therefore the patient must be carefully assessed for other causes including hydrocephalus, shunt malfunction, over-hydration, too rapid withdrawal of steroids, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothalamic dysfunction, hemorrhage, anticonvulsant toxicity, etc. If a correctable cause cannot be identified, delay therapy up to 2 weeks and proceed only if patient has improved substantially. Proceed with 20% reduction of both carboplatin and vincristine.

**Peripheral neuropathy**

For peripheral neuropathy from vincristine including weakness, paresthesia, ileus requiring IV therapy, stridor or ptosis or visual change, hold vincristine until symptoms are markedly improved. Resume at 66% dose or 1.0 mg/m$^2$ (1.5 mg max). Escalate to full dose as tolerated. For jaw pain, constipation, mild foot drop, do not modify dose unless causing significant patient discomfort. Then the vincristine may be reduced to 80% or 1.2 mg/m$^2$ (1.5 m$^2$) and escalate as tolerated.

#### 6.3.1.16.5 Allergic reactions

Allergic reactions may occur in 10 to 30% of children receiving frequent carboplatin. These reactions can include facial flushing, urticaria, agitation, abdominal pain, edema, and sometimes bronchospasm leading to hypoxia and even respiratory arrest.

Patients receiving carboplatin should be monitored by an experienced nurse throughout the infusion and for 1 hour after.

Patients with any respiratory compromise as a result of carboplatin therapy should not receive carboplatin again and will be discontinued from the study. They will continue into post-treatment follow up.

Patients with mild or questionable reactions without respiratory compromise may continue on therapy with pre-treatment as per below.

Carboplatin allergies should be documented as an adverse event in the eCRF.

Carboplatin should always be given in a setting with rapid access to pediatric advanced life-supporting support capability.

Consideration should be given to provide effective measures to prevent any recurrences of allergic reactions.

[redacted]

The following are offered as a supplement to institutional practice. If an allergic reaction occurs it should be treated as for any other drug reactions as follows:

1. Stop the carboplatin infusion
2. Rapid assessment and management of the airway
3. If airway compromise or acute bronchospasm, give Epinephrine 0.01 ml/kg (maximum 0.5 mL) of 1:1000 solution SQ and repeat in 20 minutes if necessary.
4. Albuterol inhaled can be used to treat resistant bronchospasm.
5. Diphenhydramine 1-2 mg/kg slow IV will help shorten the duration of the reaction, but does not have an immediate effect.
6. Glucocorticoids may have no effect for 6 to 12 hours, but may help prevent relapse of severe reactions.
7. Patients with mild to moderate reactions (urticaria or mild bronchospasm) should be observed for a minimum of 6 hours. Those with moderate to severe reactions may relapse and should be observed in the hospital at least overnight.
8. Prevention of recurrence:
    a. Children with respiratory compromise should no longer receive carboplatin and are discontinued from the study.
    b. Children with mild or questionable reactions can continue carboplatin with close monitoring and pre-treatment with steroids and diphenhydramine. For optimal effect, give Prednisone 1 mg/kg q6 hours PO or Prednisolone 1 mg/kg IV q6 hours for 3 to 4 doses prior to carboplatin, with the last dose one hour before carboplatin. Also give diphenhydramine 1 mg/kg IV or PO one hour before carboplatin. All carboplatin should be given in a monitored setting with resuscitation drugs and equipment readily available. A guideline for desensitization and continuation of treatment if a patient's tumor is responding well to carboplatin treatment has been published (Broom 1996).

#### 6.3.1.17 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and have to be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline (if elevated at baseline) AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

[redacted]

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and $< 5$) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug.
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

## 6.4 Concomitant medications

### 6.4.1 Permitted concomitant therapy

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of post treatment follow up. Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the Concomitant Medications 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 on the Medical History eCRF.

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

[redacted]

### 6.4.2 Permitted concomitant therapy requiring caution and/or action

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 patients for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Appendix 1.
- 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.
- The renal effects of nephrotoxic compounds (e.g. aminoglycosides) may be potentiated by carboplatin and should be used with caution.

#### 6.4.2.1 Anti-cancer Surgery

For patients enrolled in the HGG cohort, anti-cancer surgery is allowed for patients enrolled on the study after at least 8 months on treatment or after radiologic progression of disease has been confirmed by investigator. Study treatment may be taken up to two days prior to surgery as deemed appropriate by the investigator. If the investigator determines that further treatment with dabrafenib and trametinib may be clinically beneficial to the patient, study treatment may be resumed when the surgical wound is stable, the patient is able to take oral medications and at least 3 days after surgery. Prior to anti-cancer surgery, investigators are required to complete a RANO evaluation.

For patients enrolled into the LGG cohort, elective anti-cancer surgery should not be performed prior to either centrally confirmed radiologic progression of disease or at least a total of 36 months of treatment plus follow-up, whichever comes first. Elective anti-cancer surgery prior to documented radiologic progression does not qualify a patient for cross over therapy within this protocol. Study treatment may be taken up to one day prior to surgery as deemed appropriate by the investigator. If the investigator determines that further treatment with dabrafenib and trametinib may be clinically beneficial to the patient, study treatment may be resumed when the patient has recovered sufficiently to consume a semi-solid diet. Prior to anti-cancer surgery, investigators are required to complete a RANO evaluation.

[redacted]

#### 6.4.2.2 Radiotherapy

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. To reduce this risk, it is recommended that dabrafenib be held for at least 3 days before and after fractionated radiotherapy and at least 1 day before and after stereostatic radiotherapy (Anker 2016). These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury. Prior to starting radiotherapy, investigators are required to complete a RANO evaluation.

Elective anti-cancer radiotherapy should not be performed prior to the either documented radiologic progression of disease or at least a total of 36 months of treatment and follow-up, whichever comes first. Elective anti-cancer radiotherapy prior to documented radiologic progression does not qualify a patient for cross over therapy (LGG cohort) within this protocol.

### 6.4.3 Prohibited concomitant therapy

The use of certain medications and illicit drugs within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of study drug 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 (except for anti-cancer surgery according to Section 6.4.2.1 and radiotherapy in Section 6.4.2.2);
- 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 inhibitor, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (Appendix 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. The list may be modified based on emerging data.
- Vincristine is a substrate for CYP3A. Drugs that are strong inhibitors or inducers of CYP3A (Appendix 1) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted, consider therapeutic substitutions for these medications.
- Vincristine is also a substrate for P-glycoprotein (P-gp). The concomitant use of potent P-pg inhibitors or inducers should be avoided.
- Simultaneous administration of phenytoin and vincristine have been reported to reduce blood levels of phenytoin and to increase seizure activity.

[redacted]

## 6.5 Patient numbering, treatment assignment or randomization

### 6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment or is not randomized (LGG cohort) for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient did not receive study drug or was not randomized (for LGG cohort).

### 6.5.2 Treatment assignment or randomization

#### HGG Cohort

All patients will receive the same treatment in the HGG cohort.

#### LGG Cohort

Patients in the LGG cohort will be randomized in a 2:1 ratio to dabrafenib with trametinib or carboplatin with vincristine.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

The investigator or his/her delegate will log on to the IRT and confirm that the LGG patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the LGG patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient.

### 6.5.3 Treatment blinding

All patients in the HGG cohort receive the same treatment therefore blinding is not applicable.

The LGG cohort is open label. Sponsor statisticians and statistical programmers will remain blinded to the identity of the treatment from the time of randomization until database lock for the LGG cohort only. Dummy randomization codes will be employed, with the actual

[redacted]

randomization codes kept strictly confidential until the time of database lock and treatment unblinding. However, independent statistician(s) and programmer(s) who will perform analyses for the DMC will have access to the randomization codes.

## 6.6 Study drug preparation and dispensation

Patients and/or caregivers will be provided with an adequate supply of study drugs for self-administration at home, including instructions for administration, until at least their next scheduled study visit.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. The study drugs will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at each visit. The site personnel will ensure that the appropriate dose of each study drug is provided at each visit.

Responsible site personnel will identify the study treatment package(s) to dispense by the medication(s) assigned by the IRT to the patient. Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

### 6.6.1 Study treatment packaging and labeling

Study treatment, dabrafenib (DRB436) and trametinib (TMT212), will be provided as global clinical open-labelled supply or commercially sourced supply. Global supplies will be packed and labeled under the responsibility of Novartis Drug Supply Management. Commercially sourced supplies will be packed and labeled as per local regulations.

Dabrafenib and trametinib in different formulations and strengths can be used once a protocol amendment with additional formulation description is approved.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, and Novartis Drug Supply Management supplied treatment will also contain a unique medication number (corresponding to study treatment and strength).

**Table 6-26 Packaging and labeling**

| Study treatments | Packaging | Labeling |
|---|---|---|
| DRB436 50mg | Capsules in bottles | DRB436 50mg HPMC |
| DRB436 75mg | Capsules in bottles | DRB436 75mg HPMC |
| DRB436 10mg | Dispersible tablets in bottles | DRB436 10mg |
| TMT212 0.5 mg | Tablets in bottles | TMT212 0.5 mg FCT |
| TMT212 2.0 mg | Tablets in bottles | TMT212 2.0 mg FCT |
| TMT212 PIB 5mg | Powder in bottle | TMT212 PIB 5mg FMI |
| Carboplatin 175 mg/m$^2$ | Refer to local product information | Refer to local product information |
| Vincristine 1.5 mg/m$^2$ | Refer to local product information | Refer to local product information |

[redacted]

### 6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

### 6.6.3 Study drug compliance and accountability

#### 6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

On PK sampling days, compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of dabrafenib and trametinib in plasma.

#### 6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### 6.6.3.3 Handling of other study treatment

Not applicable.

### 6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

# 7 Visit schedule and assessments

## 7.1 Study flow and visit schedule

Table 7-1 is the visit evaluation schedule for all HGG patients and LGG patients randomized to the dabrafenib and trametinib treatment arm. Table 7-2 is the visit evaluation schedule for LGG patients crossed over to dabrafenib plus trametinib treatment. Table 7-3 is the visit evaluation

[redacted]

schedule for LGG patients randomized to the chemotherapy treatment arm. These tables list all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Screening assessments must occur within 28 days of Week 1 (Day 1), as per Table 7-1. A urine pregnancy test must be completed on Day 1 and confirmed negative prior to dosing.

For Visits on Weeks 1 through 5, there is a general ±2 day visit window. For all subsequent visits, there is a general ±7 day visit window, except during the post-treatment follow which is every 16 weeks with ±14 day visit window.

