Official Title: A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of Cobimetinib in Pediatric and Young Adult Patients With Previously Treated Solid Tumors

NCT Number: NCT02639546

Document Date: Protocol Version 11: 11-April-2019

PROTOCOL

TITLE:	**A PHASE I/II, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF COBIMETINIB IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS**
PROTOCOL NUMBER:	GO29665
VERSION NUMBER:	11
EUDRACT NUMBER:	2014-004685-25
IND NUMBER:	124,530
TEST PRODUCT:	Cobimetinib (RO5514041)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 20 December 2014
DATES AMENDED:	Version 2: 18 May 2015; Version 3: 5 August 2015; Version 4 (VHP): 2 February 2016; Version 4 (Canada): 3 March 2016; Version 5: 16 June 2016; Version 6: 3 November 2016; Version 7: 7 February 2017; Version 8: 10 May 2017; Version 9: 9 May 2018; Version 10: 6 July 2018 Version 11: See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Apr-2019 15:22:36

PROTOCOL AMENDMENT, VERSION 11: RATIONALE

Protocol GO29665 has been amended primarily to reduce the frequency of tumor assessments (i.e. MRI scans) and ophthalmologic examinations (i.e. optical coherence tomography [OCT]) for patients with indolent tumor types (Low-Grade Glioma, Plexiform Neurofibroma) who have received long-term study therapy. Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 4.5.5 and Appendix 1 have been updated to reduce the frequency of tumor assessments for patients who have completed at least 12 cycles of cobimetinib therapy and who do not meet criteria for progressive disease to reduce the burden of undergoing regular imaging studies (including radiation exposure in those patients followed by CT scan).
- Plasma samples collection (Appendix 1) has been updated to align with the new tumor assessments schedule (amended to reduce frequency, as stated in bullet above).
- Section 4.5.6 and Appendix 1 have been updated to reduce the frequency of ophthalmologic examinations for patients who have completed 6 cycles of cobimetinib therapy and who have not developed retinal pathology or other Adverse Events (AEs) involving the retina because retinopathy events typically occur very early in the treatment course of cobimetinib. As noted in the Investigator's Brochure, the median time to initial onset of serous retinopathy was 1 month (range: 0–9 months), so patients who are tolerating study drug without retinal AEs require less frequent evaluation.
- Section 5.2.3 has been updated to exclude epistaxis grade 1 (defined by National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE v4.0] criteria as "Mild symptoms; intervention not indicated") from the AESI (Adverse Event Special of Interest) reporting requirement for hemorrhage events. Minor nosebleeds that do not require medical intervention are common in children and are not consistent with the common understanding of the term 'hemorrhage' that would warrant expedited reporting to the Sponsor. Grade 1 epistaxis will still be reportable as an AE.
- Appendix 1 (Schedule of Assessments) and footnote f have been updated to clarify blood sample collection requirement for patients who consented to the optional on-study biopsy for exploratory research.
- Corrections of typographical errors have been made to Appendix 10 dosing tables: Dose level 3 = 1mg/kg, suspension (4.8 mg/mL) and Dose Level –1 (Minus One) = 0.45 mg/kg/day, Suspension (4.8 mg/mL).
- Language has been updated to indicate that Visual Acuity should be reported in Snellen units (Section 4.5.6).

Additionally, standard protocol updates were made to update or clarify reporting of adverse events (Sections 5.3.5.7, 5.3.5.10, and 5.4.3.3), protocol deviations processes

(Section 9.2), and to align with Roche standard operating procedures and policies (Sections 4.5.9, 4.5.11.6, 7.5, and 8.1). Furthermore, minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I/II, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF COBIMETINIB IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I/II, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF COBIMETINIB IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS**
PROTOCOL NUMBER:	GO29665
VERSION NUMBER:	11
EUDRACT NUMBER:	2014-004685-25
IND NUMBER:	124,530
TEST PRODUCT:	Cobimetinib (RO5514041)
PHASE:	Phase I/II
INDICATION:	Solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Safety (Primary) Objective

The primary objective for this study is as follows:

- To evaluate the safety and tolerability of cobimetinib in children and young adults, including estimation of the maximum-tolerated dose (MTD) or the maximum-administered dose (MAD) and characterization of dose-limiting toxicities (DLTs)

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of cobimetinib in children and young adults

Efficacy Objective

The efficacy objective for this study is as follows:

- To evaluate the anticancer activity of cobimetinib in children and young adults with solid or brain tumors, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and overall survival (OS)

Dose-Finding Objective

An additional objective for this study is as follows:

- To identify recommended Phase II doses for cobimetinib tablet and suspension formulations in pediatric patients on the basis of safety, PK, and efficacy outcome measures

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To explore the relationship between cobimetinib exposure and changes in levels of pharmacodynamic (PD) biomarkers in children and young adults

- To explore non-inherited biomarkers that may be predictive of response to cobimetinib (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to cobimetinib, or susceptibility to developing adverse events, may provide evidence of cobimetinib activity, or may increase the knowledge and understanding of disease biology
- To explore inherited biomarkers (i.e., variants in germline DNA) that may be predictive of response to cobimetinib (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to cobimetinib, or susceptibility to developing adverse events, or may increase the knowledge and understanding of disease biology
- To explore potential relationships between PK parameters for cobimetinib and other outcome measures (such as safety or efficacy outcome measures)
- To evaluate tumor characteristics before and after treatment on the basis of available magnetic resonance imaging (MRI) and positron emission tomography (PET) scans
- To evaluate specific aspects of the acceptability of the cobimetinib formulations

Study Design

Description of Study

Study Design

This is a Phase I/II, multicenter, open-label, dose-escalation study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of cobimetinib in pediatric and young adult patients with solid tumors with known or potential RAS/RAF/MEK/ERK pathway activation for which standard therapy has proven to be ineffective (i.e., relapsed or refractory tumors) or intolerable or for which no curative standard-of-care treatment options exist.

Patients will be enrolled via an interactive web response system in two stages: a dose-escalation stage and an expansion stage at the recommended dose. During the dose-escalation stage, cohorts of 3–6 pediatric patients (age $\geq$ 6 months to $<$ 18 years) will be evaluated at escalating dose levels to determine the MTD or MAD of cobimetinib in pediatric patients with advanced solid tumors. The MTD or MAD of each cobimetinib formulation (tablet and suspension) will be determined in separate dose escalations. Once the MTD or MAD has been established, pediatric patients (age $\geq$ 6 months to $<$ 18 years) will be enrolled in the expansion stage and treated at the recommended dose, which will be at or below the MTD or MAD, as determined by the Sponsor; adult patients $\geq$ 18 years of age with pediatric tumor types can be enrolled on this study but only during the expansion stage; these adult patients will be treated at the adult flat dose. Approximately 70 patients are expected be enrolled in the dose-escalation and initial expansion stages of this study, at approximately 30 investigative sites in Europe and North America. If an efficacy signal is observed during the first expansion step for the initial response assessment, up to an additional 30 patients per cohort may be enrolled in the second expansion step for the additional response assessment.

Safety Assessment

All patients will be closely monitored for adverse events throughout the study and for at least 30 days after the last dose of study treatment. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Other safety assessments include echocardiograms, ophthalmologic examinations, and dermatologic examinations.

Pharmacokinetic Assessment

To characterize the PK properties of cobimetinib, blood samples will be taken at defined timepoints after dosing.

Efficacy Assessment

Tumor assessments will be performed in the final week of every other cycle, starting with Cycle 2. Response will be determined by the investigator using the modified International Neuroblastoma Response Criteria (mINRC) for patients with neuroblastoma, Response Assessment in Neuro-Oncology (RANO) criteria for patients with high-grade glioma (HGG), Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for patients with other tumors and

Response Assessment in Neuro-Oncology for Low Grade Glioma (RANO) criteria for patients with low-grade glioma (LGG) in the expansion stage in addition to RECIST v1.1.

Study Drug Dosing

Patients in both dose-escalation and expansion stages will receive cobimetinib orally on Days 1–21 of each 28-day treatment cycle (21/7 dosing schedule) until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Cohorts of 3–6 pediatric patients each will be treated at escalating doses of cobimetinib according to a rolling 6 design. The first patient at each dose level must complete at least 5 days of treatment (Days 1–5 of Cycle 1) without a DLT before subsequent patients can be treated at the same dose level.

The DLT assessment window is defined as Days 1–28 of Cycle 1. Adverse events identified as DLTs will be reported to the Sponsor within 24 hours.

Two formulations will be available for the protocol: a tablet (20 mg) and a suspension (4.8 mg/mL). An MTD or MAD will initially be determined for tablets in patients 6 years and above. Once the MTD or MAD is identified for tablets, enrollment of patients using the suspension will commence following review of relevant data from the tablet dose escalation. The starting dose for the suspension will be a minimum of one dose level below the MTD or MAD of the tablets. Additional dose escalation with the suspension may proceed according to the dose-escalation rules until an MTD or MAD is identified for the suspension. On the basis of an ongoing review of safety data and available PK data, increases in dose level or continued enrollment for either formulation may be halted by the Sponsor as deemed appropriate.

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD or MAD assessments. These patients will be replaced at that same dose level unless there are 3 or more patients already treated and all were evaluated with no DLT at that level. Patients who miss five or more doses (i.e., $>$ 18% of the cumulative dose) during the DLT assessment window for reasons other than toxicity will also be replaced. Patients who ingest moderate or strong CYP3A inducers or inhibitors, ingest prohibited foods/supplements, or receive supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described below as part of the DLT definition) may be replaced at the discretion of the Medical Monitor.

Patients who experience a DLT during the assessment window (first 28 days) may not subsequently continue drug at full dose, even if the drug is withheld until resolution of the toxic event. The investigator should use guidance (and if guidance is not specified, investigator discretion) to determine whether the patient should permanently discontinue study drug or withhold study drug until toxicity resolves to Grade 1 or lower, then resume study drug at a dose corresponding to a reduction of one dose level.

After the MTD or MAD has been determined for a formulation, pediatric and young adult patients will be enrolled in tumor type cohorts to obtain additional safety, tolerability, and PK data, as well as any preliminary evidence of anti-cancer activity. Pediatric ($<$ 18 years of age) patients will be treated at or below the formulation-specific MTD or MAD identified in the dose-escalation stage of this study. Young adult patients ($\geq$ 18 years of age) will be treated at the recommended adult dose.

The Sponsor reserves the right to determine whether enrollment into the expansion stage using tablets will proceed concurrently with or subsequent to dose-escalation for suspension. Enrollment in expansion cohorts may commence after internal monitoring committee (IMC) has reviewed PK and safety data obtained in the dose escalation phase.

Each tumor type will be considered a distinct tumor type cohort. Different tumor type cohorts may not all enroll simultaneously. Tumor type cohorts will be chosen after IMC review, prior to inclusion in the expansion stage of the study. Chosen tumor type cohorts for the expansion stage may also include subgroups of tumor types included in the dose-escalation stage, with inclusion based on confirmed (rather than expected) RAS/RAF/MEK/ERK-pathway activation (based on local testing of sample from time of diagnosis or any subsequent timepoint prior to enrollment) with approval of medical monitor). Two phases of response assessment are planned for the expansion stage: an initial response assessment and an additional response

assessment. An initial response assessment will be performed after a minimum of 10 patients, treated at the recommended dose for expansion stage, have been enrolled in a tumor type cohort and followed for approximately 12 months, to determine whether to expand the cohort for additional response assessment.

Cohort expansion will be started once a pre-established number of responses for that tumor type are confirmed. A decision to pursue additional enrollment in a tumor type cohort may be approved by the Sponsor or Medical Monitor before the initial response assessment. Cohort expansion, including the number of patients needed for the additional response assessment, will take into account practical considerations (e.g., enrollment feasibility), nonclinical findings, biomarker analysis, safety profiles, and any other relevant information.

If the frequency of Grade 3 or 4 toxicities or other unacceptable toxicities at the initial dose level in the expansion stage suggest that this dose is intolerable, accrual at that dose level will be halted. Consideration will then be given to enrolling patients at a lower dose level.

The Sponsor may decide to stop enrollment of patients $\geq$ 18 years of age at any time during the study to ensure adequate enrollment of patients $<$ 18 years of age. To meet study completion criteria below, the Sponsor may restrict enrollment of patients $\geq$ 10 years of age if too few patients $<$ 10 years of age are being enrolled.

The Sponsor intends to stop study enrollment once all of the following criteria are met:

- The dose-escalation phase of both tablet and suspension formulations are complete
- At least 20 patients $<$ 18 years of age have been treated with study drug
- At least one tumor type cohort has completed response assessment (either initial response assessment or additional response assessment)
- At least 10 patients $<$ 10 years of age have been treated with study drug

Enrollment in a tumor type cohort will be stopped if any one of the following criteria is met:

- The number of patients needed for initial response assessment is reached and the number of responders does not meet the requirement for tumor type cohort expansion
- The number of patients needed for additional response assessment is reached
- The Sponsor has stopped the study

Some exceptions may apply to these general stopping rules, including but not limited to the following:

- Enrollment in the study may be stopped if enrollment has been open for more than 2 years and at least 20 patients have been treated with the study drug.
- Enrollment in a given tumor type cohort may be extended by the Sponsor if there is strong evidence of a positive efficacy signal in a slow enrolling and rare tumor type cohort, thus allowing for additional data to be collected.

Number of Patients

Approximately 70 patients are expected be enrolled in the dose-escalation and initial expansion stages of this study, at approximately 30 investigative sites in Europe and North America. If an efficacy signal is observed during the first expansion step for the initial response assessment, up to an additional 30 patients per cohort may be enrolled in the second expansion step for the additional response assessment.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Signed Child's Informed Assent, when appropriate as determined by patient's age and individual site and country standards
- For dose-escalation stage, tablets: Age at study entry $\geq$ 6 years to $<$ 18 years

- For dose-escalation stage, suspension: age at study entry ≥ 6 months to < 18 years

  Patients < 1 year of age will not be enrolled until ≥ 6 patients ≥ 1 year to < 18 years of age have received at least one cycle of therapy with suspension and until safety and PK assessment of these patients has been conducted.
- For expansion stage: Age at study entry ≥ 6 months (≥ 6 years if suspension is not available) to < 30 years

  Patients ≥ 6 months to < 1 year of age may not be enrolled until ≥ 6 patients ≥ 1 year to < 18 years of age have received at least one cycle of therapy with suspension in the dose-escalation phase and until safety and PK assessment of these patients has been conducted.

  In exceptional cases of relapsed pediatric tumors in patients ≥ 30 years of age, the Sponsor will consider waiving the age requirement with approval of the Medical Monitor. This waiver is restricted to patients with pediatric-specific diseases (e.g., neuroblastoma) for whom clinical trials are unlikely to be available, and will not be extended to patients with tumors that typically occur both in children and adults (e.g., HGG). The Sponsor may decide to stop enrollment of patients ≥ 18 years of age at any time during the study to ensure adequate enrollment of patients < 18 years of age.
- Able to comply with the requirements of the study protocol, in the investigator's judgment
- Tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable, or for which no standard therapy exists.
- Tumors with known or expected RAS/RAF/MEK/ERK pathway involvement. Diagnosis MUST be one of the following tumor types:

  Central nervous system gliomas, including high- and low-grade gliomas, and diffuse intrinsic pontine glioma (DIPG)

  For initial expansion stage, evidence of RAS/RAF/MEK/ERK-pathway activation is required (based on local testing of sample from time of diagnosis or any subsequent timepoint prior to enrollment) and must be approved by medical monitor for inclusion.

  Embryonal rhabdomyosarcoma and other non-rhabdomyosarcoma soft tissue sarcomas

  Neuroblastoma

  Melanoma

  Malignant peripheral nerve sheath tumor

  Rhabdoid tumors, including atypical teratoid/rhabdoid tumor

  Tumors from the following groups that, in the judgment of the investigator, are life threatening, resulting in severe symptoms (including severe pain), or are in close proximity to vital structures:

  Neurofibromatosis 1 (NF1)-associated tumors (including plexiform neurofibroma)

  Schwannoma

  Any solid tumor or brain tumor that occurs in a patient with another RASopathy (such as Noonan syndrome)

  Any solid or brain tumor that has been molecularly profiled and shown to have RAS/RAF/MEK/ERK pathway activation, with approval of the Medical Monitor.
- Tumor diagnosis must be histologically or cytologically confirmed either at the time of diagnosis or at the time of relapse, except in the following scenario:

  DIPG and optic pathway gliomas do not require histologic confirmation if radiographic findings are sufficient to make diagnosis and institutional standard of care does not mandate biopsy for diagnosis.
- Current disease state for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life

- Disease that is measurable as defined by mINRC, RANO criteria for HGG, RANO criteria for LGG, or RECIST v1.1 (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
- Availability of tumor tissue at study enrollment is mandatory. Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission, and/or willingness to undergo a core or excisional biopsy prior to enrollment are acceptable. Fine-needle aspiration, brush biopsy, and lavage samples are not acceptable.

  For patients submitting archival tissue, a minimum of 15 slides are required. Patients with fewer than 15 slides available may be eligible for study entry following approval of the Medical Monitor.
- Lansky Performance Status or Karnofsky Performance Status $\geq 50\%$
- Life expectancy ≥ 3 months, in the investigator's judgment
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Female patients must remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 3 months after the last dose of study drug. Female patients must refrain from donating eggs during this same period.

  True abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.
- For male patients with a female partner of childbearing potential or a pregnant female partner: Agreement to remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug

  True abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For male patients: agreement to refrain from donating sperm during the treatment period and for at least 3 months after the last dose of study drug
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 28 days prior to initiation of study drug:

  ANC $\geq 0.75 \times 10^9$/L (unsupported)

  Platelet count $\geq 75 \times 10^9$/L (unsupported)

  Hemoglobin ≥ 8 g/dL (transfusion is acceptable to meet this criterion)

  Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) for age

  AST and ALT $\leq 2.5 \times$ ULN for age

  Serum creatinine $\leq 1.5 \times$ ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m^2

- Fractional shortening (FS) $\geq$ 30% and left ventricular ejection fraction (LVEF) $\geq$ 50% at baseline, as determined by echocardiography or multigated acquisition scan within 28 days prior to initiation of study drug

    Depending on institutional standard, either FS or LVEF is adequate for enrollment if only one value is measured; if both values are measured, then both values must meet criteria above.
- Body weight must be $\geq$ 20 kg if suspension is not available

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or lactating, or intending to become pregnant during the study

    Females of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
- Prior treatment with cobimetinib or other MEK inhibitor (prior sorafenib use is permissible)
- Treatment with high-dose chemotherapy and stem-cell rescue (autologous stem cell transplant) within 3 months prior to initiation of study drug
- Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within 4 weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug. This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
- Treatment with thoracic or mediastinal radiotherapy within 6 weeks prior to initiation of study drug
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives), immunotherapy, biologic therapy, or herbal cancer therapy within 4 weeks or $<$ 5 half-lives, whichever is shorter, prior to initiation of study drug
- Treatment with a long-acting hematopoietic growth factor within 2 weeks prior to initiation of study drug or a short-acting hematopoietic growth factor within 1 week prior to initiation of study drug
- Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug
- Requirement for initiation of corticosteroids or an increase in the dose of corticosteroids within 1 week prior to initiation of study drug
- Treatment with St. John's wort or hyperforin or drugs that are strong inhibitors or inducers of CYP3A within 1 week prior to initiation of study drug
- Ingestion of grapefruit juice within 1 week prior to initiation of study drug
- Any toxicity (excluding alopecia and ototoxicity) from prior treatment that has not resolved to Grade $\leq$ 1 (per NCI CTCAE v4.0) at screening except as otherwise permitted in the inclusion/exclusion criteria
- Major surgical procedure or significant traumatic injury within 4 weeks prior to initiation of study drug, or anticipation of need for major surgical procedure during the course of the study

    Placement of a vascular access device or minor surgery is permitted if the site has healed prior to initiation of study drug.
- Known active infection (excluding fungal infection of the nail beds) within 28 days prior to initiation of study drug that has not completely resolved
- History of Grade $\geq$ 2 CNS hemorrhage
- History of CNS hemorrhage within 28 days of study entry. This criterion may be waived at the investigator's request if the CNS hemorrhage was asymptomatic, with approval of the Medical Monitor.

- For brain tumor patients, use of anticoagulants within 1 week of study drug initiation.
- History or evidence of retinal pathology on ophthalmologic examination that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity
- Known hypersensitivity to any component of the study drug
- Inability to swallow oral medications
- Impaired gastrointestinal absorption
- Prior allogenic bone marrow transplantation or prior solid organ transplantation
- Any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or places the patient at unacceptable risk from treatment complications
- Current drug or alcohol use or dependence that would interfere with adherence to study requirements, in the opinion of the investigator

Length of Study

The study will run for approximately 7 years, from screening of the first patient until last patient, last visit (LPLV).

End of Study

The end of this study is defined as the date when the LPLV occurs, or 5 years after the last patient is enrolled, whichever occurs first. The Sponsor reserves the right to present interim data to health authorities for compliance purposes.

For an individual patient the completion of the study (i.e., the last visit) will occur when the patient withdraws consent, has completed follow-up, has been lost to follow-up, dies, or when the trial is stopped.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and nature of DLTs
- Nature, frequency, severity, and timing of adverse events, including serious adverse events and adverse events of special interest
- Changes in vital signs, physical findings, and clinical laboratory results during and following cobimetinib administration
- Growth patterns (relative to age-specific standards for height and weight) accounting for baseline growth of the patient
- Development patterns (relative to onset of menarche [for females] and pubertal changes) accounting for baseline development of the patient

Pharmacokinetic Outcome Measure

The PK outcome measure for this study is as follows:

- To characterize cobimetinib PK in pediatric patients, the following PK parameters following single and multiple doses will be estimated: maximum plasma concentration observed, time to maximum concentration), total exposure (area under the concentration–time curve from 0 to 24 hours [AUC_{0-24}]), and apparent clearance

Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- ORR, defined as the percentage of patients with a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non–measurable but evaluable disease at baseline (except neuroblastoma patients), on two consecutive occasions ≥4 weeks apart, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, for the RANO criteria for patients with LGG, and RECIST v1.1 for patients with other tumors
- PFS, defined as the time from initiation of study drug to the first documented occurrence of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, RECIST v1.1 for patients with other tumors and RANO criteria for patients with LGG in the expansion stage in addition to RECIST v1.1, or death from any cause, whichever occurs first

The secondary efficacy outcome measures for this study are as follows:

- DOR, defined as the time from the first tumor assessment that supports the patient's objective response to the time of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, RECIST v1.1 for patients with other tumors, and RANO criteria for patients with LGG in the expansion stage in addition to RECIST v1.1, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study drug to death from any cause

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Levels of potential PD biomarkers (potentially including, but not limited to, p-MEK, p-ERK, and Ki67) measured in tumor tissue collected at baseline, on treatment, and at the time of disease progression
- Correlation between non-inherited and inherited biomarkers in plasma (potentially including, but not limited to *BRAF* mutations, BRAF fusions, *RAS* mutations, and NF1 alterations) with safety, PK, or efficacy outcome measures
- To explore potential relationships between cobimetinib pharmacokinetics and other outcome measures (such as safety or efficacy outcome measures)
- ORR for LGG by RECIST, defined as the percentage of patients with measurable disease who have a complete or partial response, on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1
- Exploratory ORR for LGG by RANO, defined as the percentage of patients with measurable disease who have a complete, partial or minor response on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RANO criteria for LGG
- Diffusion activity in tumors before and after cobimetinib treatment, as demonstrated on available MRI scans
- Metabolic activity in tumors before and after cobimetinib treatment, as demonstrated on available PET scans
- Acceptability Survey

<u>Investigational Medicinal Products</u>

The test product (investigational drug) for this study is cobimetinib available as 20 mg tablets or suspension (4.8 mg/mL).

Cobimetinib will be taken orally once daily on Days 1–21 of each 28-day treatment cycle (21/7 dosing schedule) until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, or patient or investigator decision to discontinue treatment. Patients will be assigned to dose levels in the order in which they are enrolled. The

starting dose for tablets will be 0.6 mg/kg in the dose-escalation stage. Pediatric patients (< 18 years of age) enrolled in the expansion stage will be treated at or below the MTD or MAD, as determined by the Sponsor. Adult patients (≥ 18 years of age) enrolled in the expansion stage will be treated with the adult recommended dose of 60 mg daily. Cobimetinib should be taken at approximately the same time each day, no earlier than 1 hour before and no later than 4 hours after the usual dosing time.

Patients under 6 years of age or weighing < 20 kg are only eligible to receive the drug in suspension.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Statistical Methods

Primary Analysis

Safety analyses will be performed on the safety-evaluable population, which is defined as patients who receive any amount of study drug. Subgroup safety analyses by tumor type cohort will also be conducted as appropriate.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All adverse events, serious adverse events, adverse events leading to death, DLTs, adverse events of special interest, and adverse events leading to study treatment discontinuation, that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events), will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Laboratory toxicities will be summarized by NCI CTCAE grade.

Determination of Sample Size

For the dose-escalation stage, the sample size is based on the dose-escalation rules described in the study design section of this document. Explicit power and Type I error considerations were not factored into the design, as the dose-escalation stage was designed to obtain preliminary safety and PK information for the study drug.

To make a preliminary assessment of the efficacy of the study drug, two phases of response assessment are planned for the expansion stage: an initial response assessment and an additional response assessment. Taking into account historical control ORRs for each pediatric tumor type, the minimum number of patients in the initial response assessment and the minimum number of responders needed for advancement to the additional response assessment were calculated. The selection of tumor type cohorts for additional response assessment, as well as the number of patients needed for the additional response assessment, will also take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information. Similar consideration will be given to other rare pediatric tumor types that are enrolled in the study and not included in the body of the protocol. No formal hypothesis testing is planned in this study.

Interim Analyses

Interim efficacy analyses will be conducted whenever a tumor type cohort has enrolled the 10 patients required for initial response assessment and patients have been followed for approximately 12 months. After a minimum of 20 patients have completed Cycle 1, an interim PK and safety analysis will be conducted.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ATRT	atypical teratoid/rhabdoid tumor
AUC	area under the concentration–time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AYA	adolescent and young adult
BCC	basal cell carcinoma
CL/F	apparent clearance
C_{max}	maximum plasma concentration observed
CMN	congenital melanocytic nevi
CSCR	central serous chorioretinopathy
CT	computed tomography
DIPG	diffuse intrinsic pontine glioma
DLT	dose-limiting toxicity
DOR	duration of objective response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FS	fractional shortening
HGG	high-grade glioma
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
INRC	International Neuroblastoma Response Criteria
IRB	Institutional Review Board
IWRS	interactive web response system
LGG	low-grade glioma
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MIBG	metaiodobenzylguanidine
mINRC	Modified International Neuroblastoma Response Criteria
MRI	magnetic resonance imaging

Abbreviation	Definition
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF1	Neurofibromatosis 1
NF2	Neurofibromatosis 2
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
RANO	Response Assessment in Neuro-Oncology
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SCC	squamous cell carcinoma
SOC	Scientific Oversight Committee
$T_{1/2}$	half-life
T_{max}	time to maximum concentration
ULN	upper limit of normal

1. BACKGROUND

1.1 RAS/RAF/MEK/ERK PATHWAY AND CANCER

The MAPK signaling cascade transduces multiple proliferative and differentiating signals within tumor cells. The ERK/MAPK pathway, one of four major mammalian MAPK pathway modules, plays a major role in the mediation of cell growth and differentiation in response to numerous extracellular signals (Johnson and Lapadat 2002; Roberts and Der 2007). Ras-GTP activates RAF kinases, which in turn activate the MEK/ERK cascade and subsequent cellular proliferation (Downward 2003; Roberts and Der 2007). To regulate cellular proliferation, activated ERKs translocate to the nucleus and regulate gene expression through the activation of several key transcription factors. Abnormal regulation of the RAS/RAF/MEK/ERK pathway contributes to uncontrolled proliferation, invasion, metastasis, and angiogenesis as well as diminished apoptosis.