[redacted]

**Table 7-1 Visit evaluation schedule for HGG and LGG dabrafenib and trametinib treatment arm**

| | | | Screening period | Treatment Period | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| Obtain Informed Consent/Assent | D | 7.1.2 | X | | | | | | | | | | | | | | | | |
| Obtain Informed Consent/Assent for post-progression treatment on dabrafenib with trametinib | D | 7.1.3.1 | | X – at the time of Treatment after Progression of Disease | | | | | | | | | | | | | | | |
| Local determination of *BRAF* V600 | D | 5.2, 7.1.2 | X | | | | | | | | | | | | | | | | |
| Tumor tissue for histopathology (HGG only) and *BRAF* central test confirmation (both HGG and LGG, paraffin block or slides) | D | 7.2.4 | X | | | | | | | | | | | | | | | | |
| IRT Registration (after ICF signature) | S | 7.1.2.1 | X | | | | | | | | | | | | | | | | |

[redacted]

| | | | Screening period | Treatment Period | | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| Eligibility checklist (within IRT) | S | 7.1.2.1 | X | | | | | | | | | | | | | | | | |
| IRT Randomization (LGG cohort only) | D | 6.5.2 | X | | | | | | | | | | | | | | | | |
| **Patient History** | | | | | | | | | | | | | | | | | | | |
| Demography | D | 7.1.2.3 | X | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | D | 5.2, 5.3 | X | | | | | | | | | | | | | | | | |
| Medical History | D | 7.1.2.3 | X | | | | | | | | | | | | | | | | |
| Seizure history | D | 7.2.2.2 | X | | | | | | | | | | | | | | | | |
| Diagnosis and extent of cancer | D | 7.1.2.3 | X | | | | | | | | | | | | | | | | |
| Prior antineoplastic therapy | D | 7.1.2.3 | X | | | | | | | | | | | | | | | | |
| Prior/concomitant medications and non-drug therapies | D | 7.1.2.3 | X | X – Continuous | | | | | | | | | | | | | | | |
| Prior surgical procedures | D | 7.1.2.3 | X | | | | | | | | | | | | | | | | |
| **Physical exam** | | | | | | | | | | | | | | | | | | | |
| Physical examination | S | 7.2.2.1 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

[redacted]

| | | | Screening period | Treatment Period | | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| Performance status (Karnofsky/Lansky) | D | 7.2.2.5 | X | X | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Height | D | 7.2.2.4 | X | | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Weight | D | 7.2.2.4 | X | X | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | D | 7.2.2.3 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| **Laboratory assessments** | | | | | | | | | | | | | | | | | | | |
| Hematology | D | 7.2.2.8.1 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Chemistry | D | 7.2.2.8.2 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Hepatitis testing for clearance (only for positive history) | D | 7.2.2.8.5 | X | | | | | | | | | | | | | | | | |
| Urinalysis | D | 7.2.2.8.3 | X | X | | | | X | X | X | X | X | X | X | X | X | X | | |
| Pregnancy test, serum (as applicable) | D | 7.2.2.8.4 | X | | | | | | | | | | | | | | | | |
| Pregnancy test, urine (as applicable) | D | 7.2.2.8.4 | | X – Day 1 and Monthly thereafter | | | | | | | | | | | | | X | | |

[redacted]

| | | | Screening period | Treatment Period | | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| Week | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 72, 88-n | | | |
| **Imaging** | | | | | | | | | | | | | | | | | | | |
| Tumor evaluation | D | 7.2.1 | X | | | | | | X | X | X | X | X | X | X | X | X | X - until PD or off study. | |
| Treatment after Progression of Disease on dabrafenib with trametinib | D | 7.1.3.1 | | X - See Section 7.1.3.1 for details | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | | | |
| Adverse events [redacted] | D | 8.1 | X – Continuous | | | | | | | | | | | | | | | | |
| Dermatological Evaluation | D | 7.2.2.6 | X | | | | X | X - Monthly (local qualified physician assessment for non-clinic visits) | | | | | | | | | X – At EOT, 3 and 6 months after the last dose of study treatment or until start of new antineoplastic therapy initiated | | |
| ECG | D | 7.2.2.10.1 | X | | | | | X | | X | | X | | X | | X | X | | |

[redacted]

| | | | Screening period | Treatment Period | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| Cardiac imaging/ ECHO | D | 7.2.2.10.2 | X | | | | | X | | X | | X | | X | | X | X | | |
| Ophthalmic examination | D | 7.2.2.7 | X | | | | | X | | X | | X | | X | | X | X | | |
| **Study drug administration** | | | | | | | | | | | | | | | | | | | |
| DRB436 administration | D | 6.1 | | X - Continuous b.i.d daily dosing | | | | | | | | | | | | | | | |
| TMT212 administration | D | 6.1 | | X – Continuous q.d. daily dosing | | | | | | | | | | | | | | | |
| **Pharmacokinetics** | | | | | | | | | | | | | | | | | | | |
| Full PK sampling DRB436 | D | 7.2.3 | | X | | X | X | | | | | | | | | | | | |
| Full PK sampling TMT212 | D | 7.2.3 | | X | | X | X | | | | | | | | | | | | |
| Sparse PK sampling DRB436 (subset of LGG patients) | D | 7.2.3 | | | | X | X | | | | | | | | | | | | |
| Sparse PK sampling TMT212 (subset of LGG patients) | D | 7.2.3 | | | | X | X | | | | | | | | | | | | |
| Meal record | D | 7.2.3.3 | | X | | X | X | | | | | | | | | | | | |

[redacted]

| | | | Screening period | Treatment Period | | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| Week | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 72, 88-n | | | |
| **Patient Reported Outcomes** | | | | | | | | | | | | | | | | | | | |
| Parent Proxy Global 7+2 Health (LGG cohort only) | D | 7.2.6 | | X | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Acceptability/Palatability Questionnaire – Dabrafenib | D | 7.2.7 | | X | | | | X | | | | | | | | | | | |
| Acceptability/Palatability Questionnaire – Trametinib | D | 7.2.7 | | X | | | | X | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| **Study Completion** | | | | | | | | | | | | | | | | | | | |
| End of Phase Disposition | D | 7.1.4 | X | | | | | | | | | | | | | | X | X | |

[redacted]

| | | | Screening period | Treatment Period | | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| Week | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 72, 88-n | | | |
| Antineoplastic therapies since discontinuation of study treatment | D | 7.1.6.1 | | | | | | | | | | | | | | | X | X | X |
| Survival Follow-up | D | 7.1.6.2 | | | | | | | | | | | | | | | | | X |

[redacted]

**Table 7-2 Visit evaluation schedule for LGG crossover patients**

| | | | | **Crossover Treatment Period for LGG patients** | | | | | | | | | | | | | **Crossover Post Treatment Period** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Category** | **Protocol Section** | **Pre-Treatment** | **Weekly Assessments (Weeks 1 to 5) ± 2 day visit window** | | | | | **Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window** | | | | | | | **Every 16 weeks ±7 day visit window** | **End of treatment (EoT)** Within 30 days after last dose | **Post Treatment Follow up** Every 16 weeks ±14 day visit window | **Survival follow up** Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| Obtain Informed Consent/Assent for post-progression treatment on dabrafenib with trametinib | D | 7.1.3.1 | | X – at the time of Treatment after Progression of Disease on dabrafenib with trametinib | | | | | | | | | | | | | | | |
| Concomitant medications and non-drug therapies | D | 7.1.2.3 | | X – Continuous | | | | | | | | | | | | | | | |
| **Physical exam** | | | | | | | | | | | | | | | | | | | |
| Physical examination | S | 7.2.2.1 | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| Performance status (Karnofsky/Lansky) | D | 7.2.2.5 | | X | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Height | D | 7.2.2.4 | | | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Weight | D | 7.2.2.4 | | X | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | D | 7.2.2.3 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | | | | | | |

[redacted]

| | | | | Crossover Treatment Period for LGG patients | | | | | | | | | | | | | Crossover Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Category** | **Protocol Section** | **Pre-Treatment** | **Weekly Assessments (Weeks 1 to 5) ± 2 day visit window** | | | | | **Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window** | | | | | | | **Every 16 weeks ±7 day visit window** | **End of treatment (EoT)** Within 30 days after last dose | **Post Treatment Follow up** Every 16 weeks ±14 day visit window | **Survival follow up** Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| **Laboratory assessments** | | | | | | | | | | | | | | | | | | | |
| Hematology | D | 7.2.2.8.1 | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Chemistry | D | 7.2.2.8.2 | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Urinalysis | D | 7.2.2.8.3 | | X | | | | X | X | X | X | X | X | X | X | X | X | | |
| Pregnancy test, serum (as applicable) | D | 7.2.2.8.4 | X | | | | | | | | | | | | | | | | |
| Pregnancy test, urine (as applicable) | D | 7.2.2.8.4 | | X – Day 1 and Monthly thereafter | | | | | | | | | | | | | X | | |
| **Imaging** | | | | | | | | | | | | | | | | | | | |
| Tumor evaluation | D | 7.2.1 | X | | | | | | X | X | X | X | X | X | X | X | X | X - until PD or off study | |
| Treatment after Progression of Disease on dabrafenib with trametinib | D | 7.1.3.1 | | X - See Section 7.1.3.1 for details | | | | | | | | | | | | | | | |

[redacted]

[redacted]

| | | | | Crossover Treatment Period for LGG patients | | | | | | | | | | | | | Crossover Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Category** | **Protocol Section** | **Pre-Treatment** | **Weekly Assessments (Weeks 1 to 5) ± 2 day visit window** | | | | | **Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window** | | | | | | | **Every 16 weeks ±7 day visit window** | **End of treatment (EoT)** Within 30 days after last dose | **Post Treatment Follow up** Every 16 weeks ±14 day visit window | **Survival follow up** Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| **Safety** | | | | | | | | | | | | | | | | | | | |
| Adverse events [redacted] | D | 8.1 | | X – Continuous | | | | | | | | | | | | | | | |
| Dermatological Evaluation | D | 7.2.2.6 | | | | | X | X - Monthly (local qualified physician assessment for non-clinic visits) | | | | | | | | | X – At EOT, 3 and 6 months after the last dose of study treatment or until start of new antineoplastic therapy initiated | | |
| ECG | D | 7.2.2.10.1 | X | | | | | X | | X | | X | | X | | X | X | | |
| Cardiac imaging/ ECHO | D | 7.2.2.10.2 | X | | | | | X | | X | | X | | X | | X | X | | |
| Ophthalmic examination | D | 7.2.2.7 | | | | | | X | | X | | X | | X | | X | X | | |
| **Study drug administration** | | | | | | | | | | | | | | | | | | | |
| DRB436 administration | D | 6.1 | | X - Continuous b.i.d daily dosing | | | | | | | | | | | | | | | |
| TMT212 administration | D | 6.1 | | X – Continuous q.d. daily dosing | | | | | | | | | | | | | | | |

[redacted]

| | | | | Crossover Treatment Period for LGG patients | | | | | | | | | | | | | Crossover Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Pre-Treatment | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | Every 16 weeks ±7 day visit window | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | **72, 88-n** | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| **Study Completion** | | | | | | | | | | | | | | | | | | | |
| End of Phase Disposition | D | 7.1.4 | | | | | | | | | | | | | | | X | X | |
| Antineoplastic therapies since discontinuation of study treatment | D | 7.1.6.1 | | | | | | | | | | | | | | | X | X | X |
| Survival Follow-up | D | 7.1.6.2 | | | | | | | | | | | | | | | | | X |

[redacted]

**Table 7-3 Visit evaluation schedule for LGG chemotherapy arm**

| | | | Screening period | Treatment Period for Induction and Maintenance phases for LGG chemotherapy | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | | | |
| Obtain Informed Consent/Assent | D | 7.1.2 | X | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | | |
| IRT Registration (after ICF signature) | S | 7.1.2.1 | X | | | | | | | | | | | | | | | |
| Eligibility checklist (within IRT) | S | 7.1.2.1 | X | | | | | | | | | | | | | | | |
| IRT Randomization | D | 6.5.2 | X | | | | | | | | | | | | | | | |
| **Patient History** | | | | | | | | | | | | | | | | | | |
| Demography | D | 7.1.2.3 | X | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | D | 5.2, 5.3 | X | | | | | | | | | | | | | | | |
| Medical History | D | 7.1.2.3 | X | | | | | | | | | | | | | | | |
| Seizure history | D | 7.2.2.2 | X | | | | | | | | | | | | | | | |

[redacted]

| | | | Screening period | Treatment Period for Induction and Maintenance phases for LGG chemotherapy | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Category** | **Protocol Section** | **Screening** | **Weekly Assessments (Weeks 1 to 5) ± 2 day visit window** | | | | | **Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window** | | | | | | | **End of treatment (EoT)** Within 30 days after last dose | **Post Treatment Follow up** Every 16 weeks ±14 day visit window | **Survival follow up** Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | | | |
| Diagnosis and extent of cancer | D | 7.1.2.3 | X | | | | | | | | | | | | | | | |
| Prior antineoplastic therapy | D | 7.1.2.3 | X | | | | | | | | | | | | | | | |
| Prior/concomitant medications and non-drug therapies | D | 7.1.2.3 | X | X – Continuous | | | | | | | | | | | | | | |
| Prior surgical procedures | D | 7.1.2.3 | X | | | | | | | | | | | | | | | |
| **Physical exam** | | | | | | | | | | | | | | | | | | |
| Physical examination | S | 7.2.2.1 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | | | | | |
| Performance status (Karnofsky/Lansky) | D | 7.2.2.5 | X | X | | | | X | X | X | X | X | X | X | X | X | X | |
| Height | D | 7.2.2.4 | X | | | | | X | X | X | X | X | X | X | X | X | X | |
| Weight | D | 7.2.2.4 | X | X | | | | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | D | 7.2.2.3 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | | | | | |
| **Laboratory assessments** | | | | | | | | | | | | | | | | | | |
| Hematology | D | 7.2.2.8.1 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

[redacted]

| | | | Screening period | Treatment Period for Induction and Maintenance phases for LGG chemotherapy | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | | | |
| Chemistry | D | 7.2.2.8.2 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Local laboratory tests | D | 7.2.2.8 | | X – Weekly or as needed per local practice throughout carboplatin with vincristine treatment | | | | | | | | | | | | | | |
| Hepatitis testing for clearance (only for positive history) | D | 7.2.2.8.5 | X | | | | | | | | | | | | | | | |
| Urinalysis | D | 7.2.2.8.3 | X | X | | | | X | X | X | X | X | X | X | X | X | | |
| Pregnancy test, serum (as applicable) | D | 7.2.2.8.4 | X | | | | | | | | | | | | | | | |
| Pregnancy test, urine (as applicable) | D | 7.2.2.8.4 | | X – Day 1 and Monthly thereafter | | | | | | | | | | | | X | | |
| **Imaging** | | | | | | | | | | | | | | | | | | |
| Tumor evaluation | D | 7.2.1 | X | | | | | | X | X | X | X | X | X | X | X | X - until PD or off study. | |
| [redacted] | | | | | | | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | | |
| Adverse events [redacted] | D | 8.1 | X – Continuous | | | | | | | | | | | | | | | |

[redacted]

| | | | Screening period | Treatment Period for Induction and Maintenance phases for LGG chemotherapy | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| **Week** | | | **-28 to -1** | **1** | **2** | **3** | **4** | **5** | **8** | **16** | **24** | **32** | **40** | **48** | **56** | | | |
| Dermatological Evaluation | D | 7.2.2.6 | X | | | | X | X - Monthly (local qualified physician assessment for non-clinic visits) | | | | | | | | X – At EOT, 3 and 6 months after the last dose of study treatment or until start of new antineoplastic therapy initiated | | |
| ECG | D | 7.2.2.10.1 | X | | | | | X | | X | | X | | X | X | X | | |
| Cardiac imaging/ ECHO | D | 7.2.2.10.2 | X | | | | | X | | X | | X | | X | X | X | | |
| Ophthalmic examination | D | 7.2.2.7 | X | | | | | X | | X | | X | | X | X | X | | |
| **Study drug administration** | | | | | | | | | | | | | | | | | | |
| Carboplatin | D | 6.1.2 | | Weeks 1 – 4<br>Weeks 7 - 10 | | | | | | Weeks 13 - 16<br>Weeks 19 - 22<br>Weeks 25 - 28<br>Weeks 31 - 34<br>Weeks 37 - 40<br>Weeks 43 - 46<br>Weeks 49 - 52<br>Weeks 55 - 58 | | | | | | | | |
| Vincristine | D | 6.1.2 | | Weeks 1 - 10 | | | | | | Weeks 13 - 15 | | | | | | | | |

[redacted]

| | | | Screening period | Treatment Period for Induction and Maintenance phases for LGG chemotherapy | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| Week | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | | | |
| | | | | | | | | | | Weeks 19 - 21<br>Weeks 25 - 27<br>Weeks 31 - 33<br>Weeks 37 - 39<br>Weeks 43 - 45<br>Weeks 49 - 51<br>Weeks 55 - 57 | | | | | | | | |
| **Patient Reported Outcomes** | | | | | | | | | | | | | | | | | | |
| Parent Proxy Global 7+2 Health | D | 7.2.6 | | X | | | | X | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | | | | | |
| **Study Completion** | | | | | | | | | | | | | | | | | | |

[redacted]

| | | | Screening period | Treatment Period for Induction and Maintenance phases for LGG chemotherapy | | | | | | | | | | | | Post Treatment Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Protocol Section | Screening | Weekly Assessments (Weeks 1 to 5) ± 2 day visit window | | | | | Every 8 Week Assessments (Weeks 8 to 56) ±7 day visit window | | | | | | | End of treatment (EoT) Within 30 days after last dose | Post Treatment Follow up Every 16 weeks ±14 day visit window | Survival follow up Every 3 months |
| Week | | | -28 to -1 | 1 | 2 | 3 | 4 | 5 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | | | |
| End of Phase Disposition | D | 7.1.4 | X | | | | | | | | | | | | | X | X | |
| Antineoplastic therapies since discontinuation of study treatment | D | 7.1.6.1 | | | | | | | | | | | | | | X | X | X |
| Survival Follow-up | D | 7.1.6.2 | | | | | | | | | | | | | | | | X |

[redacted]

### 7.1.1 Molecular pre-screening

There is no molecular pre-screening for this study.

### 7.1.2 Screening

Written informed consent/assent must be obtained prior to any screening procedures. The window for screening each patient will be up to 28 days before the first dose, including a serum pregnancy test for women of childbearing potential. A urine pregnancy test must conducted and confirmed negative on Day 1 before dosing. Adverse events will also be recorded at this visit. Screening assessments to confirm eligibility should be performed as per the schedule of assessments (Table 7-1, Table 7-2, Table 7-3).

Local *BRAF* V600 mutation result may be used to qualify patients for enrollment, as part of the study inclusion criteria listed in Section 5.2. The CRF page for method of local *BRAF* V600 mutation testing, including the methodology used for local assessment, must be completed for patients whose tumor sample was tested by a local institutional assay. *BRAF* V600 mutation result must be locally documented prior to Day 1 (HGG cohort) or randomization (LGG cohort). The *BRAF* V600 mutation status will be assessed using a validated tissue-based test. Molecular-based *BRAF* V600 testing should be used where available and is strongly preferred over non-molecular methods, e.g. immunohistochemistry. Liquid biopsy-based *BRAF* V600 results cannot be used to enroll patients. *BRAF* V600 mutation results will be subjected to retrospective central confirmation by a Novartis designated laboratory. For the retrospective central confirmation all subjects will be required to provide a tumor tissue sample at screening prior to study treatment, as either a tumor block or a minimum of 20 FFPE slides (see Table 7-8). Central confirmation of *BRAF* V600 mutation status is not required for enrollment, if local test results are positive for *BRAF* V600 mutation. Patients will not be excluded if central testing is later found to be discordant or uninformative (e.g. inadequate sample).

For patients who do not have a *BRAF* V600 mutation result documented locally, a tumor sample must be submitted for central testing of *BRAF* mutation status during screening. The minimum requirements for this sample are listed in Table 7-8.

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated within the screening window (within 28 days from the first dose). In this case, the patient will not be required to sign another ICF, and the original patient ID number assigned will be used. In the event that the laboratory test(s) cannot be performed within 28 days of the original screening visit, or the re-test(s) do not meet the entrance criteria, or eligibility criteria have changed and are not met anymore, the patient is considered a screen failure.

A new ICF/assent will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study.

[redacted]

#### 7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The key eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

#### 7.1.2.2 Information to be collected on screening failures

Patient who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure.

The demographic information, informed consent/assent, Inclusion/Exclusion and Screening Phase Disposition pages must be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

#### 7.1.2.3 Patient demographics and other baseline characteristics

The data that will be collected on patient characteristics at screening includes:

- Demography (Year of birth, calculated age, sex, childbearing status, race, ethnicity)
- Histologically confirmed diagnosis of High Grade Glioma (Grade III or IV glioma) or Low Grade Glioma (Grade I or II glioma), as defined by WHO histological classification system, 2016.
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent/assent). Frequency of seizures prior to the first day of dosing should be assessed and recorded on the Medical History eCRF. For LGG patients, the indication to treatment must be reported which may include clinical and/or neurological symptoms. Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.

Furthermore the following assessments will be performed:

- [redacted]
- Central confirmation of HGG histopathology (HGG cohort only) and *BRAF* V600 mutation (HGG and LGG cohorts) (Tumor tissue required)
- Radiological assessments (e.g. MRI) to confirm measurable disease per RANO response criteria (locally determined and central confirmation required before enrollment)

[redacted]

- Vital signs
- Height, weight
- Physical examination
- [redacted]
- Performance status (Karnofsky/Lansky)
- Laboratory evaluations (hematology, chemistry, urinalysis)
- Pregnancy testing (for menstruating females and women of childbearing potential)
- Hepatitis testing (for patients with a history of hepatitis)
- ECG
- ECHO
- Ophthalmology exam
- Dermatological exam

### 7.1.3 Treatment period

Following completion of screening procedures and verifying patient eligibility, patients will complete registration in IRT and start study treatment. HGG patients and LGG patients randomized to dabrafenib with trametinib will have weekly visits for the first 5 weeks, followed by visits every 8 weeks until the end of the first year; subsequent visits will occur every 16 weeks. LGG patients randomized to chemotherapy will follow the same visit schedule for protocol assessments, but will be required to return to the clinical site for additional chemotherapy dosing visits per Section 6.1.2.

For details of assessments, refer to Table 7-1, Table 7-2 for LGG crossover patients and Table 7-3.

Concomitant medication, adverse events and SAE monitoring will be continuous throughout the trial.

Patients will be treated with study treatment until disease progression, unacceptable toxicity, death or discontinuation from the study treatment due to any other reason.

#### 7.1.3.1 Treatment after Progression of Disease

Patients will be permitted to continue dabrafenib with trametinib beyond investigator-assessed, RANO-defined PD, as long as they meet the following criteria:

- Investigator assessed clear evidence of clinical benefit
- Tolerance of study drug
- Continuation of study treatment is in the best interest of the patient as determined by the Investigator
- Patient/legal guardian is willing to continue on the study and signed ICF for treatment beyond progression

If the Investigator determines that all above criteria are met, the patient may continue study treatment and follow all study related procedures, including tumor assessments, as scheduled in Table 7-1, Table 7-2 for LGG crossover patients and Table 7-3. After each tumor assessment,

[redacted]

the investigator must confirm if the patient is still benefitting from study treatment, and document this in the patient's chart and the appropriate CRF pages.

### 7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study for any reason at any time. If a patient decides to discontinue from the investigational treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/assent, tumor assessments must continue to be performed every 16 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent/assent.

Patients must be discontinued under the following circumstances:

- Pregnancy
- Study Terminated by Sponsor
- Patient/guardian decision
- Physician decision (investigator may discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being)
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7. The investigator must also contact the IRT to register the patient's discontinuation from the study.

In some circumstances patients may be allowed to continue to receive study treatment beyond disease progression as per RANO criteria (Section 7.1.3.1). These patients will continue assessments as outlined in Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3, and will complete the End of Treatment visit only after permanent discontinuation of study treatment.

#### 7.1.4.1 Replacement policy

Patients will not be replaced on study.

However, if a patient is considered as non-evaluable for the per-protocol set (PPS), enrollment of a new patient will be considered if there is less than the required number of evaluable patients.

### 7.1.5 Withdrawal of consent

Patients/legal guardian may voluntarily withdraw assent/consent to participate in the study for any reason at any time. Withdrawal of assent/consent occurs only when a patient/legal guardian:

[redacted]

- Does not want to participate in the study any longer, and
- Does not allow further collection of personal data.