RAS/RAF/MEK/ERK pathway activation can be induced directly via gain-of-function mutations or indirectly via induction of growth factor signaling. An advantage of targeting MEK is that the RAS/RAF/MEK/ERK pathway is a convergence point where a number of upstream signaling pathways can be blocked with the inhibition of MEK. MEK inhibitors differ from most other kinase inhibitors in that they do not compete with ATP binding, which confers a high specificity. Inhibitors of MEK are expected to be efficacious in tumors that are highly dependent on proliferative signals from the RAS/RAF/MEK/ERK signaling pathway. To illustrate this concept, malignant melanoma frequently carries a *BRAF*^{V600E} mutation, which leads to a constitutively active form of BRAF that subsequently leads to downstream MEK/ERK phosphorylation and activation. Early clinical trials have demonstrated significant clinical responses to MEK inhibitors, both alone (see Section 1.2.2.3) and in combination with direct BRAF inhibitors.

Pediatric solid and brain tumor entities with evidence of RAS/RAF/MEK/ERK involvement and preclinical evidence of MEK inhibitor activity include:

- Low-grade glioma: RAS/RAF/MEK/ERK activation is universal in pediatric low-grade glioma. MEK/ERK phosphorylation is mediated in the majority of pediatric low-grade gliomas via a 7q34 duplication, which encodes a constitutively active KIAA1549-BRAF fusion protein (Forshew et al. 2009; Jacob et al. 2009; Sievert et al. 2009). Pediatric astrocytomas with this mutation demonstrate in vitro resistance to BRAF inhibitors due to paradoxical activation of wild-type BRAF still present within the tumor (Sievert et al. 2013), which suggests that this class of patients requires downstream pathway targeting. Subsequent sequencing has demonstrated alternate activating RAS/RAF/MEK/ERK pathway mutations in tumors without the KIAA1549-BRAF fusion protein (Zhang et al. 2013). A murine xenograft of BRAF^{V600E}-mutant low-grade astrocytoma cell line, BT-40, has demonstrated complete regression to targeted MEK inhibitor therapy with selumetinib (AZD6244; Kolb et al. 2010), suggesting the possibility that downstream pathway targeting may be viable for a variety of BRAF-mediated low-grade gliomas.

- High-grade glioma (HGG): Pediatric HGGs carry *BRAF*^{V600E} mutations in approximately 10%–20% of cases (Schindler et al. 2011), and activating tyrosine kinase mutations leading to RAS activation are present in up to 68% of HGGs, including diffuse intrinsic pontine glioma (DIPG; Wu et al. 2014). In vitro administration of MEK inhibitors PD0325901 and selumetinib to glioblastoma cell lines demonstrated universal inhibition of ERK phosphorylation as well as growth inhibition in neurofibromatosis 1 (NF1)-mutant cell lines LN229 and U373 (See et al. 2012). Significant ($p<0.001$) delay in tumor growth and prolongation in event-free survival was observed with selumetinib therapy in two of four murine glioblastoma xenografts (Kolb et al. 2010). Case reports have indicated significant clinical response in patients, including complete remission, of HGGs to vemurafenib monotherapy (Bautista et al. 2014; Robinson et al. 2014).
- Rhabdomyosarcoma: Whole exome sequencing of 147 rhabdomyosarcoma samples demonstrated frequent occurrence of tumors with a mutation leading to RAS/RAF/MEK/ERK pathway activation, typically in embryonal rhabdomyosarcoma (ERMS) without presence of PAX fusion genes. Specifically, activating mutations in NRAS, KRAS, HRAS, and upstream RAS-effectors NF1 and FGF4 collectively occurred in 24% of rhabdomyosarcoma and 37% of PAX fusion negative tumors (Shern et al. 2014). Xenografts of embryonal rhabdomyosarcoma cell line RD, which carries an activating Q61H NRAS mutation, demonstrated approximately 50% reduction in growth rate compared to control when treated with U0126, a specific MEK inhibitor, with demonstrable reduction of downstream ERK phosphorylation. Growth arrest and abrogation of ERK phosphorylation was similarly observed in vitro in ERMS cell line TE671 (Marampon et al. 2009). In vitro synergistic effect of selumetinib on human cell line viability was also observed when given in combination with a PI3K inhibitor (Renshaw et al. 2013).
- Non-rhabdomyosarcoma soft tissue sarcomas: Data are limited regarding RAS/RAF/MEK/ERK pathway in other pediatric soft tissue sarcomas. Adult patient myxofibrosarcoma and pleomorphic liposarcoma samples demonstrate a Ras-activating NF1 deletion in approximately 10% of cases (Barretina et al. 2010). Murine soft tissue sarcomas induced by targeted NF1 deletion experience delay in tumor growth with targeted MEK inhibition (Dodd et al. 2013), suggesting that MEK inhibitors are candidate agents for other pediatric soft tissue sarcomas.
- Neuroblastoma: Loss-of-function germline and somatic mutations in NF1 are associated with poor outcomes in neuroblastoma, which are mediated by RAS/RAF/MEK/ERK pathway activation that results in retinoic acid resistance (Hölzel et al. 2010). Whole genome sequencing of paired diagnostic and relapse specimens demonstrated clonal evolution with appearance of novel RAS/RAF/MEK/ERK pathway mutations in 18 of 23 of samples (78%). In vitro and in vivo exposure of cell lines to MEK inhibitors (including cobimetinib, in in vitro models) showed differential response depending on presence and type of RAS mutation, with oncogenic RAS mutations rendering cell lines most sensitive to MEK inhibition (Eleveld et al. 2015). Neuroblastoma RAS/RAF/MEK/ERK pathway activation can also result from NF1 downregulation by an ubiquitin-proteasome-dependent pathway (Han et al. 2011). Administration of a

MEK inhibitor to cell lines in vitro restores retinoic acid sensitivity, which is indicative of the targetability of this pathway in neuroblastoma (Hölzel et al. 2010). Administration of the MEK inhibitor trametinib to two neuroblastoma cell lines with NRAS Q61K mutations resulted in pronounced in vitro response (Vujic et al. 2015).

- Melanoma and congenital melanocytic nevi (CMN): Adult melanoma is commonly characterized by presence of constitutively active BRAFV600E and is highly responsive to MEK inhibition (see cobimetinib Investigator's Brochure). Pediatric conventional melanomas (those that arise from ultraviolet exposure) carry activating BRAF mutations at high frequency (11 of 13 cases; Lu et al. 2014). Pediatric melanoma can also arise from CMN, severe cutaneous lesions that can cover up to 80% of the body surface area and are characterized by activating NRAS Q61 mutations (Lu et al. 2014; Kinsler et al. 2013). The presence of CMN can also lead to neurocutaneous melanosis, a syndrome of neurologic abnormalities triggered by infiltrates of melanocytes that contain the same NRAS mutation seen in cutaneous lesions (Kinsler et al. 2013).
- Rhabdoid tumors/atypical teratoid/rhabdoid tumor (ATRT): Rhabdoid tumors, including ATRT of the brain, are rare poorly differentiated tumors induced by biallelic inactivating mutations of INI1 (SMARCB1), a chromatin regulator. Prognosis is dismal, with a median survival of <12 months from diagnosis (Strother 2005). Tumors can arise from transformed malignant brain tumors, and BRAFV600E can be present in rhabdoid/ATRT with comorbid INI1 loss. High levels of KRAS expression in ATRTs have been observed irrespective of pathway mutation status, with intermediate- or high-level downstream expression of pERK observed in approximately one-third of ATRTs. This observation led to in vitro experiments demonstrating blockade of ERK activation, suppression of cell growth, induction of apoptosis, and decreased cell cycle progression in vitro in pERK-expressing ATRT tumor cell lines treated with selumetinib (Weingart et al. 2015). Mice xenografted with the rhabdoid tumor cell line BT-29 demonstrated nearly doubled ($p<0.001$) event-free survival when treated with selumetinib relative to control (Kolb et al. 2010).
- NF1-related tumors and malignant peripheral nerve sheath tumor: NF1 is an autosomal dominant genetic disorder characterized by mutations in NF1, loss of which results in increased RAS/RAF/MEK/ERK pathway activation. Patients with this disorder are susceptible to development of a spectrum of benign and malignant tumors, including plexiform neurofibroma and malignant peripheral nerve sheath tumor. Targeting the RAS/RAF/MEK/ERK pathway with MEK inhibition effectively treats in vivo models of NF1-associated disease. The MEK inhibitor PD0325901 suppressed growth of murine neurofibromas, induced by enforced loss of NF1 in Schwann cells. In addition to inhibiting cell growth via decreased ERK phosphorylation in vitro, PD0325901 also diminished tumor growth and prolonged survival of mice xenografted with patient-derived MPNST cells (Jessen et al. 2013).
- Neurofibromatosis 2 (NF2)-related tumors: Although not classically considered a RASopathy, NF2 is caused by a loss-of-function mutation in the gene encoding Merlin, which normally inhibits RAS activation by decoupling RAS from growth factor signaling (Morrison et al. 2007). NF2 leads to development of Schwannomas

(malignant tumors typically of the eighth cranial nerve), and accumulation of multiple tumors in patients is typically fatal. Schwannoma cell cultures show decreased proliferation and increased apoptosis after in vitro exposure to a MEK inhibitor (Neff et al. 2012).

- Solid tumors arising in a RASopathy (Rauen 2013): In addition to NF1, other genetic disorders have mutations in genes that lead to activation of the RAS/RAF/MEK/ERK pathway. Collectively these are referred to as RASopathies, many of which predispose patients to cancer. An example is Noonan syndrome, which is characterized by activating mutations in RAS pathway genes including *PTPN11*, *KRAS*, *NRAS*, *SHOC2*, *SOS1*, and *RAF1*. Children with Noonan syndrome who go on to develop cancer most commonly present with hematologic malignancies but solid tumors occur sporadically, including neuroblastoma, gliomas, and hepatoblastoma (Jongmans et al. 2011).

1.2 BACKGROUND ON COBIMETINIB

Cobimetinib is a potent and highly selective small molecule inhibitor of MEK, a key component of the RAS/RAF/MEK/ERK pathway.

1.2.1 Nonclinical Studies with Cobimetinib

Cobimetinib inhibited proliferation of a variety of human tumor cell lines via inhibition of MEK. In addition, cobimetinib inhibited ERK phosphorylation in xenograft tumor models (breast, lung, colon, and melanoma) and stimulated apoptosis. Cobimetinib accumulated in tumor xenografts and remained at high concentrations in the tumor after plasma concentrations had declined. The activity of cobimetinib to inhibit ERK1 phosphorylation was more closely correlated with its concentration in tumor tissue than in plasma. In general, there was good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models. Tumor regression was observed in several human tumor xenograft models in a dose dependent fashion with up to 100% regression at the highest doses tested. The models studied included colorectal cancer, malignant melanoma, breast carcinoma, and anaplastic lung carcinoma.

The pharmacologic and pharmacokinetic (PK) properties of cobimetinib were characterized in a series of nonclinical studies. In addition, the nonclinical toxicity of cobimetinib was characterized in single-dose and repeat-dose general toxicity studies in rats and dogs; in vitro genotoxicity studies; rat embryo lethality/teratogenicity studies; a rat juvenile toxicity study; and cardiovascular, neurobehavioral, and respiratory safety pharmacology studies. The toxicity profile, including target organs and tolerability, was similar in juvenile and adult rats. These studies are summarized in the cobimetinib Investigator's Brochure.

Like other MEK inhibitors, cobimetinib has a cytotoxic effect in vitro on pediatric cancer cell lines. To date, 36 cell lines derived from pediatric solid and brain tumors and 22 cell lines from pediatric leukemia and lymphoma have been evaluated for cellular viability and IC_{50} calculation. Major findings include the following:

- Of 18 neuroblastoma cell lines evaluated at doses up to 10 μM, six (33%) cell lines (CHP-212, NB(TU)1-10, SK-N-AS, BE(2)-M17, KP-N-SI9s, and SK-N-DZ) had IC_{50} less than 0.3 μM. Of these six lines, two had NRAS Q61K mutations and one had KRAS G12A mutation.
- Pediatric melanoma cell lines with known $BRAF^{V600E}$ mutations were susceptible to low concentrations of cobimetinib, with IC_{50} levels of 0.015 μM or less.
- Of the 58 cell lines assessed, 18 cell lines exhibited RAS/RAF/MEK/ERK pathway activation as defined by oncogenic mutations in NRAS, KRAS, HRAS, or BRAF, by FLT3 internal tandem duplication, or by NF1 homozygous deletion. Of the 18 cell lines with known RAS/RAF/MEK/ERK activation, 9 (50%) cell lines showed sensitivity to cobimetinib with an IC_{50} of < 0.3 μM, whereas only 4 (10%) of 40 cell lines without these mutations showed sensitivity at this level.
- Responses were observed in cell lines with activating RAS mutations from diseases that do not ordinarily carry RAS mutations. The osteosarcoma cell line 143B, a cell line transformed by murine sarcoma virus encoding a homolog of human KRAS, demonstrated IC_{50} of 0.351 μM, but significantly less effect was noted in other osteosarcoma lines. The medulloblastoma cell line ONS-76 with an activating NRAS Q61R mutation (Gajjar et al. 2014; Barretina et al. 2012) responded to cobimetinib with IC_{50} of 0.074 μM.

Several MEK-inhibitors have shown efficacy in in vivo mouse models of pediatric cancers (see Section 1.1). Additionally, cobimetinib has now been evaluated in a neuroblastoma murine xenograft model. Xenografts were derived from SK-N-AS cells, a neuroblastoma cell line with an NRAS Q61K mutation. Cobimetinib was orally administered at multiple doses (1, 3, 5, and 7.5 mg/kg). At the highest tested dose, cobimetinib inhibited tumor growth by 49% (as measured by area under the concentration-time curve [AUC]/day) relative to vehicle, and the time to progression (to five times the initial tumor size) increased from 6.5 days to 11.5 days. ERK phosphorylation was reduced in murine tumors after cobimetinib dose administration; an effect was observed within 2 hours after cobimetinib dosing, and maximal effect was observed at 8 hours post-dosing (Genentech, Inc., unpublished results).

In summary, inhibition of the RAS/RAF/MEK/ERK pathway has been observed with several MEK small molecule inhibitors including cobimetinib. This activity was observed across a spectrum of pediatric tumors in vitro, mainly in RAS pathway activated tumor types, and in vivo in a RAS-mutant neuroblastoma xenograft model.

1.2.2 Clinical Studies with Cobimetinib

As of September 2017, cobimetinib has been administered alone or used with other agents in 21 clinical or clinical pharmacology trials in adults, and under two single-center, investigator-initiated, single-patient, compassionate-use trials (see the cobimetinib Investigator's Brochure for details).

1.2.2.1 Clinical Pharmacokinetics

Clinical PK data from studies conducted in adults indicate that cobimetinib has a moderate rate of absorption, with time to maximum concentration (T_{max}) ranging from 1 hour to 6 hours across all doses. Cobimetinib has linear pharmacokinectics in the dose range of 0.05 mg/kg to 100 mg. On the basis of the mean terminal half-life ($T_{1/2}$) of approximately 43.6 hours, a 2- to 3-fold accumulation is expected with daily oral dosing, and steady-state exposures should be achieved in 8–10 days. Cobimetinib has minimal renal elimination and is mainly metabolized.

In vitro data indicate that cobimetinib is a substrate of CYP3A4 and UGT2B7, both of which are expressed before or soon after birth.

Detailed information on the clinical PK of cobimetinib is provided in the cobimetinib Investigator's Brochure.

1.2.2.2 Clinical Safety

Clinical safety data from patients treated with cobimetinib as a single agent are derived from Study MEK4592g, a Phase I, multicenter, non-randomized, open-label, dose-escalation study that evaluated the safety and PK of oral cobimetinib administered daily in adult patients with solid tumors. The study tested multiple doses, two formulations, and two dosing schedules. Fifty-six patients received cobimetinib for 21 days followed by no treatment for 7 days (21/7 dosing schedule) at one of the following doses: 0.05, 0.10, or 0.20 mg/kg in a liquid formulation or 10, 20, 40, 60, or 80 mg in a capsule formulation. Forty-one patients received cobimetinib for 14 days followed by no treatment for 14 days (14/14 dosing schedule) at one of the following doses: 60, 80, 100, or 125 mg in a capsule formulation.

The maximum-tolerated dose (MTD) and the recommended dose for Phase II was 60 mg for the 21/7 dosing schedule and 100 mg for the 14/14 dosing schedule. The most frequent adverse events attributed to cobimetinib were diarrhea, rash, fatigue, and edema for patients on the 21/7 dosing schedule and diarrhea, rash, fatigue, vomiting, nausea, edema, eye disorders (including blurred vision), and abdominal pain for patients on the 14/14 dosing schedule.

An additional cohort of 18 adult patients was enrolled at 60 mg on the 21/7 dosing schedule to evaluate the effect of cobimetinib on the PK of midazolam and dextromethorphan, sensitive substrates of CYP3A4 and CYP2D6, respectively. There was no clinically meaningful difference in the PK of midazolam or dextromethorphan.

Thus, cobimetinib does not cause any inhibition or induction of CYP3A4 or cause any inhibition of CYP2D6.

Refer to the cobimetinib Investigator's Brochure for additional details on the clinical safety of cobimetinib, given alone or in combination with other agents to patients or healthy subjects.

1.2.2.3 Clinical Efficacy

Clinical efficacy data from patients treated with cobimetinib as a single agent are derived from Study MEK4592g.

As of 25 May 2012, best overall tumor response per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, had been assessed for 74 of 97 patients with advanced solid malignancies treated with cobimetinib alone who had measurable lesions and at least one post-baseline tumor assessment. Overall, 6 patients (6.2%) (all of whom had melanoma) had a confirmed partial response, 28 patients (28.9%) had stable disease, and 40 patients (41.2%) had disease progression.

Among the 18 patients treated with cobimetinib who received doses of midazolam and dextromethorphan to evaluate drug-drug interaction, 4 patients had stable disease, 8 patients had disease progression, 2 patients had an unconfirmed response, and 4 patients discontinued prior to overall response assessment.

Three patients (1 patient with prolonged stable disease and 2 patients with a confirmed partial response) were ongoing in the study at the time of database lock (25 May 2012): a patient with carcinoid tumor in the small bowel (1369 days on study) and 2 patients with melanoma (753 days and 546 days on study).

Refer to the cobimetinib Investigator's Brochure for additional details on the clinical efficacy of cobimetinib, given alone or in combination with other agents.

1.2.2.4 Approved Indications

Cobimetinib is approved for use in the United States, European Union, and other regions for use in adults in combination with Zelboraf® (vemurafenib) for the treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation. The largest study evaluating safety and efficacy of cobimetinib to date is the Study GO28141, a Phase III, randomized, double-blind, placebo-controlled study of vemurafenib plus placebo versus vemurafenib plus cobimetinib in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma. Refer to the Investigator’s Brochure for results of this study.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Pediatric cancer that is recurrent or refractory represents an area of high unmet medical need. Despite the progress made after 40 years of clinical research using combinations of chemotherapy, radiotherapy, and surgery, disease survival and overall survival (OS) rates have not significantly improved for children with relapsed or refractory tumors.

Cobimetinib is a potent and highly selective inhibitor of MEK, a central component of the RAS/RAF/MEK/ERK pathway that has been implicated in the pathogenesis of a number of pediatric tumor types. Molecularly targeted agents like cobimetinib can potentially provide a measure of benefit while reducing the negative impact on quality of life that is associated with cytotoxic chemotherapy.

In nonclinical studies, cobimetinib inhibited proliferation of a variety of human tumor cell lines. In addition, cobimetinib inhibited ERK phosphorylation in xenograft tumor models (breast, lung, colon, and melanoma) and stimulated apoptosis. Tumor regression was observed in several human tumor xenograft models.

In Study MEK4592g, a Phase I study of single-agent cobimetinib in adult patients with solid tumors (n = 97), adverse events observed were generally tolerable and manageable, especially when compared with those associated with cytotoxic agents, such as alkylating agents. Treatment–related adverse events included diarrhea, rash, fatigue, vomiting, nausea, edema, eye disorders, and abdominal pain.

Among 74 evaluable patients in Study MEK4592g, 6 patients (6.2%) (all of whom had melanoma) had a confirmed partial response, 28 patients (28.9%) had stable disease, and 40 patients (41.2%) had disease progression.

Because of the critical biological pathway targeted by cobimetinib, the spectrum of activity of this drug may include diverse pediatric tumor types. This study will evaluate the safety, tolerability, PK, and preliminary efficacy of cobimetinib in pediatric and young adult patients with solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable. A recommended dose will be identified in the dose-escalation stage of the study. Additional patients will be enrolled and treated at the recommended dose in the expansion stage.

Understanding the activity of cobimetinib as a single agent in the pediatric relapsed or refractory setting may allow for the addition of this drug to regimens currently available to treat newly diagnosed malignancies in pediatric patients.

1.3.1 Rationale for Inclusion of Patients with Brain Tumors

Preclinical studies of cobimetinib in normal mice demonstrated low concentrations of drug and a lack of pERK inhibition in brain tissue (Choo et al. 2012). Cobimetinib is a substrate of the efflux transporter P-glycoprotein (P-gp), and knockout mice lacking P-gp achieve high concentrations of cobimetinib in the brain, indicating that low brain

concentrations of cobimetinib are mediated by drug efflux (Choo et al. 2014). Preclinical animal model brain concentrations of small molecule P-gp substrates do not necessarily predict clinical outcomes; for instance, vemurafenib demonstrates clinical intracranial anti-tumor efficacy despite brain:plasma concentration ratio of less than 1% in mice (Dummer et al. 2014, Mittapalli et al. 2012, Robinson et al. 2014). Drug efflux in this situation is likely reduced by blood-brain or blood-tumor barrier compromise, especially following the standard chemoradiotherapy and surgery approach taken in first-line treatment of this disease (Choo et al. 2014, Holdhoff et al. 2011). Thus, children with brain tumors with RAS/RAF/MEK/ERK activation may have clinical responses to cobimetinib and will be eligible for enrollment in this study.

2. OBJECTIVES

This study will evaluate the safety, tolerability, PK, and preliminary efficacy of orally administered cobimetinib in pediatric ($\geq$6 months of age) and young adult ($<$30 years of age) patients with solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable. Specific objectives for the study are outlined below.

2.1 SAFETY OBJECTIVE

The primary objective for this study is as follows:

- To evaluate the safety and tolerability of cobimetinib in children and young adults, including estimation of the MTD or the maximum administered dose (MAD) and characterization of dose-limiting toxicities (DLTs)

2.2 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is as follows:

- To characterize the PK of cobimetinib in children and young adults

2.3 EFFICACY OBJECTIVE

The efficacy objective for this study is as follows:

- To evaluate the anticancer activity of cobimetinib in children and young adults with solid or brain tumors, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and OS

2.4 DOSE-FINDING OBJECTIVE

An additional objective for this study is as follows:

- To identify recommended Phase II doses for cobimetinib tablet and suspension formulations in pediatric patients on the basis of safety, PK, and efficacy outcome measures (see Section 3.4)

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore the relationship between cobimetinib exposure and changes in levels of pharmacodynamic (PD) biomarkers in children and young adults
- To explore non-inherited biomarkers that may be predictive of response to cobimetinib (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to cobimetinib, or susceptibility to developing adverse events, may provide evidence of cobimetinib activity, or may increase the knowledge and understanding of disease biology
- To explore inherited biomarkers (i.e., variants in germline DNA) that may be predictive of response to cobimetinib (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to cobimetinib, or susceptibility to developing adverse events, or may increase the knowledge and understanding of disease biology
- To explore potential relationships between PK parameters for cobimetinib and other outcome measures (such as safety or efficacy outcome measures)
- To evaluate tumor characteristics before and after treatment on the basis of available magnetic resonance imaging (MRI) and positron emission tomography (PET) scans
- To evaluate specific aspects of the acceptability of the cobimetinib formulations

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase I/II, multicenter, open-label, dose-escalation study designed to evaluate the safety, tolerability, PK, and preliminary efficacy of cobimetinib in pediatric and young adult patients with solid tumors with known or potential RAS/RAF/MEK/ERK pathway activation for which standard therapy has proven to be ineffective (i.e., relapsed or refractory tumors) or intolerable or for which no curative standard-of-care treatment options exist.

Patients will be enrolled via an interactive web response system (IWRS) in two stages: a dose-escalation stage and an expansion stage at the recommended dose. During the dose-escalation stage, cohorts of 3–6 pediatric patients (age $\geq$6 months to $<$18 years) will be evaluated at escalating dose levels to determine the MTD or MAD of cobimetinib in pediatric patients with advanced solid tumors. The MTD or MAD of each cobimetinib formulation (tablet and suspension) will be determined in separate dose escalations (as described in Section 3.1.1). Once the MTD or MAD has been established, pediatric patients (age $\geq$6 months to $<$18 years) will be enrolled in the expansion stage and treated at the recommended dose, which will be at or below the MTD or MAD, as determined by the Sponsor; adult patients $\geq$18 years of age with pediatric tumor types

can be enrolled on this study but only during the expansion stage; these adult patients will be treated at the adult flat dose (see Section 3.1.2). Approximately 70 patients are expected be enrolled in the dose-escalation and initial expansion stages of this study, at approximately 30 investigative sites in Europe and North America. If an efficacy signal is observed during the first expansion step for the initial response assessment, up to an additional 30 patients per cohort may be enrolled in the second expansion step for the additional response assessment.

All patients will be closely monitored for adverse events throughout the study and for at least 30 days after the last dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v4.0. Other safety assessments include echocardiograms, ophthalmologic examinations, and dermatologic examinations.

To characterize the PK properties of cobimetinib, blood samples will be taken at defined timepoints after dosing (see Appendix 2).

Tumor assessments will be performed in the final week of every other cycle, starting with Cycle 2 (see Section 4.5.5 for more information). Response will be determined by the investigator using the modified International Neuroblastoma Response Criteria (mINRC) for patients with neuroblastoma (see Appendix 3), Response Assessment in Neuro-Oncology (RANO) criteria for patients with HGG (see Appendix 4), RECIST v1.1 (see Appendix 6) for patients with other tumors, and RANO criteria for patients with low-grade glioma (LGG; see Appendix 5) in the expansion stage in addition to RECIST v1.1 .