If a patient/legal guardian withdraws assent/consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient/legal guardian 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 patient/legal guardian are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient'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 patient'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.

### 7.1.6 Follow up for safety evaluations

All patients must have safety evaluations for at least 30 days after the last dose of study treatment as per Table 7-1, Table 7-2 for LGG crossover patients, or Table 7-3. Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

#### 7.1.6.1 Post treatment follow up

After discontinuation of study treatment, all patients will be followed for safety for at least 30 days after the last dose of study treatment except in the case of death, loss to follow-up or withdrawal of consent/assent. All patients who discontinue study treatment for reasons other than disease progression, death, lost to follow up, or withdrawal of consent/assent will move into Post Treatment Follow Up phase.

Tumor evaluations during this period will continue as per Table 7-1, Table 7-2 or Table 7-3 until central independently confirmed disease progression by RANO criteria, withdrawal of assent/consent by patient/guardian to tumor status follow-up, or lost to follow-up. Patients who start a new anti-cancer therapy prior to disease progression will continue tumor evaluations following the same above schedule until radiographic evidence of disease progression is centrally confirmed.

Skin examinations should be performed at 3 and 6 months after the last dose of study drug or until the start of a new anti-cancer therapy. Safety assessments including physical exams and

[redacted]

growth/developmental follow up will continue according to Table 7-1, Table 7-2 or Table 7-3 and Section 7.1.6.

Patients who discontinue study treatment due to disease progression by RANO criteria that has been confirmed by central independent assessment, and begin new anti-cancer therapy at EOT will enter Survival follow-up period.

#### 7.1.6.2 Survival follow-up

All patients will be followed for survival once they discontinue study treatment and complete protocol required efficacy assessments, and the required skin evaluation per Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3. Survival follow-up assessments will be done every 12 weeks or earlier if a survival update is required to meet safety or regulatory needs. Survival information can be obtained by clinical visits or telephone calls until death, the patient is lost to follow-up, the patient/legal guardian withdraws assent/consent or study discontinuation.

### 7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent/assent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent/assent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

## 7.2 Assessment types

### 7.2.1 Efficacy assessments

Tumor response will be assessed locally and centrally based on the Response Assessment in Neuro-Oncology (RANO) criteria for solid tumors (Wen, 2010). The imaging assessment collection plan is presented in Table 7-4. Details of the central review process will be described in the independent review charter by the assigned imaging vendor.

Imaging data will be centrally collected and checked for quality by an imaging vendor designated by Novartis. The decision regarding patient management will remain with the local investigator.

Information regarding prior interventions (e.g. radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening, prior and on-study interventions, and cytology results should be transmitted to the imaging vendor for review by an independent medical radiologist. Sites must ensure the data transmitted is consistent with the data entered in the clinical database.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/assent, tumor assessments must continue to be performed every 16 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent/assent.

[redacted]

**Table 7-4 Imaging Assessment Collection Plan**

| Procedure [a] | Screening | During Treatment/Follow-up | End of Treatment |
|---|---|---|---|
| Tumor evaluation<br>Brain MRI | Mandated | • Every 8 weeks (+/- 7 days) during the first 56 weeks.<br>• Every 16 weeks (+/- 7 days) thereafter while on treatment as well as during post-treatment follow up.<br>• PR and CR must be confirmed by repeat assessments performed ≥4 weeks after the criteria for response are first met.<br>• At any time there is suspicion of clinical disease progression. | Mandated |
| MRI Spine | As clinically indicated per investigator discretion | | |
| [a] Refer to Section 7.2.1.1 | | | |

### 7.2.1.1 Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the study ICF, can be considered as the baseline images for this study. The following assessments are required at screening/baseline:

- Brain MRI - Contrast enhanced brain MRI is preferred. However, if MRI contrast is contraindicated, CT with or without contrast is allowed, but highly discouraged.
- MRI spine may be obtained if clinically indicated according to investigator discretion

#### Required conditions for baseline tumor assessment

- During screening, patients must have locally determined and centrally confirmed measurable disease at least twice the imaging slice thickness to be used for efficacy assessment
- Patients with only non-measurable lesions are not eligible
- Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since more than 3 weeks from the radiotherapy, it can be considered as a measurable lesion.

Since measurable disease is an eligibility requirement, study sites should send the baseline imaging scans and any required vendor forms to the imaging CRO immediately following scan acquisition during screening. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically. The baseline imaging will undergo expedited central review and the results of the central review will be communicated to the site. If the central review determines measurable disease, then the patient can be enrolled in the study. If the central review does not determine measurable disease, the patient should not be enrolled in the study; additional follow-up can be requested.

#### 7.2.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 7-4 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) during the first year, subsequently every 16 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up or withdrawal of consent/assent. Imaging assessments should be scheduled using the enrollment date as the reference date (not the previous tumor assessment), and should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments performed.

**Local imaging results are to be used for treatment decisions by the investigator.**

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a patient, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed ≥4 weeks after the criteria for response are first met.

MRI spine may be obtained during study treatment if clinically indicated according to the discretion of the investigator.

Each lesion that is identified at baseline must be followed by the same method and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging vendor for quality control and central review.

### 7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as collecting of the adverse events at every visit (see Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). For details on AE collection and reporting, refer to Section 8.

For LGG patients randomized to carboplatin and vincristine, investigators should follow local institutional and local SmPC guidelines for any additional safety monitoring that may be required during administration of carboplatin and vincristine. This includes audiometry testing on patients where there is suspicion of hearing loss or when it is institutional practice to conduct such testing during administration of carboplatin. Events of hearing loss should be reported as Adverse Events and recorded on the electronic case report form (eCRF).

Significant findings that were present prior to the signing of informed consent/assent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent/assent must be recorded on the Adverse Event page of the patient's eCRF.

[redacted]

#### 7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, assessment of the skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance, assessment of the skin, lungs, cardiovascular system, abdomen (liver and spleen), and neurological exam as clinically indicated. A short physical exam will be at all visits starting from Week 8.

[redacted]

For the assessment schedule refer to the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3).

[redacted]

#### 7.2.2.3 Vital signs

Vital signs include blood pressure, body temperature, pulse measurements. Vital signs should be taken before any study medication is given on each assessment day (i.e. pre-dose).

Blood pressure will be taken:

- After the patient has been sitting for five minutes. The appropriate cuff size is used to ensure accurate measurement.
- Measurements will be taken per local practice.

If the blood pressure reading is outside the age appropriate normal ranges, repeat the measurement, waiting 1-2 minutes between readings, to verify the initial reading. Repeat measurements will be documented in the patient's eCRF.

For the assessment schedule refer to the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3).

#### 7.2.2.4 Height and weight

Height in centimeters (cm) will be measured as a requirement to monitor growth, and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured where indicated in the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3).

[redacted]

#### 7.2.2.5 Performance status

The performance status will be assessed according to Karnofsky for patients >16 years of age or Lansky for patients ≤ 16 years of age at screening (see Appendix 2). Performance status will be assessed according the scheduled assessment in Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3).

#### 7.2.2.6 Dermatological Evaluation

Skin examination should be performed prior to initiation of study treatment, and during the study on a monthly basis throughout therapy and at End of Treatment. After discontinuation of study treatment, skin examinations should be performed at 3 and 6 months after the last dose of study treatment or until the start of a new anti-neoplastic therapy according to the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). Monitoring of the skin can be performed by a qualified local physician at the discretion of the investigator during non-clinic visits. If possible, the same local physician should perform each exam throughout the study to ensure consistency between evaluations.

#### 7.2.2.7 Ophthalmologic exam

Patients are required to have standard age-appropriate ophthalmologist examinations performed by an ophthalmologist according to the schedule of assessments in Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). Based on the investigator's discretion, the examination may include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, dilated indirect fundoscopy with special attention to retinal abnormalities, and optical coherence tomography. During the study, ophthalmologic exams may be repeated as clinically warranted. If any changes are noted during the required age-appropriate exam, or otherwise clinically indicated, a detailed ophthalmologic exam is mandatory (with sedation if necessary).

#### 7.2.2.8 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Central laboratory results should be used to determine study eligibility, however if there is an immediate need to determine study eligibility and commence treatment on study, then local lab result may be used for assessment of eligibility. In this case, central laboratory samples should still be collected for evaluation. Sites do not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made, and in those cases locally unscheduled testing may be performed.

For LGG patients receiving carboplatin plus vincristine, local laboratory results can be used as required during chemotherapy when a central lab is not scheduled per Visit Evaluation Schedule (Table 7-1, Table 7-2 or Table 7-3) or when central lab results will not be received in time for dosing. Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during

[redacted]

the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.03. Additional analyses are left to the discretion of the investigator. The frequency of the assessments is indicated in the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3).

**Table 7-5 Central Clinical laboratory parameters collection plan**

| Test Category | Test Name |
|---|---|
| Hematology | Hemoglobin, Platelets, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, other) |
| Chemistry | Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium, Creatinine, Magnesium, Sodium, Potassium, glucose (non-fasting), Phosphate, Total bilirubin, direct bilirubin, Total protein, Blood Urea Nitrogen (BUN) or Urea |
| Urinalysis | Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)<br><br>If there are any significant findings on the dipstick then a microscopic evaluation should be measured: Microscopic Panel (Red Blood Cells and White Blood Cell sediments, Casts, Crystals, Bacteria, Epithelial cells) |
| Hepatitis | For patients with a history of chronic HBV and/or HCV: Viral hepatitis serology, Hepatitis B surface antigen and Hepatitis B core antibody (IgM) and/or Hepatitis C RNA |
| Additional tests | Serum pregnancy test at screening (females of childbearing potential).<br>Urine pregnancy test on Day 1, monthly throughout the study and at EOT (females of childbearing potential) |

#### 7.2.2.8.1 Hematology

Hematology tests are to be performed by the central laboratory according to the Visit Schedule outlined in the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). The hematology panel is listed in Table 7-5.

#### 7.2.2.8.2 Clinical chemistry

Blood chemistry assessments are to be performed by the central laboratory according to the Visit Schedule outlined the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). The clinical chemistry panel includes items listed in Table 7-5.

[redacted]

#### 7.2.2.8.3 Urinalysis

Urinalysis includes items listed in Table 7-5 and will be performed according to the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). Any significant findings on dipstick will be followed up with a microscopic evaluation.

#### 7.2.2.8.4 Pregnancy and assessments of female fertility

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

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become menarchal during the study. All menarchal females and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors as precocity, socio (educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric patient and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of patient should be considered in accordance with the local law and ethics.

All women of child bearing potential must undergo a serum pregnancy test at screening (Day -28 to Day -1). On Day 1 and monthly thereafter a urine pregnancy test will be performed as per the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). On Day 1, the urine pregnancy test must be confirmed negative before dosing.

Urine pregnancy test kits will be provided to patients for administering the test at home using the kit provided. For all urine pregnancy tests performed at home, the site personnel will follow-up with the patient to collect the date and test results and document the information in the patient's source document and entered in the clinical database. If local requirements dictate otherwise, local regulations should be followed.

Patients with a positive pregnancy test result during screening must be excluded from the study.

In case of pregnancy during study participation, the patient must permanently stop study treatment immediately, and the pregnancy must be reported on the Clinical Trial Pregnancy Form. If a positive pregnancy test is performed in between study visits, the patient must immediately notify the investigator.

#### 7.2.2.8.5 Hepatitis screen

Patients with medical history of Hepatitis B or C may be enrolled in the study if there is laboratory evidence of cleared HBV and/or HCV at screening.