Patients in both dose-escalation and expansion stages will receive cobimetinib orally according to the guidance provided in Appendix 10 on Days 1–21 of each 28-day treatment cycle (21/7 dosing schedule) until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, or patient or investigator decision to discontinue treatment.

The schedule of assessments is provided in Appendix 1 and the schedule of PK and PD assessments is provided in Appendix 2.

3.1.1 Dose-Escalation Stage

Cohorts of 3–6 pediatric patients each will be treated at escalating doses of cobimetinib in accordance with the dose-escalation rules described below. The first patient at each dose level must complete at least 5 days of treatment (Days 1–5 of Cycle 1) without a DLT (as defined in Section 3.1.1.1) before subsequent patients can be treated at the same dose level.

The DLT assessment window is defined as Days 1–28 of Cycle 1. Adverse events identified as DLTs, as defined below (see Section 3.1.1.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

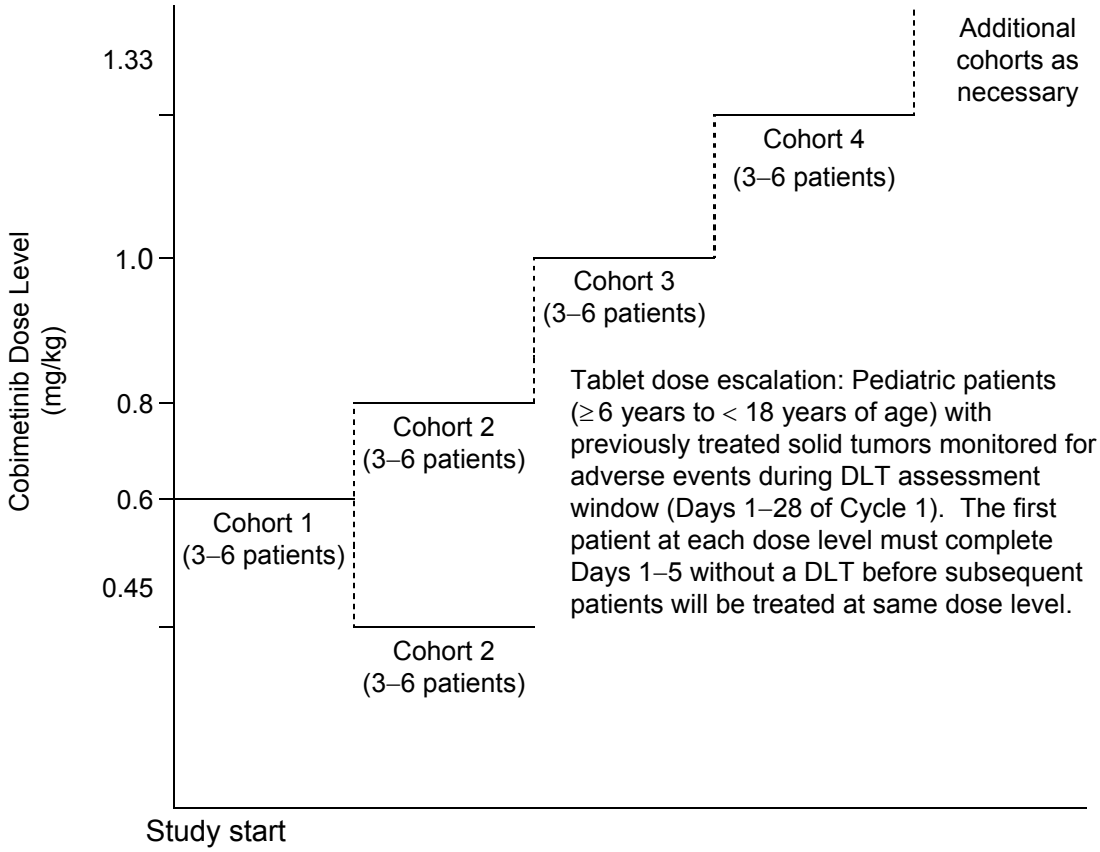
Two formulations will be available for the protocol: a tablet (20 mg) and a suspension (4.8 mg/mL). An MTD or MAD will initially be determined for tablets in patients 6 years and above. Once the MTD or MAD is identified for tablets, enrollment of patients using the suspension will commence following review of relevant data from the tablet dose escalation. The starting dose for the suspension will be a minimum of one dose level below the MTD or MAD of the tablets (see Section 3.1.1.2 for age requirements for suspension). Additional dose escalation with the suspension may proceed according to the dose escalation rules (Section 3.1.1.2) until an MTD or MAD is identified for the suspension. On the basis of an ongoing review of safety data and available PK data, increases in dose level or continued enrollment for either formulation may be halted by the Sponsor as deemed appropriate.

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD or MAD assessments. These patients will be replaced at that same dose level unless there are 3 or more patients already treated and all were evaluated with no DLT at that level. Patients who miss five or more doses (i.e., $>$18% of the cumulative dose) during the DLT assessment window for reasons other than toxicity will also be replaced. Patients who ingest moderate or strong CYP3A inducers or inhibitors (defined in Appendix 11), ingest prohibited foods/supplements (defined in Section 4.4.3), or receive supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described below as part of the DLT definition) may be replaced at the discretion of the Medical Monitor.

Patients who experience a DLT during the assessment window (first 28 days) may not subsequently continue drug at full dose, even if the drug is withheld until resolution of the toxic event. The investigator should use guidance in Section 5.1.1 and Table 2 (and if guidance is not specified, investigator discretion) to determine whether the patient should permanently discontinue study drug or withhold study drug until toxicity resolves to Grade 1 or lower, then resume study drug at a dose corresponding to a reduction of one dose level.

A study schema for the dose-escalation stage is displayed in Figure 1.

Figure 1 Study Schema: Dose-Escalation Stage



DLT = dose-limiting toxicity.

Note: All patients will receive cobimetinib orally once daily on Days 1–21 of each 28-day cycle. Dose escalation for suspension will proceed in the same way after MTD of tablets has been established, starting at one dose level below the determined MTD or MAD of the tablets, and allowing for enrollment of patients 6 months to 6 years of age as permitted in Section 3.1.1.2.

3.1.1.1 Definition of Dose-Limiting Toxicity

Any one of the following events will be considered a DLT if it occurs during the DLT assessment window and is assessed by the investigator to be related or possibly related to cobimetinib (rules for attributing causality are defined in Section 5.3.4):

- Grade ≥ 4 neutropenia (ANC $< 0.5 \times 10^9$/L) lasting > 7 days
- Grade ≥ 4 neutropenia with documented infection
- Febrile neutropenia, defined as ANC< 500/mm3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour
- Grade ≥ 4 (i.e., life threatening) anemia of any duration

- Grade ≥ 4 thrombocytopenia lasting > 48 hours or any thrombocytopenia requiring a platelet transfusion, with the following exception:

    For patients who have undergone autologous stem cell transplant or ^{131}I-metaiodobenzylguanidine (MIBG) therapy, Grade ≥ 4 thrombocytopenia lasting > 7 days or any thrombocytopenia requiring a platelet transfusion on two or more separate dates will be considered a DLT.

- Grade ≥ 3 thrombocytopenia with bleeding
- Elevation of serum hepatic transaminase (ALT or AST) $\geq 5 \times$ the upper limit of normal (ULN)

    For patients with elevated hepatic transaminase levels at baseline as a result of liver metastases, hepatic transaminase $\geq 5 \times$ baseline and $< 10 \times$ baseline for > 3 days, or any hepatic transaminase $\geq 10 \times$ baseline, will be considered a DLT.

- Elevation of serum bilirubin $\geq 3 \times$ ULN
- For patients reliably able to report visual symptoms: Grade ≥ 2 visual disturbance that does not resolve to Grade ≤ 1 within 72 hours after interruption of cobimetinib treatment
- Retinal pathology of any grade, or Grade ≥ 2 uveitis or iritis
- Grade ≥ 2 hemorrhage of any type
- Intracranial hemorrhage of any grade
- Grade ≥ 4 CPK elevation
- Rhabdomyolysis of any grade
    - Rhabdomyolysis includes elevations of CPK in conjunction with either clinical features (such as muscle pain, signs of renal failure, dark red or brown urine) or with laboratory evidence of renal insufficiency (including Grade 2 or higher increased creatinine or creatinine clearance [or radioisotope glomerular filtration rate] < 70 mL/min/1.73 m^2), or investigator judgment that a clinical scenario is consistent with rhabdomyolysis.
- Grade ≥ 2 ventricular dysfunction or symptomatic congestive heart failure
- Reduction in left ventricular ejection fraction (LVEF) below 50% (or shortening fraction below 28%) AND either symptomatic heart failure or a $\geq 10\%$ relative reduction from baseline measurement

    Note: The relative reduction must be $\geq 10\%$ of baseline function, not an absolute decrease of ≥ 10 percentage points.

- Grade ≥ 4 (i.e., life threatening) vomiting or diarrhea of any duration

- Grade ≥3 non-hematologic, non-hepatic, non-ocular adverse event, with the following exceptions, which will not be considered DLTs:

  Grade ≥3 diarrhea or rash that resolves to Grade ≤2 within 7 days after interruption of cobimetinib treatment.

  Grade 3 fever.

  Grade 3 mucositis or stomatitis that resolves to Grade ≤2 within 3 days.

  Grade ≥3 nausea or vomiting that responds to standard-of-care therapy within 3 days.

  Grade 3 fatigue lasting ≤3 days.

  Grade 3 laboratory abnormalities that are asymptomatic and considered by the investigator not to be clinically significant.

3.1.1.2 Dose-Escalation Rules

The starting dose of cobimetinib for tablets will be 0.6 mg/kg, administered to patients in the first cohort by mouth once daily on Days 1–21 of each 28-day treatment cycle. The dose will be increased by up to approximately 33% of the preceding dose level for each successive cohort, until an MTD or MAD is determined. The following doses will be considered:

Dose Level	Cobimetinib Dose [a]
-1	0.45 mg/kg
1 (starting dose)	0.6 mg/kg
2	0.8 mg/kg
3	1.0 mg/kg
4	1.33 mg/kg
5 or more	TBD

TBD = to be determined.

[a] See Appendix 10 for calculated doses per weight for each formulation.

Intrapatient dose escalation is not allowed except in the following instance: once an MTD/MAD has been established, any patient still being treated at a dose lower than the recommended dose for expansion stage will be dose-escalated to the recommended dose at the start of the next cycle of therapy, unless prior dose reductions or treatment interruptions due to therapeutic toxicity have occurred in that patient.

Because maturity of CYP3A4 enzymes does not occur until 1 year of age (see Section 3.3.1), patients <1 year of age will not be eligible for enrollment until a safety and PK assessment of the first 6 patients treated with suspension for at least one cycle of therapy has been conducted.

Relevant demographic, adverse event, laboratory, dose administration, and all available PK data will be reviewed prior to dose-escalation decisions and prior to initiation of suspension dose escalation, which will be made by the Medical Monitor in consultation with the Principal Investigators and the Internal Monitoring Committee (IMC).

In order to minimize safety risks during dose escalation but to ensure optimal access for children to the trial, dose escalation will commence according to the rolling 6 design. In this design, up to a maximum of 6 patients can be enrolled concomitantly at the same dose level. The dose level allocated to a new patient is based on the number of patients currently enrolled and evaluated, the number of patients experiencing DLT, and the number of patients whose evaluation is pending at the time of new patient entry. De-escalation occurs when two or more DLTs occur at a dose level, whereas escalation can be performed when 3/3, 4/4, 5/5, 5/6, or 6/6 patients are evaluated without a DLT. Otherwise, patients can be included at the same level up to a total of 6 patients per dose level. Dose escalation will proceed according to the rules shown in Table 1 (adapted from Doussau et al. 2012 and Skolnik et al. 2008).

Table 1 Dose Determination for the Next Patient in Rolling 6 Design

Number of Patients Enrolled	Number of Patients with DLTs	Number of Patients without DLT	Number of Patients with Data Pending	Enrolling Dose Level (MTD Not Exceeded)	Enrolling Dose Level (MTD Previously Exceeded)
2	0,1	Any	Any	Same	
2	2	0	0	Dose decrease	
3	0	0,1,2	3,2,1	Same	
3	0	3	0	Dose increase	
3	1	0,1,2	2,1,0	Same	
3	≥2	Any	Any	Dose decrease	
4	0	0,1,2,3	4,3,2,1	Same	Same
4	0	4	0	Dose increase	Same
4	1	0,1,2,3	3,2,1,0	Same	Same
4	≥ 2	Any	Any	Dose decrease	Dose decrease
5	0	0,1,2,3,4	5,4,3,2,1	Same	Same
5	0	5	0	Dose increase	Same
5	1	0,1,2,3,4	4,3,2,1,0	Same	Same
5	≥2	Any	Any	Dose decrease	Dose decrease
6	0	0,1,2,3,4	6,5,4,3,2	Suspend	Suspend
6	0	5,6	1,0	Dose increase	MTD
6	1	0,1,2,3,4	5,4,3,2,1	Suspend	Suspend
6	1	5	0	Dose increase	MTD
6	≥2	Any	Any	Dose decrease	Dose decrease

MTD = maximum tolerated dose.

Notes: Same = next patient would be treated at the same dose.

Dose increase = next patient would be treated at a higher dose.

Dose decrease = next patient would be treated at a lower dose.

Suspend = enrollment will be suspended until enough patients have been evaluated.

Dose escalation will proceed according to Table 1 and in accordance with the rules listed below.