[redacted]

[redacted]

### 7.2.2.10 Cardiac assessments

#### 7.2.2.10.1 Electrocardiogram (ECG)

Standard 12-lead ECG should be performed according to the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3). ECGs will be collected as single measurements in the supine position.

If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities. In the event that a QTcF value of ≥ 501 ms is observed, obtain two or more additional ECGs over a brief period, and then use the average QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued as per Section 6.3.1.7.

An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Clinically significant abnormalities present when the patient signed informed consent/assent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent/assent must be recorded on the Adverse Events CRF page.

Two copies of the ECG tracing should be obtained at the time of the ECG, to be kept in the source documents and in the study file at the study site for retrospective collection by the sponsor if necessary. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, and date.

#### 7.2.2.10.2 Cardiac imaging - Echocardiogram

Echocardiogram will be performed according to the Visit Evaluation Schedule (Table 7-1, Table 7-2 for LGG crossover patients or Table 7-3).

Cardiology consultations should be performed on patients who experience >10% absolute decrease in LVEF from baseline and whose cardiac ejection fraction is less than the institution's LLN.

Copies of all ECHOs are to be kept in the source documents at the study site for retrospective collection by the sponsor if necessary.

[redacted]

### 7.2.3 Pharmacokinetics

Pharmacokinetic blood samples will be collected for the analysis of plasma concentrations of dabrafenib, its metabolites hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib (GSK2285403, GSK2298683 and GSK2167542, respectively), and trametinib.

Full PK blood samples will be collected as described in Table 7-6 for all patients in the HGG cohort and the first 20 LGG patients randomized to dabrafenib plus trametinib treatment. For the remaining LGG patients on dabrafenib plus trametinib treatment, sparse PK blood samples will be collected as described in Table 7-7. An unscheduled PK blood sample may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion. PK samples will not be collected from LGG patients after they crossover from carboplatin with vincristine treatment.

The date and exact time of dosing, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF pages. Any sampling problems (e.g., patient took study drug before blood sample, scheduled sampling time is missed, sample is not drawn according to the schedule) should be noted as a comment on the eCRF.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed, and medication should resume at the next scheduled dose. The occurrence and frequency of any vomiting must be noted in the adverse events section of the eCRF. In addition, the date and exact time of vomiting should only be recorded if it occurs within 4 hours of dosing on the days of full PK sampling. If a vomiting episode occurs within the first 4 hours post-dosing during the day of the last dose prior to trough PK samples the exact time (whenever possible) must be noted on the PK Dose and Administration Record eCRF.

Concentrations of dabrafenib, its metabolites and trametinib will be summarized; a detailed description of the planned PK analyses is given in Section 10.5.2.

#### 7.2.3.1 Pharmacokinetic blood collection and handling

Blood samples will be taken either by direct venipuncture or through an indwelling cannula (e.g., inserted in a forearm vein, or central venous line).

At the specified time points described in Table 7-6 and Table 7-7, one single 1 mL blood draw will be collected into a tube containing EDTA and gently inverted several times to thoroughly mix the anticoagulant. The blood tube will be centrifuged to separate plasma and transferred into separate pre-labeled tubes for dabrafenib. Plasma samples will be stored frozen in an upright position until shipment.

Refer to the [CDRB436G2201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

[redacted]

**Table 7-6 Full Pharmacokinetic blood collection log – HGG cohort and subset of LGG cohort**

| | | | | | | | Sample volume [mL] | | |
|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Day** | **Scheduled timepoint** | **Dose reference ID Dabrafenib*** | | **Dose reference ID Trametinib*** | | **PK Sample No*** | **Patients <10kg** | **Patients ≥10kg and <25kg** | **Patients ≥25kg** |
| 1 | 1 | Post-dose 0.5 hr ±5mins | 101 | | 201 | | 101 | N/A | 1 mL | 1 mL |
| | | Post-dose 2 hr ±5mins | 101 | | 201 | | 102 | N/A | 1 mL | 1 mL |
| | | Post-dose 4 hr ±20mins | 101 | | 201 | | 103 | N/A | 1 mL | 1 mL |
| 3 | 1 | Pre-dose[a] -30mins | 102 | 12[b] | 202 | 14[b] | 104 | 1 mL | 1 mL | 1 mL |
| | | Post-dose 0.5 hr ±5mins | 102 | | 202 | | 105 | N/A | N/A | 1 mL |
| | | Post-dose 1 hr ±5mins | 102 | | 202 | | 106 | N/A | 1 mL | 1 mL |
| | | Post-dose 2 hrs ±5mins | 102 | | 202 | | 107 | 1 mL | 1 mL | 1 mL |
| | | Post-dose 3 hrs ±20mins | 102 | | 202 | | 108 | N/A | 1 mL | 1 mL |
| | | Post-dose 4 hrs ±20mins | 102 | | 202 | | 109 | 1 mL | 1 mL | 1 mL |
| | | Post-dose 6 hrs ±20mins | 102 | | 202 | | 110 | N/A | N/A | 1 mL |
| | | Post-dose 8 hrs ±20mins | 102 | | 202 | | 111 | N/A | 1 mL | 1 mL |
| 4 | 1 | Pre-dose[a] -30mins | 103 | 13[b] | 203 | 15[b] | 112 | 1 mL | 1 mL | 1 mL |
| Unscheduled PK Sample[c] | | | --- | 16[d] | | 17[d] | 1001+ | 1 mL | 1 mL | 1 mL |

[a] Pre-dose PK samples will be collected immediately prior to the start of study drug administration.
[b] The first Dose Reference ID (DRID no.) is for current dose, while the second DRID no. is for the last dose the patient received prior to the collection of the PK sample.
[c] Unscheduled PK samples will be uniquely, sequentially numbered 1001, 1002, etc.
[d] Last dose the patient received prior to the collection of the unscheduled PK
Note: *DRID and sample numbers implemented in the above table are for Novartis internal reference.

**Table 7-7 Sparse Pharmacokinetic blood collection log for subset of LGG cohort**

| | | | | | | | Sample volume [mL] | | |
|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Day** | **Scheduled timepoint** | **Dose reference ID Dabrafenib*** | | **Dose reference ID Trametinib*** | | **PK Sample No*** | **Patients <10kg** | **Patients ≥10kg and <25kg** | **Patients ≥25kg** |
| 3 | 1 | Pre-dose[a] -30mins | 301 | 21[b] | 401 | 23[b] | 201 | 1 mL | 1 mL | 1 mL |
| | | Post-dose[e] 1-3 hr | 301 | | 401 | | 202 | N/A | N/A | 1 mL |

[redacted]

| Week | Day | Scheduled timepoint | Dose reference ID Dabrafenib* | | Dose reference ID Trametinib* | | PK Sample No* | Sample volume [mL] Patients <10kg | Patients ≥10kg and <25kg | Patients ≥25kg |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Post-dose[f] 5-10 hr | 301 | | 401 | | 203 | N/A | 1 mL | 1 mL |
| 4 | 1 | Pre-dose[a] -30mins | 302 | 22[b] | 402 | 24[b] | 204 | 1 mL | 1 mL | 1 mL |
| Unscheduled PK Sample[c] | | | --- | 25[d] | | 26[d] | 2001+ | 1 mL | 1 mL | 1 mL |

[a] Pre-dose PK samples will be collected immediately prior to the start of study drug administration.
[b] The first Dose Reference ID (DRID no.) is for current dose, while the second DRID no. is for the last dose the patient received prior to the collection of the PK sample.
[c] Unscheduled PK samples will be uniquely, sequentially numbered 2001, 2002, etc.
[d] Last dose the patient received prior to the collection of the unscheduled PK
[e] PK samples can be collected anytime between 1-3 hours after the morning dose
[f] PK samples can be collected anytime between 5-10 hours after the morning dose
Note: *DRID and sample numbers implemented in the above table are for Novartis internal reference.

### 7.2.3.2 Analytical method

Plasma concentrations of dabrafenib and its metabolites hydroxy-dabrafenib (GSK2285403), carboxy-dabrafenib (GSK2298683), and desmethyl-dabrafenib (GSK2167542) and trametinib will be measured using validated liquid chromatography/mass spectrometry/ mass spectrometry (LC/MS/MS) methods. The lower limit of quantification (LLOQ) for dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib is 1 ng/mL and 0.25 ng/mL for trametinib for a 50 µL aliquot of human plasma. The LLOQ for carboxy-dabrafenib is 5 ng/mL for a 25 µL aliquot of human plasma. Concentrations below the LLOQ will be treated as zero.

[redacted]

### 7.2.3.3 Meal record

Meal records must be kept for all patients on PK days as indicated in Table 7-1. The date, start and end time, and percentage consumed for all meals on PK days must be recorded in the CRFs.

[redacted]

[redacted]

[redacted]

### Other assessments

No additional tests will be performed on patients entered into this study.

### 7.2.5 Resource utilization

Not applicable.

### 7.2.6 Patient reported outcomes (LGG cohort only)

Patient reported outcomes (PRO) will be assessed using the PROMIS Parent Proxy Global Health 7+2 for LGG patients. The PRO will measure the patient's overall evaluation of his or her physical, mental, and social health. PRO data will be collected using an electronic tablet device and administered in the patient's local language. Patients should be given the questionnaire to be completed before any clinical assessments are performed. Site personnel must review the questionnaire for completeness, and document patient's refusal to complete all or any part of the questionnaire. Completed questionnaire and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, investigators should not encourage the patient to change responses reported in the completed questionnaire. Investigators must follow reporting instructions outlined in Section 8. Questionnaires are administered according to the Table 7-1 and Table 7-3 until the patient disease progression per RANO criteria.

### 7.2.7 Acceptability and Palatability Questionnaires

All patients who receive the dabrafenib oral suspension and/or trametinib oral solution will complete the respective questionnaire to evaluate the palatability and acceptability/tolerability of the pediatric formulations. The dabrafenib oral suspension and trametinib oral solution questionnaires must be completed after the dosing of dabrafenib with trametinib according to Table 7-1.

# 8 Safety monitoring and reporting

## 8.1 Adverse events

### 8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent/assent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent/assent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable, investigational treatment resumed)

[redacted]

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (as per RANO criteria) should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

### 8.1.2 Laboratory test abnormalities

#### 8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

### 8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be

[redacted]

appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

Dabrafenib and trametinib events of special interest include:

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension
- Complicated pyrexia and/or grade 3 and grade 4
- Pre-Renal and intrinsic renal failure
- Uveitis
- New primary/secondary malignancy
- Hypersensitivity
- Hyperglycemia
- Deep venous thrombosis/pulmonary embolism
- Pancreatitis
- Neutropenia

Potential emergent new AEs will be monitored during the course of the study.

#### 8.1.3.1 Definitions and reporting

Refer to Section 8.1.1.

## 8.2 Serious adverse events

### 8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:

[redacted]

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent/assent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

### 8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent/assent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant

[redacted]

ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## 8.3 Emergency unblinding of treatment assignment

Since this study is an open-label study, there is no need for treatment unblinding instructions or unblinding codes.

## 8.4 Pregnancies

To ensure patient safety, each pregnancy occurring after signing the informed consent/assent and 16 weeks after stopping treatment with trametinib monotherapy or dabrafenib in combination with trametinib, and 2 weeks after stopping treatment with dabrafenib monotherapy, whichever is longer must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

## 8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This additional safety information, if any, will be included in the patient informed consent/assent and should be discussed with the patient during the study as needed.

## 8.6 Data Monitoring Committee

A data monitoring committee (DMC) will independently monitor the safety of patients enrolled in this study. The DMC will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient into the LGG cohort. The DMC will be responsible to review safety data from the HGG and LGG cohorts approximately every 6 months for the first two years, and then, if agreed by DMC members, to provide such data every 12 months thereafter from start of enrollment. This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early.

[redacted]

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter and the statistical analysis plan.