- If 2 or more of the first 6 DLT-evaluable patients in a cohort experience a DLT, the MTD will have been exceeded; subsequent patients must be treated at a lower dose level.
- If the dose level at which the MTD is exceeded is ≥25% higher than the preceding dose level, an intermediate dose level may also be evaluated. Otherwise, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., < 33%) experience a DLT will be declared the MTD.
- If the MTD is not exceeded at any dose level, the highest dose administered in this study will be declared the MAD.

Enrollment in the dose-escalation stage for a particular formulation will be stopped if at least 6 DLT-evaluable patients are treated at that formulation's MTD or MAD.

On the basis of an ongoing review of real-time safety data and available PK data, increases in dose level may be halted by the Sponsor as deemed appropriate.

3.1.2 Expansion Stage

After the MTD or MAD has been determined for a formulation, pediatric and young adult patients will be enrolled in tumor type cohorts to obtain additional safety, tolerability, and PK data, as well as any preliminary evidence of anti-cancer activity. Pediatric (< 18 years of age) patients will be treated at or below the formulation-specific MTD or MAD identified in the dose-escalation stage of this study. Young adult patients (≥ 18 years of age) will be treated at the recommended adult dose (see Section 4.3.2).

The Sponsor reserves the right to determine which formulation(s) will be taken forward into the expansion stage and whether enrollment into the expansion stage using tablets (if applicable) will proceed concurrently with or subsequent to dose-escalation for suspension. Enrollment in expansion cohorts may commence after the IMC has reviewed PK and safety data obtained in the dose escalation phase (see Section 3.1.3).

Each tumor type will be considered a distinct tumor type cohort. Different tumor type cohorts may not all enroll simultaneously. Tumor type cohorts will be chosen after IMC review, prior to inclusion in the expansion stage of the study. Chosen tumor type cohorts for the expansion stage may also include subgroups of tumor types included in the dose-escalation stage, with inclusion based on confirmed (rather than expected) RAS/RAF/MEK/ERK-pathway activation (based on local testing of sample from time of diagnosis or any subsequent timepoint prior to enrollment) with approval of medical monitor). Two phases of response assessment are planned for the expansion stage: an initial response assessment and an additional response assessment (as defined in Table 6 in Section 6.1). An initial response assessment will be performed after a minimum of 10 patients, treated at the recommended dose for expansion stage, have

been enrolled in a tumor type cohort and followed for approximately 12 months, to determine whether to expand the cohort for additional response assessment. For purposes of initial response assessment, patients "treated at the recommended dose for expansion stage" includes those patients who initiate therapy at the eventual recommended dose for expansion, whether they are treated during the dose escalation stage or during the expansion stage. Patients who are dose-reduced from the recommended dose due to therapeutic toxicity will still be included for response assessment. Patients in dose-escalation who are treated below the recommended dose for expansion, and subsequently dose-escalated to the recommended dose, will not be included for response assessment.

Cohort expansion will be started once a pre-established number of responses for that tumor type are confirmed (per Table 6). A decision to pursue additional enrollment in a tumor type cohort may be approved by the Sponsor or Medical Monitor before the initial response assessment. Cohort expansion, including the number of patients needed for the additional response assessment, will take into account practical considerations (e.g., enrollment feasibility), preclinical findings, biomarker analysis, safety profiles, and any other relevant information. A study schema for the expansion stage is displayed in Figure 2.

If the frequency of Grade 3 or 4 toxicities or other unacceptable toxicities at the initial dose level in the expansion stage suggest that this dose is intolerable, accrual at that dose level will be halted. Consideration will then be given to enrolling patients at a lower dose level.

The Sponsor may decide to stop enrollment of patients $\geq$ 18 years of age at any time during the study to ensure adequate enrollment of patients $<$ 18 years of age. To meet study completion criteria below, the Sponsor may restrict enrollment of patients $\geq$ 10 years of age if too few patients $<$ 10 years of age have been enrolled.

The Sponsor intends to stop study enrollment once all of the following criteria are met:

- The dose-escalation phase of both tablet and suspension formulations are complete
- At least 20 patients $<$ 18 years of age have been treated with study drug
- At least one tumor type cohort has completed response assessment (either initial response assessment or additional response assessment)
- At least 10 patients $<$ 10 years of age have been treated with study drug

Enrollment in a tumor type cohort will be stopped if any one of the following criteria is met:

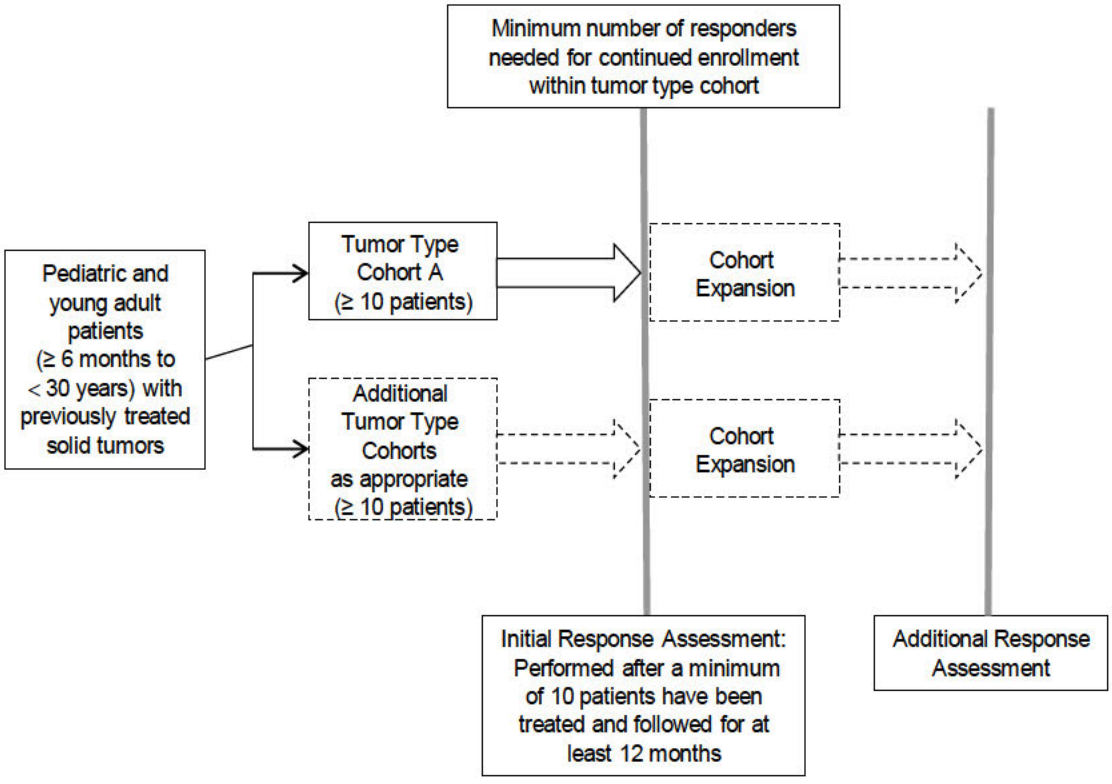
- The number of patients needed for initial response assessment is reached and the number of responders does not meet the requirement for tumor type cohort expansion

- The number of patients needed for additional response assessment is reached
- The Sponsor has stopped the study

Some exceptions may apply to these general stopping rules, including but not limited to the following:

- Enrollment in the study may be stopped if enrollment has been open for more than 2 years and at least 20 patients have been treated with the study drug.
- Enrollment in a given tumor type cohort may be extended by the Sponsor if there is strong evidence of a positive efficacy signal in a slow enrolling and rare tumor type cohort, thus allowing for additional data to be collected.

Figure 2 Study Schema: Expansion Stage



Notes: All patients will receive cobimetinib orally once daily on Days 1–21 of each 28-day cycle. Cohort expansion, including the number of patients needed for the additional response assessment, will take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information.

3.1.3 Internal Monitoring Committee and Scientific Oversight Committee

An IMC will be established to monitor patient safety throughout the study and provide a recommendation on the dose to be taken forward into the expansion stage after

completion of the dose-escalation stage. The IMC will include Sponsor representatives from Clinical Science, Biostatistics, Safety Science, and Clinical Pharmacology. IMC members should not have regular contact with the sites as part of their responsibilities.

In addition to the ongoing assessment of the incidence and nature of DLTs, adverse events (particularly Grades ≥ 3), serious adverse events, deaths, and laboratory abnormalities by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study (including prior to suspension dose escalation and prior to initiation of expansion cohorts). Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to obtain IMC recommendations on management of any new safety issues.

A Scientific Oversight Committee (SOC), which will consist of experts external to the Sponsor (including at least two members not involved in study activities), will also be established for this study. The SOC will enhance safety monitoring and leverage external experts' scientific expertise by providing advice on data interpretation. The SOC will function as a consultative body to the Sponsor, providing individual expert opinions.

Specific operational details, such as committee composition, frequency and timing of meetings, and member roles and responsibilities, will be detailed in an IMC and SOC Charter.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, or 5 years after the last patient is enrolled, whichever occurs first. The Sponsor reserves the right to present interim data to health authorities for compliance purposes.

For an individual patient the completion of the study (i.e., the last visit) will occur when the patient withdraws consent, has completed follow-up, has been lost to follow-up, dies, or when the trial is stopped.

The primary analysis will be conducted after the enrollment has been completed and all enrolled patients have been followed for at least 12 months. Clinical Study Report (CSR) will be submitted to health authorities.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Cobimetinib Dose and Schedule

Cobimetinib will be administered by mouth once daily on Days 1–21 of each 28-day treatment cycle. The traditional starting point for pediatric oncology Phase I studies of cytotoxic agents is 80% of the adult dose (Lee et al. 2005) and for targeted agents according to the toxicity profile 80%–100% of the adult dose appears safe (Paoletti et al. 2013). In the dose-escalation stage, the first cohort of 3 patients treated with tablets will receive cobimetinib at a dose of 0.6 mg/kg, or approximately 80% of the adult Phase III dose.

The mean elimination $T_{1/2}$ of most substrates approaches adult levels at 2–6 months of age. In vitro data suggest that, although liver enzymes in general have not matured fully, a significant amount and activity of enzymes are present at this age (Bartelink et al. 2006). In vitro data indicate that cobimetinib is a substrate of CYP3A4 and UGT2B7, both of which are expressed before or soon after birth. The activity of both CYP3A4 and UGT2B7 reaches 100% of adult activity by 1 year of age (Kearns et al. 2003). Given the maturation profile of the two enzymes principally involved in cobimetinib metabolism, significant differences in cobimetinib metabolism are not expected to be observed among pediatric patients, even those as young as 6 months of age. Per Section 3.1.1.2, patients <1 year of age will not be eligible for enrollment until a safety and PK assessment of the first 6 patients treated with suspension for at least one cycle of therapy has been conducted and until all available pediatric data from tablet and suspension cohorts has been reviewed by the IMC.

If a drug is mainly metabolized by UGT or CYP2D6, the plasma clearance seems to be correlated with body weight (Bartelink et al. 2006). Thus, doses in this study will be based on patient body weight.

3.3.1.1 Rationale for Tablet and Suspension Dosing Strategy

Cobimetinib has good solubility in water (0.74 mg/mL, at 37°C). A mass balance study in humans has shown that the fraction of dose absorbed is 0.88, indicating high fraction absorbed and hence permeability. Given the high solubility and permeability of cobimetinib, differences due to formulation change are not anticipated. During development of cobimetinib in adult populations, it was seen that different formulations provided comparable exposures (see cobimetinib Investigator's Brochure), and that cobimetinib absorption was not dissolution-rate limited. Hence, the suspension is expected to provide similar exposures as would be obtained upon administration of the tablet, and therefore equivalent doses administered to pediatric patients will provide comparable exposures. As bioequivalence has not been directly proven between the existing tablet and powder for suspension formulations in a relative bioavailability study, the Sponsor will initiate dose escalation for the suspension at least one dose level below that of the tablet MTD/MAD to ensure study drug administration via suspension does not result in overexposure or excessive toxicity.

Both tablet and suspension formulations are being utilized to ensure adequate age-appropriate dosing for the study. Enrollment to receive the tablet will be restricted to patients ≥ 6 years of age due to the size of the tablet. Enrollment to receive the tablet will further be restricted to patients weighing ≥20 kg, because tablet dosing (defined in Appendix 10) in patients < 20 kg could potentially cause excessive variation in cumulative administered dose per kilogram (>10%) within a dose level cohort.

To ensure that patients treated with tablets receive a cumulative dose most closely approximating their body weight, patients will be assigned a cumulative weekly dose in 20-mg increments, with distribution of tablets as evenly as possible throughout the week. For example, if a patient's dose is 60 mg in a week, the dosing would be 20 mg on Days 1, 3, and 5 of that week. Given the $T_{1/2}$ of cobimetinib (approximately 2 days), the intermittent dosing of cobimetinib is not expected to result in significant fluctuations in the average cobimetinib concentrations, and steady state exposures will be achieved approximately 10 days after start of dosing.

3.3.2 Rationale for Patient Population

The late-phase program of cobimetinib in adults is focused on indications with limited existence in children, thus significantly reducing the population of pediatric patients potentially able to receive the drug. Given the occurrence of alterations in the RAS/RAF/MEK/ERK pathway in a large range of pediatric malignancies, the pursuit of a broad mechanism-of-action–derived approach to include pediatric tumors may maximize the opportunity to determine which pediatric patients may benefit from treatment with cobimetinib. Importantly, the safety of cobimetinib as a single agent must be demonstrated and toxicity must be analyzed to provide treating physicians with clear guidance for administration of cobimetinib and monitoring of patients in the pediatric setting. With this in mind, the trial will draw from a broad spectrum of pediatric tumor types, each of which has evidence of growth promotion through the RAS/RAF/MEK/ERK pathway either in nonclinical model systems or retrospective clinical tumor analyses.