## 8.7 Steering Committee

A steering committee (SC) will be established comprising of investigators participating in the trial prior to initiation of the trial.

The SC will ensure transparent management of the study, both HGG and LGG cohorts, according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

# 9 Data collection and management

## 9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Patient Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

[redacted]

## 9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent/assent form (a signed copy is given to the patient/legal guardian).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent/assent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

## 9.3 Data collection

Electronic Data Capture (EDC) is used for this study. The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Pharmacokinetic (PK) [redacted] will be collected in this study. Designated investigator staff will enter the required information onto the PK [redacted] sample collection eCRFs. [redacted] The field monitor will review the relevant eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancies as required. The field monitor will also review requisition forms for completeness.

Radiological scans used for tumor assessments will be centrally collected and reviewed.

Data entered into IRT will be transferred electronically to Novartis as described in the Data Transfer Specifications for designated IRT vendor.

[redacted]

## 9.4 Database management and quality control

Novartis personnel will review the data in the eCRFs entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). Data that will be processed centrally include:

- IRT data including information regarding screening, drug assignment and discontinuation
- Central imaging review (i.e. MRI scans)
- Centrally analyzed laboratory data including clinical, PK, [redacted] and safety parameters

Data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

# 10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined.

The data for the HGG and LGG cohorts will be analyzed independently with timing of analyses based on specific independent criteria for each cohort outlined in this protocol.

Note that there may be a need to support the initial submission of an indication based on the primary analysis data with safety and PK interim data from both cohorts. Thus the initial planning of the primary analysis for a specific cohort should anticipate that a safety interim or update analysis of the other cohort may also be required.

The primary endpoint for the HGG cohort will be analyzed at the time of the interim analysis and the study may be stopped for futility according to the criteria described in the Interim Analysis Section (Section 10.7). If the HGG cohort is not stopped at interim analysis then the

[redacted]

primary analysis of the HGG cohort will be conducted at the time when all treated patients have either completed at least 32 weeks of treatment or have discontinued earlier. These data will be summarized in the primary Clinical Study Report (CSR). The final analysis of the HGG cohort will be conducted at the end of the study as specified in Section 4.3. All available data from all HGG cohort patients up to the end of study cutoff date will be analyzed.

The primary analysis for the LGG cohort will be conducted when all treated patients have either completed at least 32 weeks of treatment or have discontinued earlier. These data will be summarized in the primary CSR.

The final analysis of LGG cohort will be conducted at the end of the study as specified in Section 4.3. All available data from all LGG cohort patients up to the end of study cutoff date will be analyzed.

All data will be summarized by treatment group and included in listings.

## 10.1 Analysis sets

### 10.1.1 Full Analysis Set

The Full Analysis Set (FAS) for the HGG cohort will include all patients to whom study treatment has been assigned and who receive at least one dose of study treatment.

For the LGG cohort the FAS comprises all patients to whom study treatment has been assigned by randomization regardless of whether or not treatment was administered. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

### 10.1.2 Safety set

The Safety Set for both HGG and LGG cohort include all patients who received at least one dose of study treatment.

For the LGG cohort, patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

### 10.1.3 Per-Protocol Set

Not applicable.

### 10.1.4 Dose-determining analysis set

Not applicable.

### 10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) for both HGG and LGG cohort consists of all patients who receive at least one (full or partial) dose of dabrafenib or trametinib and provide at least one evaluable pharmacokinetic (PK) blood sample.

The definition of an evaluable PK blood sample will be further specified in the SAP.

[redacted]

### 10.1.6 Other analysis sets

#### 10.1.6.1 Evaluable set

The Evaluable Set (ES) consists of all evaluable patients in the FAS who have centrally confirmed measurable disease, positive *BRAF* V600 mutation, an adequate tumor assessment at baseline, and a follow-up tumor assessment at least 8 weeks after starting treatment (unless disease progression is observed before that time) or have discontinued for any reason. For the HGG cohort, the evaluable set also requires that the patient's tumor is centrally confirmed by histopathology to be HGG.

The evaluable set will be used for sensitivity analyses.

## 10.2 Patient demographics/other baseline characteristics

For each cohort, demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group based on the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, $25^{th}$ and $75^{th}$ percentiles, minimum, and maximum will be presented.

Relevant medical histories and current medical at baseline will be summarized separately by system organ class and preferred term.

## 10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below for each cohort. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

For the dabrafenib plus trametinib combination in each cohort the duration of exposure in weeks to dabrafenib and trametinib as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized separately for dabrafenib and trametinib by means of descriptive statistics using the safety set. The duration of exposure will also be presented for the study treatment of dabrafenib in combination with trametinib.

For the carboplatin with vincristine control arm in the LGG cohort duration of exposure will be analyzed similarly.

The number of patients with dose adjustments *(reductions, interruption, or permanent discontinuation)* and the reasons will be summarized by treatment group (with the individual drugs also summarized separately) and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group.

[redacted]

## 10.4 Primary objective

### HGG Cohort:

The primary objective of the HGG cohort is to evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by overall response rate (ORR) by central independent review assessment using RANO criteria.

### LGG Cohort:

The primary objective of the HGG cohort is to compare the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by overall response rate (ORR) by independent review assessment using RANO criteria.

### 10.4.1 Variable

For the HGG cohort, the primary variable used to evaluate the anti-tumor activity of dabrafenib in combination with trametinib is the overall response rate (ORR), defined as the proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) as assessed per Response Assessment in Neuro-Oncology (RANO) criteria by the independent reviewer.

For the LGG cohort, the primary variable used to evaluate the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine is the overall response rate (ORR), defined as the proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) as assessed per Response Assessment in Neuro-Oncology (RANO) criteria by the independent reviewer.

### 10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis in the HGG cohort will be performed on the FAS. Point estimate and the exact binomial confidence intervals (CIs) (Clopper and Pearson 1934) of ORR will be provided. The lower bound of the CIs will be used to provide evidence that the true ORR is greater than a certain specific response rate.

The 95% CI, via the lower limit, is used to establish the levels of response which are exceeded by taking the combination therapy according to a robust standard of evidence (i.e. one-sided alpha=0.025). For example, out of 40 patients who have been enrolled and have completed at least 32 weeks of treatment or have discontinued treatment earlier, if 14 responses (35%) are observed then the corresponding 95% CI will exclude 20% which is greater, than the typical standard of care response rate previously observed (Lashford 2002; Nicholson 2007; Ruggiero 2006; Warren 2012; Hummel 2013).

With respect to the HGG cohort, the study also aims to provide evidence that trametinib gives added value to the dabrafenib and trametinib combination over and above dabrafenib monotherapy treatment. Since a lower standard of evidence is usually required to show such added value the lower limit of an 80% CI is used to identify the response rates which will be exceeded by taking the combination therapy based on a reduced level of evidence (one-sided alpha of 0.1). For example, if 18 responses (45%) out of the 40 patients are observed then the lower bound of 80% CI will exclude 32%, which is the response rate of dabrafenib monotherapy

[redacted]

observed from the study [BFR116013, CDRB436A2102]. In addition, the 95% CI can also be used to provide more robust evidence of the added benefit of trametinib. For example, if 20 responses (50%) are observed, then the lower bound of 95% CI will also exclude 32%.

### LGG Cohort

The primary efficacy analysis in the LGG cohort is the comparison of ORR based on independent review assessment between the two treatment arms. The following statistical hypothesis will be tested:

$H_{01}: ORR_t \leq ORR_c$ vs. $H_{A1}: ORR_t > ORR_c$

where $ORR_t$ is the ORR in the Trametinib plus Dabrafenib arm and $ORR_c$ is the ORR in the carboplatin with vincristine arm. The analysis to test these hypotheses and compare the two treatment groups will consist of a Mantel Haenszel chi-square test at one-sided 2.5% level of significance.

The primary efficacy analysis will be performed on the FAS.

ORR will be summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934).

## 10.4.3 Handling of missing values/censoring/discontinuations

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

## 10.4.4 Supportive and sensitivity analyses

The following supportive and sensitivity analyses will be performed for the HGG and LGG cohorts as appropriate.

The primary analysis on the FAS will be repeated on the evaluable set. The analyses of ORR, DOR, and PFS will be repeated based on radiological response assessed by independent review by only incorporating the radiographic data in the FAS. In addition, ORR, DOR and PFS will be evaluated using a ITT approach i.e including all response assessments irrespective of new anti-neoplastic therapy using the FAS.

If the primary efficacy analysis shows that the 95% CI of ORR excludes 20% for HGG and statistically significant for LGG, the following subgroups may be considered:

The primary efficacy endpoint ORR and secondary endpoint DOR by investigator and central independent assessments may be summarized by risk categories such as that determined by methylation analysis based on FAS and Evaluable set. The risk categories will be specified in a later SAP amendment prior to database lock [redacted].

The SAP will pre-specify analyses that will be conducted using crossover data, if applicable.

[redacted]

Additional supportive [redacted] analyses may be conducted to support the primary objective of the HGG and LGG cohorts if appropriate, and the details of these analyses will be defined in the SAP.

## 10.5 Secondary objectives

### HGG Cohort

With respect to the HGG cohort, the secondary objectives are to evaluate the overall response rate (ORR) by investigator assessment, duration of response (DOR), time to response (TTR), clinical benefit rate (CBR), progression-free survival (PFS) by both investigator assessment and central independent assessment, as well as overall survival (OS), and safety.

### LGG Cohort

With respect to the LGG cohort the secondary objectives related to efficacy in this study are to compare the two treatment groups with respect to the overall response rate (ORR) by investigator assessment, duration of response (DOR), time to response (TTR), clinical benefit rate (CBR), and progression-free survival (PFS) by both investigator assessment and central independent assessment as well as overall survival (OS), safety, and patient reported outcome (PRO).

All secondary efficacy analyses will be performed based on the FAS and will be repeated for the Evaluable set. All secondary endpoints will be listed and summarized separately for each cohort by treatment group.

For the LGG cohort, a hierarchical approach will be taken to control for the overall type-I error rate for testing of multiple endpoints: PFS will be formally tested only if the primary endpoint ORR is statistically significant and then OS will be formally tested if PFS is also significant. No other multiplicity adjustments are planned for secondary endpoints testing.

### ORR by investigator assessment (HGG Cohort)

For the HGG cohort, the evaluation of ORR will be repeated by investigator assessment as per RANO criteria. ORR will be summarized using descriptive statistics (N, %) along with 2-sided exact 95% confidence intervals (CIs) (Clopper and Pearson 1934). 80% confidence intervals will also be provided for the HGG cohort.

### ORR by investigator assessment (LGG Cohort)

For the LGG Cohort the evaluation of ORR will be repeated by investigator assessment assessment as per RANO criteria.

The Cochrane-Mantel-Haenszel chi-square test will be used to compare ORR between the two treatment groups, at the one-sided 2.5% level of significance.

### Duration of response

Among patients with a confirmed response (PR or CR) per RANO, duration of response (DOR) is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. DOR will be listed by patient and may be

[redacted]

described using Kaplan-Meier curves and relevant statistics if appropriate. Only the subset of patients who show a confirmed complete or partial tumor response will be included. Censoring rules for DOR will be outlined in detail in the SAP. DOR will be analyzed as per investigator assessment and as per central independent assessment, separately.

### Progression free survival

Progression-free survival (PFS) is defined as the time from the date of first dose of study treatment (for HGG cohort) or date of randomization (for LGG cohort) to the date of first documented disease progression per RANO criteria or death due to any cause.

A patient who has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, PFS will be censored at the time of the last adequate tumor evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD. Censoring rules for PFS will be described in detail in the SAP.

PFS assessed by the investigators and the central independent reviewers will be described using Kaplan-Meier methods and appropriate summary statistics.

For the LGG cohort the hazard ratio for PFS will be calculated, along with its 95% confidence interval, using a Cox model. A log-rank test at the one-sided 2.5% level of significance will be used to compare the two treatment groups.

PFS estimates (and 95% CIs) for both cohorts will be provided for key timepoints (i.e. 12, 24, 36 months).

### Time to response (TTR)

Time to response (CR or PR) is the time from start date of study treatment (for HGG cohort) or date of randomization (for LGG cohort) to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS will be included in the time to response calculations. Patients without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., LPLV-FPFV) for patients with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for patients without a PFS event. TTR will be listed and summarized by treatment group.

The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case.

TTR will be analyzed using investigator and independent reviewer assessments separately.

[redacted]

### Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later (i.e >= 161 days) from randomization, allowing for the ±1 week visit window for tumor assessments.

For the HGG cohort, CBR will be summarized using descriptive statistics (N, %) along with 2-sided exact 95% confidence intervals (CIs) (Clopper and Pearson 1934).

For the LGG Cohort, CBR will be summarized by treatment group along with 2-sided exact 95% confidence intervals (CIs). Cochrane-Mantel-Haenszel chi-square test will be used to compare CBR between the two treatment groups, at the one-sided 2.5% level of significance.

### Overall survival

Overall survival (OS) is defined as the time from the date of first dose of study treatment (for HGG cohort) or date of randomization (for LGG cohort) to the date of death due to any cause. OS time for patients who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact.

OS will be described using Kaplan-Meier methods and appropriate summary statistics.

For the LGG cohort, the hazard ratio for OS will be calculated, along with its 95% confidence interval, using a Cox model. A log-rank test at the one-sided 2.5% level of significance will be used to compare the two treatment groups.

In addition, 2-year OS estimate with corresponding 95% CIs will be provided by treatment groups.

## 10.5.1 Safety objectives

Safety will be assessed separately for the HGG and LGG cohorts. For the LGG cohort the data will be analyzed by treatment arm.

### 10.5.1.1 Analysis set and grouping for the analyses

For all safety analyses in both cohorts, the safety set will be used. All listings and tables will be presented by all patients.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

The safety summary tables will include only data collected during the on-treatment period. However, all safety data will be listed with data collected during the pre-treatment and post-treatment period flagged.

[redacted]

#### 10.5.1.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/ or preferred term, severity (based on CTCAE grades), type of AE, and relation to study treatment.

Serious adverse events (SAE), non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged. A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

#### 10.5.1.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE y4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

A listing of laboratory values will be provided by laboratory test, patient, and study day. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities).

[redacted]

[redacted]

#### 10.5.1.4 Other safety data

### ECG

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each patient during the study. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced.

### Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

Data from other tests (including ECHO, performance status, dermatological evaluation, [redacted]) will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/Abnormal values for safety data will be further specified in the SAP and will be used for shift tables. Any other information collected will be listed as appropriate.

Analyses will be performed on the safety set for both study cohorts.

#### 10.5.1.5 Supportive analyses for secondary objectives

Not applicable.

#### 10.5.1.6 Tolerability

Tolerability will be summarized in terms of dose reductions or drug interruption due to an AE.

#### 10.5.1.7 Palatability

Data on palatability assessments (bitterness, sweetness, texture and overall taste) will be summarized and listed.

### 10.5.2 Pharmacokinetics

The PAS will be used in all pharmacokinetic data analysis and PK summary statistics for each cohort.

#### 10.5.2.1 Non-compartmental Analysis

On Day 15 PK parameters for dabrafenib, its metabolites and trametinib will be calculated with standard non-compartmental methods using Phoenix WinNonlin (Pharsight, Mountain View, California in US). The PK parameters listed in Table 10-1 will be estimated and reported, when feasible as per the SAP.

[redacted]

**Table 10-1 Non-compartmental pharmacokinetic parameters**

| | |
|---|---|
| AUClast | The AUC from time zero to the last measurable concentration sampling time (tlast) (ng*h/mL) |
| AUCtau | The AUC calculated to the end of a dosing interval (tau) at steady-state (ng*h/mL); tau= 12 hrs |
| Cmax | The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL) |
| Tmax | The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h) |
| Ctrough | Measured concentration at the end of a dosing interval at steady state (taken directly before next administration) (ng/mL)The trough (predose) plasma concentration determined directly from the raw concentration-time data |

### 10.5.2.2 Basic table, figure and listing

Validity of PK samples will be confirmed by checking sampling time window, steady state condition and occurrence of vomiting with respect to time of dose. Only confirmed PK concentrations will be used in the analyses.

Summary statistics of plasma concentration of dabrafenib, its relevant metabolites and trametinib will be reported by visit and actual leading dose (i.e. the dose taken on the day prior to the PK sampling day) for all patients that provided at least one evaluable PK sample. Summary statistics include n, arithmetic mean, median, SD, geometric mean, coefficient of variation (CV) (%) and geometric CV (%), minimum and maximum. Zero concentrations will not be included in the geometric mean calculation Graphical presentation will be provided on mean concentration at each scheduled time point for PK sub-population where the full PK profile is available.

### 10.5.2.3 Data handling principles

Plasma concentration values below the lower limit of quantification (LLOQ) will be set to zero by the bioanalyst, and will be displayed as zero in the listings and flagged. Values below the LLOQ will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. Any missing pharmacokinetic parameters or concentrations will not be imputed.

[redacted]

[redacted]

[redacted]

### 10.5.4 Resource utilization

Not applicable.

[redacted]

### 10.5.5 Patient-reported outcomes

Patient reported outcome (PRO) will only be evaluated in the LGG cohort. One PRO questionnaire will be used: the PROMIS Parent Proxy Global Health 7+2. The 7+2 item parent proxy pediatric global health measure include a one global health score plus a single score from pain and a score from fatigue interference item which are scored independently. These two items are administered but do not contribute to the global health score. Rather, they are "signal" items that provide initial score estimates for pain interference and fatigue. Scoring of PRO data and methods for handling of missing items or missing assessments will be according to the scoring manual and user guide for each respective patient questionnaire. No imputation procedures will be applied for missing items or missing assessments. Descriptive statistics will be used to summarize the scored scales of PROMIS Parent Proxy Global Health 7+2 at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. In addition, a repeated measures model for longitudinal data will be used to estimate differences in PROMIS Parent Proxy Global Health 7+2 scores between treatment groups. The number of subjects completing each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment time point. No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied. The FAS will be used for analyzing PRO data.

## 10.7 Interim analysis

### 10.7.1 HGG Cohort

An interim analysis for futility (HGG cohort only) will be implemented to allow possible termination of recruitment and the study in the event that there is insufficient efficacy. The patients for inclusion in the formal interim analysis for futility will be made shortly after 16 patients in the FAS have been enrolled. The interim analysis will be conducted when this initial group of patients to be included in the analysis have all had at least 20 weeks of follow-up or have withdrawn early. However, any decision to stop or continue the study will be made based on all data available at the IA cut-off taking the futility analysis into account.

The futility criteria will be considered met if the observed overall response rate (ORR) assessed by independent reviewer is less than or equal to 25% which is considered a threshold for clinical relevance. This will trigger consideration for stopping the study taking account of all available data and not just the response data required for determination of futility.

The choice of futility threshold has also taken account of operating characteristics which suggest that the chance of the futility criteria being met is high if the true underlying response rate is in a low range (e.g. <=20%); whereas if the true rate is considerably higher, as expected, then there is a very low chance of declaring futility at the IA. Full details of the futility criteria and operating characteristics are provided below in Table 10-2 and Table 10-4.

### Futility criteria

Given the data observed in the IA, the probability of the lower bound of 95% CI at the primary analysis exceeding a certain response rate (i.e. 20%) conditional on the observed number of responders observed at the IA can be calculated. The conditional probability can be calculated using beta-binomial distribution (posterior predictive distribution). Let Y represent the number of responders from m future patients at the primary analysis and x is the number of responders among n patients at the interim analysis. The (posterior) predictive distribution of Y conditioned on the observed data at the interim analysis (x responders out of n patients) is a beta-binomial distribution described by

$$p(Y = y|x,n) = \binom{m}{y} \frac{B(a_0+x+y, b_0+n-x+m-y)}{B(a_0+x, b_0+n-x)}$$

where a minimally informative unimodal Beta distribution B(a0, b0) (Neuenschwander et al 2008) is used with mean equal to 20%, i.e., the prior distribution will be Beta (0.25, 1) for the POS calculations at the interim analysis.

Table 10-2 shows the predictive probabilities that the 95% CI excludes 20% at the primary analysis under different interim results. For example, with 16 patients at IA, if 4 responses are observed (i.e. 25% response rate), the probability of the 95% CI excluding 20% at the primary analysis is 13.7%.

**Table 10-2 Predictive probability of the lower bound of 95% CI exceeding 20% at the primary analysis under different interim results**

| # of responses | Observed response rate at IA given n=16 (%) | Predictive probability that the 95% CI excludes 20% at the primary analysis (%)[a] |
|---|---|---|
| 1 | 6.3 | < 0.1 |
| 2 | 12.5 | 0.5 |
| 3 | 18.8 | 3.5 |
| 4 | 25.0 | 13.7 |
| 5 | 31.3 | 34.4 |
| 6 | 37.5 | 61.0 |
| 7 | 43.8 | 83.1 |
| 8 | 50.0 | 94.9 |
| 9 | 56.3 | 99.0 |

[a]The predictive probabilities are calculated from a beta-binomial distribution.

[redacted]

In addition to the interim futility analysis described above if the LGG primary analysis is subsequently reported prior to the HGG primary analysis then an update/interim analysis of HGG safety data only may be required to support the LGG submission.

Also, an additional interim analysis of key safety and PK data of the adolescent patients in the HGG cohort may be performed to support a heath authority request for data in adolescent patients. There will be no efficacy or futility conclusion drawn based on this interim analysis.

### 10.7.2 LGG Cohort

No formal interim analysis is planned for the LGG cohort. The primary analysis will be performed after all patients have completed Week 32 or discontinued prior to Week 32. A final analysis will be performed after all patients have been on the study for at least two years (or otherwise discontinued from the study). Formal testing of the primary endpoint with full alpha will be performed at the primary analysis.

## 10.8 Sample size calculation

### 10.8.1 HGG Cohort

Based on the exact binomial distribution, approximately 40 patients will be enrolled if the study is not stopped for futility at the time of the interim analysis.

The exact 95% and 80% CIs for potential observed ORR for 40 patients are shown in Table 10-3.

The 95% CI, via the lower limit, is used to establish the levels of response which are exceeded by taking the combination therapy according to a robust standard of evidence (i.e. one-sided alpha=0.025).

Due to the uncertainties regarding the historical control data there is no specific “success” threshold level that we can apply that the lower limit should be greater than  to give robust evidence that dabrafenib and trametinib combination therapy is better than historical control; however, the study sample size gives reasonable operating characteristics for an illustrative threshold historical level of 20%, which is higher than the range expected based on the information given in the literature (Section 1.1.3).

The study also aims to provide evidence that trametinib gives added value to the dabrafenib and trametinib combination over and above dabrafenib monotherapy treatment. Since a lower standard of evidence is usually required to show such added value, the lower limit of an 80% CI is used to identify the response rates which will be exceeded by taking the combination therapy based on a reduced level of evidence (one-sided alpha of 0.1). Again it is difficult to ascertain a definitive  threshold for “success” for evaluation in these circumstances but the number of patients in this trial give reasonable operating characteristics for an illustrative threshold level of 32%, which is the response rate observed in dabrafenib monotherapy patients in the study [BRF116013, CDRB436A2102] although based on limited data. Note that the 95% CIs can also be used to provide more robust evidence of the benefit of trametinib by looking at the lower limit compared to possible levels of dabrafenib monotherapy response.