The Sponsor expects that the majority of enrolled patients will be <18 years of age. Patients even as young as 6 months of age may experience tumor types such as neuroblastoma for which cobimetinib is a rational potential therapy, and these patients will be included in the trial upon availability of a suspension formulation. However, there may be young adult patients with "pediatric-type" tumors who are treated in pediatric oncology facilities. In a specific analysis of adolescent and young adult (AYA) patients in the United States, limited clinical trial participation correlated with the relative lack of improvement in survival prolongation and cancer death rates (Bleyer et al. 2006). The lower participation of AYAs in clinical trials has created significant knowledge gaps with respect to cancer biology, treatment, and other factors affecting the survival of AYAs with cancer. As part of the Sponsor's commitment to the development of personalized medicine, AYAs up to 30 years of age (and in exceptional cases of relapsed pediatric tumors, beyond 30 years of age) will be included in the expansion stage of the study.

3.3.3 Rationale for Biomarker Assessments

The Sponsor is committed to the collection of biomarker samples in all clinical studies. The objective of biomarker profiling is to enable development of treatments specifically targeted for optimum patient benefit. The rationale for the planned biomarker analyses is explained below. However, because the body of knowledge of potential new biomarkers is evolving, the definitive list of analyses may be modified on the basis of new information.

This study will explore biomarkers associated with response to MEK inhibition in archival or fresh tumor tissue specimens obtained at baseline.

Given the genetic heterogeneity of the patients who will enroll in this study, the magnitude of response to MEK inhibition may be different in certain pediatric tumors. To identify candidate predictive biomarkers, molecular analyses of tumor tissue and plasma may include assessment of genetic and activation status of the targeted RAS/RAF/MEK/ERK pathway, potential escape mechanisms such as receptor tyrosine kinases and PI3K/PTEN pathways, and components of the tumor stroma (e.g., tumor infiltrating lymphocytes). These analyses may be conducted at the DNA, RNA, protein, and cell levels. In addition, expression of pathway-relevant prognostic biomarkers and alternative drug targets may be explored. These analyses are essential for the identification of patients who will benefit the most from cobimetinib.

It has been shown that tumor-specific mutations can be identified in plasma ('circulating tumor DNA). Assessment of RNA and DNA may be evaluated in tumor tissue collected at baseline and plasma collected at baseline and during the study. Analysis and correlation of mutations in tumor tissue and plasma will help to further evaluate the option of using plasma for the detection of tumor-specific mutations.

3.4 OUTCOME MEASURES

3.4.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and nature of DLTs
- Nature, frequency, severity, and timing of adverse events, including serious adverse events and adverse events of special interest
- Changes in vital signs, physical findings, and clinical laboratory results during and following cobimetinib administration
- Growth patterns (relative to age-specific standards for height and weight) accounting for baseline growth of the patient
- Development patterns (relative to onset of menarche [for females] and pubertal changes) accounting for baseline development of the patient

3.4.2 Pharmacokinetic Outcome Measure

The PK outcome measure for this study is as follows:

- To characterize cobimetinib PK in pediatric patients, the following PK parameters following single and multiple doses will be estimated: maximum plasma concentration observed (C_{max}), T_{max}, total exposure (area under the concentration–time curve from 0 to 24 hours [AUC_{0-24}]), and apparent clearance (CL/F).

3.4.3 Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- ORR, defined as the percentage of patients with a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non–measurable but evaluable disease at baseline (except neuroblastoma patients), on two consecutive occasions ≥4 weeks apart, as determined by the investigator using mINRC for patients with neuroblastoma (see Appendix 3), RANO criteria for patients with HGG (see Appendix 4; Wen et al. 2012), for the RANO criteria for patients with LGG (see Appendix 5) and RECIST v1.1 for patients with other tumors (see Appendix 6).
- PFS, defined as the time from initiation of study drug to the first documented occurrence of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma (see Appendix 3), RANO criteria for patients with HGG (see Appendix 4; Wen et al. 2012), RECIST v1.1 for patients with other tumors (see Appendix 6), and RANO criteria for patients with LGG (see Appendix 5) in the expansion stage in addition to RECIST v1.1, or death from any cause, whichever occurs first

The secondary efficacy outcome measures for this study are as follows:

- DOR, defined as the time from the first tumor assessment that supports the patient's objective response to the time of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma (see Appendix 3), RANO criteria for patients with HGG (see Appendix 4; Wen et al. 2012), RECIST v1.1 for patients with other tumors (see Appendix 6), and RANO criteria for patients with LGG (see Appendix 5) in the expansion stage in addition to RECIST v1.1. , or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study drug to death from any cause

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Levels of potential PD biomarkers (potentially including, but not limited to, p-MEK, p-ERK, and Ki67) measured in tumor tissue collected at baseline, on treatment, and at the time of disease progression

- Correlation between non-inherited and inherited biomarkers in plasma (potentially including, but not limited to, *BRAF* mutations, BRAF fusions, *RAS* mutations, and NF1 alterations) with safety, PK, or efficacy outcome measures
- To explore potential relationships between cobimetinib PK and other outcome measures (such as safety or efficacy outcome measures)
- ORR for LGG, defined as the percentage of patients with measurable disease who have a complete or partial response on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1
- Modified ORR for LGG, defined as the percentage of patients with measurable disease who have a complete, partial, or minor response on two consecutive occasions ≥4 weeks apart, as determined by the investigator using the RANO criteria for LGG (see Appendix 5).
- Diffusion activity in tumors before and after cobimetinib treatment, as demonstrated on available MRI scans
- Metabolic activity in tumors before and after cobimetinib treatment, as demonstrated on available PET scans
- Acceptability survey

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll approximately 70 pediatric or young adult patients with solid tumors with known or expected RAS/RAF/MEK/ERK pathway activation for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Signed Child's Informed Assent, when appropriate as determined by patient's age and individual site and country standards
- For dose-escalation stage, tablets: Age at study entry ≥6 years to <18 years
- For dose-escalation stage, suspension: age at study entry ≥6 months to <18 years

  Patients <1 year of age will not be enrolled until ≥6 patients ≥ 1 year to < 18 years of age have received at least one cycle of therapy with suspension and until safety and PK assessment of these patients has been conducted.

- For expansion stage: Age at study entry ≥6 months (≥ 6 years if suspension is not available) to <30 years

  Patients ≥6 months to <1 year of age may not be enrolled until ≥ 6 patients ≥ 1 year to < 18 years of age have received at least one cycle of therapy with suspension in the dose-escalation phase and until safety and PK assessment of these patients has been conducted).

  In exceptional cases of relapsed pediatric tumors in patients ≥30 years of age, the Sponsor will consider waiving the age requirement with approval of the Medical Monitor. This waiver is restricted to patients with pediatric-specific diseases (e.g., neuroblastoma) for whom clinical trials are unlikely to be available, and will not be extended to patients with tumors that typically occur both in children and adults (e.g., HGG). The Sponsor may decide to stop enrollment of patients ≥18 years of age at any time during the study to ensure adequate enrollment of patients <18 years of age.
- Able to comply with the requirements of the study protocol, in the investigator's judgment
- Tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable, or for which no standard therapy exists.
- Tumors with known or expected RAS/RAF/MEK/ERK pathway involvement. Diagnosis MUST be one of the following tumor types:

  Central nervous system gliomas, including high- and low-grade gliomas, and DIPG

  For initial expansion stage, evidence of RAS/RAF/MEK/ERK-pathway activation is required (based on local testing of sample from time of diagnosis or any subsequent timepoint prior to enrollment) and must be approved by medical monitor for inclusion.

  Embryonal rhabdomyosarcoma and other non-rhabdomyosarcoma soft tissue sarcomas

  Neuroblastoma

  Melanoma

  Malignant peripheral nerve sheath tumor

  Rhabdoid tumors, including ATRT

  Tumors from the following groups that in the judgment of the investigator, are life threatening, resulting in severe symptoms (including severe pain), or are in close proximity to vital structures:

  NF1-associated tumors (including plexiform neurofibroma)

  Schwannoma

  Any solid tumor or brain tumor that occurs in a patient with another RASopathy (such as Noonan syndrome)

Any solid or brain tumor that has been molecularly profiled and shown to have RAS/RAF/MEK/ERK pathway activation, with approval of the Medical Monitor.

- Tumor diagnosis must be histologically or cytologically confirmed either at time of diagnosis or at time of relapse, except in the following scenario:

  DIPG and optic pathway gliomas do not require histologic confirmation if radiographic findings are sufficient to make diagnosis and institutional standard of care does not mandate biopsy for diagnosis.

- Current disease state for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
- Disease that is measurable as defined by mINRC, RANO criteria for HGG, RANO criteria for LGG, or RECIST v1.1 (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
- Availability of tumor tissue at study enrollment is mandatory. Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission, and/or willingness to undergo a core or excisional biopsy prior to enrollment are acceptable. Fine-needle aspiration, brush biopsy, and lavage samples are not acceptable.

  For patients submitting archival tissue, a minimum of 15 slides are required. Patients with fewer than 15 slides available may be eligible for study entry following approval of the Medical Monitor. See Section 4.5.9 for detailed tissue requirements.

- Lansky Performance Status or Karnofsky Performance Status (see Appendix 7 and Appendix 8, respectively) $\geq 50\%$
- Life expectancy ≥ 3 months, in the investigator's judgment
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Female patients must remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 3 months after the last dose of study drug. Female patients must refrain from donating eggs during this same period.

  True abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.

- For male patients with a female partner of childbearing potential or a pregnant female partner: Agreement to remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug

  True abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For male patients: agreement to refrain from donating sperm during the treatment period and for at least 3 months after the last dose of study drug
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 28 days prior to initiation of study drug:

  ANC $\geq 0.75 \times 10^9$/L (unsupported)

  Platelet count $\geq 75 \times 10^9$/L (unsupported)

  Hemoglobin ≥ 8 g/dL (transfusion is acceptable to meet this criterion)

  Bilirubin $\leq 1.5 \times$ ULN for age

  AST and ALT $\leq 2.5 \times$ ULN for age

  Serum creatinine $\leq 1.5 \times$ ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m^2
- Fractional shortening (FS) $\geq 30\%$ and LVEF $\geq 50\%$ at baseline, as determined by echocardiography or multigated acquisition scan (MUGA) within 28 days prior to initiation of study drug

  Depending on institutional standard, either FS or LVEF is adequate for enrollment if only one value is measured; if both values are measured, then both values must meet criteria above.
- Body weight must be $\geq$ 20 kg if suspension is not available

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or lactating, or intending to become pregnant during the study

  Females of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
- Prior treatment with cobimetinib or other MEK inhibitor. Prior sorafenib use is permissible.
- Treatment with high-dose chemotherapy and stem-cell rescue (autologous stem cell transplant) within 3 months prior to initiation of study drug

- Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within 4 weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug. This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
- Treatment with thoracic or mediastinal radiotherapy within 6 weeks prior to initiation of study drug
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives), immunotherapy, biologic therapy, or herbal cancer therapy within 4 weeks or <5 half-lives, whichever is shorter, prior to initiation of study drug
- Treatment with a long-acting hematopoietic growth factor within 2 weeks prior to initiation of study drug or a short-acting hematopoietic growth factor within 1 week prior to initiation of study drug
- Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug
- Requirement for initiation of corticosteroids or an increase in the dose of corticosteroids within 1 week prior to initiation of study drug
- Treatment with St. John's wort or hyperforin or drugs that are strong inhibitors or inducers of CYP3A (refer to Section 4.4.2) within 1 week prior to initiation of study drug
- Ingestion of grapefruit juice within 1 week prior to initiation of study drug
- Any toxicity from prior treatment that has not resolved to Grade ≤ 1 (per NCI CTCAE v4.0) at screening, except

  Alopecia

  Ototoxicity

  Parameters otherwise permitted in the inclusion/exclusion criteria (such as hematologic, biochemical, or performance status criteria)
- Major surgical procedure or significant traumatic injury within 4 weeks prior to initiation of study drug, or anticipation of need for major surgical procedure during the course of the study

  Placement of a vascular access device or minor surgery is permitted if the site has healed prior to initiation of study drug.
- Known active infection (excluding fungal infection of the nail beds) within 28 days prior to initiation of study drug that has not completely resolved
- History of Grade ≥ 2 CNS hemorrhage.
- History of CNS hemorrhage within 28 days of study entry. This criterion may be waived at the investigator's request if the CNS hemorrhage was asymptomatic, with approval of the Medical Monitor.

- For brain tumor patients, use of anticoagulants within 1 week of study drug initiation
- History or evidence of retinal pathology on ophthalmologic examination that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy (CSCR), neovascular retinopathy, or retinopathy of prematurity
- Known hypersensitivity to any component of the study drug
- Inability to swallow oral medications
- Impaired gastrointestinal absorption
- Prior allogenic bone marrow transplantation or prior solid organ transplantation
- Any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or places the patient at unacceptable risk from treatment complications
- Current drug or alcohol use or dependence that would interfere with adherence to study requirements, in the opinion of the investigator

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. Patients will be assigned to dose levels in the order in which they are enrolled.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Cobimetinib packaging will be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law as well as the protocol number. The packaging and labeling of the study drugs will be in accordance with the Sponsor's standards and local regulations. Local packaging and labeling requirements may differ in some countries.

Upon delivery of the investigational products to the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals, and temperature conditions. Site personnel should report any deviations or product complaints to the study monitor upon discovery.

Cobimetinib will be stored at the clinical site under the required storage conditions as indicated on the study drug labels. Patients or their caregivers will be asked to store cobimetinib at the required storage conditions noted in Section 4.3.1.1 and Section 4.3.1.2, out of the reach of children or other co-inhabitants.