[redacted]

**Table 10-3 Exact Binomial 95 and 80 percent Confidence Intervals Around Potential Observed ORRs for N=40**

| Number of responders | Observed ORR (%) | 95% exact CI (%) | 80% exact CI (%) |
|---|---|---|---|
| 12 | 30.0 | 16.6, 46.5 | 20.5, 41.2 |
| 13 | 32.5 | 18.6, 49.1 | 22.7, 43.8 |
| 14 | 35.0 | 20.6, 51.7 | 24.9, 46.3 |
| 15 | 37.5 | 22.7, 54.2 | 27.1, 48.9 |
| 16 | 40.0 | 24.9, 56.7 | 29.4, 51.4 |
| 17 | 42.5 | 27.0, 59.1 | 31.7, 53.9 |
| 18 | 45.0 | 29.3, 61.5 | 34.1, 56.3 |
| 19 | 47.5 | 31.5, 63.9 | 36.4, 58.8 |
| 20 | 50.0 | 33.8, 66.2 | 38.8, 61.2 |
| 21 | 52.5 | 36.1, 68.5 | 41.2, 63.6 |
| 22 | 55.0 | 38.5, 70.7 | 43.7, 65.9 |

For example, out of the 40 patients, with 14 responses (35%), the lower bound of 95% CI would be higher than 20%; with 18 responses (45%), the 80% CI would be higher than 32%; and with 20 responses (50%), the 95% CI would be higher than 32%.

Table 10-4 and Table 10-5 show the operating characteristics under different true ORR with respect to different criteria. The tables show probability of meeting the futility consideration criteria (less than 5 responders out of 16 patients), probability of the confidence interval excluding the target response rate at the primary analysis, and probability that the futility criteria is not met at IA but the confidence interval does not exclude the target response rate at the primary analysis.

At this sample size, when the true ORR is ≤ 20%,

- the probability of meeting the futility consideration criteria at interim analysis is > 79%,
- the probability of the 95% CI excluding 20% at the primary analysis is >1.6%,
- and the probabilities of the 95% CI and the 80% CI excluding 32% at the primary analysis are both < 0.1% respectively.

Within 40 patients, if the true ORR is 55% or higher, then

- the probability of meeting the futility consideration criteria at IA is < 2%,
- the probabilities of the 95% CI excluding 20% and the 80% CI excluding 32% at the primary analysis are both > 90% respectively,
- and the probability that the 95% CI excludes 32% is > 78%.

**Table 10-4 Operating Characteristics with regard to the 95% CI excluding 20% response rate**

| True ORR (%) | Probability to meet futility consideration criteria at IA (%) | Probability that the futility consideration criteria is not met at IA and the 95% CI excludes 20% at primary analysis (%) | Probability that the futility consideration criteria is not met at IA and the 95% CI does not exclude 20% at primary analysis (%) |
|---|---|---|---|
| 20 | 79.8 | 1.6 | 18.6 |
| 25 | 63.0 | 8.5 | 28.4 |
| 30 | 45.0 | 25.2 | 29.8 |
| 35 | 28.9 | 49.1 | 22.0 |

[redacted]

| True ORR (%) | Probability to meet futility consideration criteria at IA (%) | Probability that the futility consideration criteria is not met at IA and the 95% CI excludes 20% at primary analysis (%) | Probability that the futility consideration criteria is not met at IA and the 95% CI does not exclude 20% at primary analysis (%) |
|---|---|---|---|
| 40 | 16.7 | 71.7 | 11.6 |
| 45 | 8.5 | 87.1 | 4.4 |
| 50 | 3.8 | 95.0 | 1.2 |
| 55 | 1.5 | 98.3 | 0.2 |
| 60 | 0.5 | 99.5 | < 0.1 |

The probabilities are calculated based on the exact binomial distribution.

**Table 10-5 Operating Characteristics with regard to the 95% and 80% CIs excluding 32% response rate**

| True ORR (%) | Probability to meet futility consideration criteria at IA (%) | Probability that the futility consideration criteria is not met at IA and the 95% CI excludes 32% at primary analysis (%) | Probability that the futility consideration criteria is not met at IA and the 95% CI does not exclude 32% at primary analysis (%) | Probability that the futility consideration criteria is not met at IA and the 80% CI excludes 32% at primary analysis (%) | Probability that the futility consideration criteria is not met at IA and the 80% CI does not exclude 32% at primary analysis (%) |
|---|---|---|---|---|---|
| 20 | 79.8 | < 0.1 | 20.2 | < 0.1 | 20.1 |
| 25 | 63.0 | 0.1 | 36.9 | 0.5 | 36.5 |
| 30 | 45.0 | 0.6 | 54.4 | 3.1 | 51.9 |
| 35 | 28.9 | 3.6 | 67.5 | 12.1 | 59.0 |
| 40 | 16.7 | 12.9 | 70.5 | 30.5 | 52.9 |
| 45 | 8.5 | 31.4 | 60.1 | 55.2 | 36.3 |
| 50 | 3.8 | 56.0 | 40.1 | 77.6 | 18.5 |
| 55 | 1.5 | 78.5 | 20.0 | 91.7 | 6.8 |
| 60 | 0.5 | 92.4 | 7.1 | 97.8 | 1.7 |

The probabilities are calculated based on the exact binomial distribution.

### 10.8.2 LGG Cohort

To detect a 30% improvement in ORR based on central independent assessed response of 50% in the dabrafenib plus trametinib arm vs 20% in the carboplatin with vincristine arm (Lassaletta 2017) with at least 80% power, 102 patients are required to be randomized in the two treatment arms in a 2:1 ratio based on using a Maentel-Haenszel chi-squared test and one-sided alpha = 2.5%.

Based on the following assumptions i.e 102 patients, 2:1 randomization ratio based on Maentel-Haenszel chi-squared test and one sided alpha of 2.5%, the study power scenarios under different true ORR are shown in Table 10-6.

[redacted]

**Table 10-6 Power scenarios under different true ORR in *BRAF* V600 mutant**

| LGG**True ORR % (carboplatin with vincristine arm vs. dabrafenib plus trametinib )** | **Power (%)** |
|---|---|
| 20% vs. 55% | 90% |
| 20% vs. 50% | 80% |
| 20% vs. 45% | 67% |
| 15% vs. 50% | 90% |
| 25% vs. 50% | 66% |

## 10.9 Power for analysis of key secondary variables

Not applicable.

# 11 Ethical considerations and administrative procedures

## 11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

## 11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent (if applicable, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form).

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

[redacted]

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

### Additional consent form

Not applicable.

## 11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

## 11.5 Publication of study protocol and results

Novartis is committed to the following high ethical standards for reporting study results for its innovative medicines, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted. Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparent in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to .novartis.com.

[redacted]

## 11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

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.

## 11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

[redacted]

## 11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

## 11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

# 12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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# 14 Appendices

## 14.1 Appendix 1 – Concomitant medications

### Table 14-1 List of medications to be used with caution during study drug treatment

| **USE WITH CAUTION**: **Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib or vincristine 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 patients 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.

[redacted]

**Table 14-2 List of prohibited medications during study drug treatment**

| **PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib or vincristine 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 or vincristine 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 |

[redacted]

## 14.2 Appendix 2 – Performance Status Criteria

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

[redacted]

## 14.3 Appendix 3 – Response Assessment in Neuro-oncology (RANO) Criteria

Anti-tumor activity will be assessed based on clinical evidence and the Response Assessment in Neuro-Oncology (RANO) criteria for solid tumors (Wen 2010, Wen 2017).

All measureable and nonmeasureable lesions should be assessed using the same techniques as at baseline. Ideally, patients 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. The RANO criteria for assessment of LGG differs from that for HGG primarily in that LGG assessments utilize T2/FLAIR imaging while HGG assessments utilize Gadolinium enhanced imaging. For purposes of this protocol, the minor response category will not be used for description of LGG response assessments.

Measurable disease is defined as bidimensionally contrast enhancing (HGG) or T2/FLAIR (LGG) lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least twice the thickness of the imaging slices with 0-mm skip. 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 of at least twice the slice thickness. 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 twice the slice thickness.

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.

Response definitions for HGG:

- 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, patient 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, patient 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

[redacted]

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 patient 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.

Response definitions for LGG:

- Complete response (CR): Complete disappearance of all measureable and nonmeasureable disease on MRI scan sustained for at least 4 weeks, and no new lesions. In addition, patient 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, and no new lesions. In addition, patient 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 measurable lesions (compared with baseline if no decrease) 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 patient does not qualify for CR, PR, or PD and has stable 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.

[redacted]

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients 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.

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.

## 14.4 Appendix 4 – WHO (2016) Grading of Tumors of the CNS

**WHO grades of select CNS tumours**

| | |
|---|---|
| **Diffuse astrocytic and oligodendroglial tumours** | |
| Diffuse astrocytoma, IDH-mutant | II |
| Anaplastic astrocytoma, IDH-mutant | III |
| Glioblastoma, IDH-wildtype | IV |
| Glioblastoma, IDH-mutant | IV |
| Diffuse midline glioma, H3 K27M–mutant | IV |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted | II |
| Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted | III |
| **Other astrocytic tumours** | |
| Pilocytic astrocytoma | I |
| Subependymal giant cell astrocytoma | I |
| Pleomorphic xanthoastrocytoma | II |
| Anaplastic pleomorphic xanthoastrocytoma | III |
| **Ependymal tumours** | |
| Subependymoma | I |
| Myxopapillary ependymoma | I |
| Ependymoma | II |
| Ependymoma, *RELA* fusion–positive | II or III |
| Anaplastic ependymoma | III |
| **Other gliomas** | |
| Angiocentric glioma | I |
| Chordoid glioma of third ventricle | II |
| **Choroid plexus tumours** | |
| Choroid plexus papilloma | I |
| Atypical choroid plexus papilloma | II |
| Choroid plexus carcinoma | III |
| **Neuronal and mixed neuronal-glial tumours** | |
| Dysembryoplastic neuroepithelial tumour | I |
| Gangliocytoma | I |
| Ganglioglioma | I |
| Anaplastic ganglioglioma | III |
| Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos) | I |
| Desmoplastic infantile astrocytoma and ganglioglioma | I |
| Papillary glioneuronal tumour | I |
| Rosette-forming glioneuronal tumour | I |
| Central neurocytoma | II |
| Extraventricular neurocytoma | II |
| Cerebellar liponeurocytoma | II |
| **Tumours of the pineal region** | |
| Pineocytoma | I |
| Pineal parenchymal tumour of intermediate differentiation | II or III |
| Pineoblastoma | IV |
| Papillary tumour of the pineal region | II or III |
| **Embryonal tumours** | |
| Medulloblastoma (all subtypes) | IV |
| Embryonal tumour with multilayered rosettes, C19MC-altered | IV |
| Medulloepithelioma | IV |
| CNS embryonal tumour, NOS | IV |
| Atypical teratoid/rhabdoid tumour | IV |
| CNS embryonal tumour with rhabdoid features | IV |
| **Tumours of the cranial and paraspinal nerves** | |
| Schwannoma | I |
| Neurofibroma | I |
| Perineurioma | I |
| Malignant peripheral nerve sheath tumour (MPNST) | II, III or IV |
| **Meningiomas** | |
| Meningioma | I |
| Atypical meningioma | II |
| Anaplastic (malignant) meningioma | III |
| **Mesenchymal, non-meningothelial tumours** | |
| Solitary fibrous tumour / haemangiopericytoma | I, II or III |
| Haemangioblastoma | I |
| **Tumours of the sellar region** | |
| Craniopharyngioma | I |
| Granular cell tumour | I |
| Pituicytoma | I |
| Spindle cell oncocytoma | I |

[redacted]