4.3.1.1 Cobimetinib Tablet Formulation

The 20 mg cobimetinib drug product is a film-coated, white, round, immediate-release tablet approximately 6.6 mm in diameter. Cobimetinib will be packaged in bottles.

The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350 and talc.

Cobimetinib tablets should not be stored above 25°C (77°F). If study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the Medical Monitor.

4.3.1.2 Cobimetinib Suspension Formulation

Cobimetinib powder for oral suspension formulation will be supplied by the Sponsor as a white to off-white dry powder in an amber glass bottle for reconstitution by the institutional pharmacist with 50 mL of drinkable water. This will result in a 4.8 mg/mL suspension. The suspension is flavored with strawberry flavor. Accurate dosing of patients will be ensured by a press-in-bottle adapter in combination with the use of an oral dispenser. For further information on the formulation, the exact reconstitution procedure, and handling of cobimetinib powder for oral suspension, see the pharmacy manual.

Cobimetinib suspension should be stored at 2°C to 8°C (36°F to 46°F). If study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the Medical Monitor.

4.3.2 Dosage, Administration, and Compliance

Cobimetinib will be taken orally once daily on Days 1–21 of each 28-day treatment cycle (21/7 dosing schedule) according to the guidance provided in Appendix 10 until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, or patient or investigator decision to discontinue treatment. The starting dose for tablets will be 0.6 mg/kg in the dose-escalation stage. Possible subsequent doses are listed in Section 3.1.1.2. Pediatric patients (< 18 years of age) enrolled in the expansion stage will be treated at or below the MTD or MAD, as determined by the Sponsor. Adult patients (≥ 18 years of age) enrolled in the expansion stage will be treated with the adult recommended dose of 60 mg daily. In case a de-escalation is required in these adult patients, please refer to Section 5.1.1. Patients who reach 18 years of age after starting study therapy will remain on weight-based dosing. Patients will be weighed at the beginning of each cycle. In Cycle 1, weight recorded during the screening period is acceptable. For subsequent cycles, weight must be recorded within 3 days prior to the Day 1 dose, and the dose will be adjusted as needed. No patients will be treated with cobimetinib on Days 22–28 of each cycle.

Patients under 6 years of age or weighing $<$20 kg are only eligible to receive the drug in suspension (see Section 3.3.1.1 for rationale). Once the suspension is available, the Sponsor will determine whether tablets will remain available to sites based on the observed safety profile and PK of the two formulations, as well as operational feasibility of providing two formulations. If a patient is eligible for treatment with either tablet or suspension formulation, and both formulations are available, the investigator will determine the most appropriate formulation for the patient and enroll the patient into study accordingly. However, patients may not switch formulations after the start of therapy unless safety differences between the two formulations mandate a change for all patients on the study.

For patients who receive tablets, cobimetinib will be administered on Days 1-21 of each cycle as whole 20-mg tablets. For pediatric patients, a cumulative weekly dose (rounded to nearest 20 mg) based on weight and dose level will be determined, and daily dose in whole tablets will be extrapolated from this dose. **Investigators must not calculate the dose on their own but must use the dosing charts in Appendix 10** to determine the correct dose amount and frequency based on dose level and patient weight.

For patients who receive suspension, cobimetinib will be administered using either a 3-mL or a 10-mL oral dispenser. The patient will take the same dose on Days 1–21 of each cycle. Investigators must not calculate the dose on their own but must use the dosing charts in Appendix 10 to determine the correct dose amount based on dose level and patient weight. Note that cobimetinib should not be administered through a nasogastric tube on this study, given that the adsorptive properties of nasogastric tubes for cobimetinib are unknown.

Cobimetinib should be taken at approximately the same time each day, no earlier than 1 hour before and no later than 4 hours after the usual dosing time. On study visit days, the dose of cobimetinib will be taken in the clinic, after pretreatment assessments have been performed.

Patients or their caregivers must record the time and date they take each dose of cobimetinib in a medication diary. Cobimetinib can be administered at the same time as food, or on an empty stomach. However, suspension cobimetinib should only be administered with the supplied oral dispenser(s) and should not be mixed into food, milk, or juice. Tablets may not be crushed or cut. Missed doses should also be recorded. Patients and their caregivers will be instructed to bring all unused study drug and the study drug diary to each study visit for assessments of compliance.

If a dose of cobimetinib is missed (i.e., not taken within 4 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

If cobimetinib treatment has been interrupted for more than 28 days for whatever reason (including adverse events), the patient will be considered to have discontinued from study drug and will enter the treatment follow-up period.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Table 2.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

The investigational medicinal product (IMP) required for completion of this study (i.e., cobimetinib) will be provided by the Sponsor. The study site will acknowledge receipt of IMP and use the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log and IWRS.

4.3.4 Post-Trial Access to Cobimetinib

The Sponsor will offer post-trial access to the study drug (cobimetinib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for solid tumors
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for solid tumors
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND FOOD

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug until 30 days after the last dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Palliative radiotherapy may be given to patients for uncontrollable pain or imminent threat to a vital organ and must be approved by the Medical Monitor. If thoracic or mediastinal palliative radiotherapy is required, however, patients must permanently discontinue cobimetinib due to the known risk of pneumonitis as an adverse drug reaction to cobimetinib (see Investigator Brochure). Patients who undergo palliative radiation may not be evaluable for response by tumor assessments but will be assessed for progressive disease.

Pain medications may be administered according to local standard practice guidelines while the patient is in the study.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before the initial dose of cobimetinib or at any time during the DLT assessment window (Days 1–28 of therapy) for patients in the dose escalation stage, as this may confound DLT analysis. However, anti-emetics and anti-diarrheal medications may be administered during the DLT assessment window if a patient develops active symptoms

necessitating such therapy in the investigator's judgment. At the discretion of the investigator, prophylactic anti-emetic or anti-diarrheal medications may otherwise be used per standard clinical practice before subsequent doses of cobimetinib.

Hematopoietic growth factors should not be administered prophylactically before the initial dose of cobimetinib or at any time during the DLT assessment window for patients (Days 1–28 of therapy) in the dose escalation stage, as this may confound DLT analysis. Hematopoietic growth factors may otherwise be administered according to local guidelines if indicated during the course of the study, after discussion with the Medical Monitor.

Case report forms will document use of prophylactic anti-emetics, anti-diarrheal medications, and hematopoietic growth factors.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Any concomitant therapy intended for the treatment of solid tumors, either approved by health authorities or experimental, including chemotherapy, radiotherapy (except as noted in Permitted Therapy, Section 4.4.1), hormonal therapy, immunotherapy, biologic therapy, or herbal therapy
- Traditional herbal or homeopathic or natural medicines

  Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

Patients who require the use of any of these agents will be discontinued from study drug and followed for safety outcomes for 30 days after the last dose of study drug or until initiation of another subsequent anti-cancer therapy, whichever comes first. These patients will also continue to be followed for survival.

In vitro data demonstrates that cobimetinib is metabolized by CYP3A4. A clinical drug-drug interaction study with a strong CYP3A inhibitor showed a 6.6-fold increase in cobimetinib AUC. Thus, it is likely that exposures of cobimetinib will be significantly lowered in the presence of strong CYP3A inducers. The medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with cobimetinib.

- Strong CYP3A inducers, including but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and St. John's wort or hyperforin
- Strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, erythromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole

- Strong and moderate CYP3A inducers and inhibitors (as defined in Appendix 11) are prohibited for patients in the dose escalation stage during the DLT assessment window

Outside the DLT assessment window in the dose escalation stage, moderate CYP3A inhibitors and inducers are to be used with caution while strong CYP3A inducers and inhibitors should be avoided.

Caution should be use with concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.3 Prohibited Food and Supplements

Given the significant effect of CYP3A inducers and inhibitors on cobimetinib metabolism (described in Section 5.2 of the Investigator's Brochure), use of the following foods is prohibited during the study and for at least 7 days prior to the initiation of study treatment, unless otherwise specified below:

- St. John's wort or hyperforin (potent CYP3A inducer)
- Grapefruit juice (potent CYP3A enzyme inhibitors)

Ingestions of prohibited foods and supplements will render the patient non-evaluable for DLTs and may warrant removal from protocol therapy. Such ingestions must be reported to the Medical Monitor for determination of whether study drug may be continued. Patients who are discontinued from study treatment for this reason will be followed for safety outcome for 4 weeks after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever comes first. These patients will also continue to be followed for survival.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 and Appendix 2 for the schedules of assessments and schedule of PK assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before any study-specific screening tests or evaluations are performed from the patient or parent/legal guardian. Informed Consent Forms and Child's Informed Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, major surgeries, cancer history (including prior cancer therapies and procedures), menstrual history, fertility history, and puberty history. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study drug will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity where permitted by health authorities.

4.5.3 Physical Examinations and Assessments

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), changes from baseline abnormalities should be recorded in the source documents. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

When age appropriate, patients will be asked specifically about vision changes as part of each physical examination in addition to interval medical history.

During the treatment period, weight will be measured within 3 days prior to Day 1 dose of each cycle. During the follow-up period, weight should be measured every 3 months for the first 2 years, every 6 months during the third year, and yearly thereafter until end of study (Section 3.2).

During the treatment period, height, head circumference (until 3 years of age), and Tanner stage should be measured every four cycles (approximately every 3 months). During the follow-up period, height, head circumference, and Tanner stage should be measured every 3 months for the first 2 years, every 6 months during the third year, and yearly thereafter until end of study (Section 3.2). Tanner staging and height should be performed until the patient has reached Tanner Stage V.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures, oxygen saturation, and temperature.

4.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Full baseline tumor assessments should be performed within 28 days prior to initiation of study drug (Day 1 of Cycle 1). Baseline assessments will consist of the entire diagnostic workup consistent with the response evaluation system used for the specific tumor type. Tumor assessments must be performed during the last week of the even-numbered cycles (i.e., at the end of Cycles 2, 4, 6, 8, etc., prior to the start of treatment in the next cycle). *For patients who have not met study criteria for progressive disease after 12 cycles, subsequent response assessments should be conducted at Cycles 16, 20, 24, and every 6 cycles thereafter.* At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected.

Response will be assessed by the investigator on the basis of physical examinations, computed tomography (CT) scans or MRI scans and additional ^{123}I-MIBG imaging for neuroblastoma patients. The following response assessment systems will be used mINRC, RANO criteria for HGG, RANO criteria for LGG, or RECIST v1.1, as appropriate for the patient's diagnosis. CT or MRI scans should evaluate neck, chest, abdomen, and pelvic region if clinically indicated. MIBG scanning should be used for response assessments in neuroblastoma patients, if positive at baseline. PET scans may be performed at the discretion of the treating physician.

Any objective response must be confirmed by repeat assessments $\geq$4 weeks after initial documentation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). To the extent that is feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

Patients with neuroblastoma must have a MIBG scan and bilateral bone marrow aspirates and biopsies done for disease evaluation. If the enrollment bone marrow aspirates and biopsies are negative for disease, subsequent bone marrow aspirates and biopsies are not needed. Patients with neuroblastoma should also have urine catecholamines (including homovanillic acid and vanillylmandelic acid) sent at screening and with all responses assessments.

Patients without neuroblastoma who have a clinical suspicion of bone marrow involvement should also have bilateral bone marrow aspirates and biopsies performed at screening. Those with positive bone marrow involvement at screening should then have bilateral bone marrow aspirates and biopsies done with each disease reassessment until the second consecutive negative biopsy.

4.5.6 Ophthalmologic Examinations

All patients will undergo ophthalmologic examinations, performed by a qualified ophthalmologist, at specified timepoints throughout the study (see Appendix 1). *For patients who have completed 6 cycles of cobimetinib therapy and who have not developed serous retinopathy, retinal detachment, or other adverse events involving the retina, ophthalmologic evaluations will be performed at Cycles 8, 10, 12, 16, 20, 24, and every 6 cycles thereafter.*

Patients will be evaluated at screening for history or evidence of retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, CSCR, neovascular retinopathy, or retinopathy of prematurity.

Ophthalmologic examinations will include age-specific visual acuity testing (*which should be reported in Snellen units*), intraocular pressure measurements, slit-lamp ophthalmoscopy, and spectral domain optical coherence tomography (OCT) at baseline, the beginning of every cycle, study drug discontinuation, and at other timepoints identified in the protocol. Indirect ophthalmoscopy and color fundus photography will be required only at baseline and at study drug discontinuation. If spectral domain OCT is not available, time domain OCT may be performed. In patients who are unable to successfully complete OCT scans due to underlying visual impairment from non-retinal causes (such as brain tumor), color fundus photography and indirect ophthalmoscopy should be performed instead of OCT at each scheduled ophthalmologic evaluation. Additionally, fluorescein angiography will be performed for identified OCT serous fluid accumulation or edema and thereafter based upon clinical findings. Binocular indirect ophthalmoscopy will be performed any time fluorescein angiography is performed. Fluorescein angiography may be deferred if patients have known contrast allergies or abnormal renal function, at the discretion of the investigator. Providers should be advised that patients <3 years of age are likely to require examination under anesthesia for successful evaluation.

4.5.7 Cardiac Function Monitoring

Cardiac echocardiograms or MUGA will be performed during screening to assess baseline cardiac function and at regular intervals beginning with the visit at Cycle 2. These exams will be repeated every third cycle thereafter (i.e., Cycles 5, 8, 11, etc.) and at the end of study visit.

4.5.8 Dermatologic Examinations

Full-body dermatologic examinations should be performed at regular intervals as outlined in the schedule of assessments (see Appendix 1). A dermatologist should be consulted for patients who develop Grade ≥ 3 skin disorders or any grade rash with concurrent signs or symptoms strongly suggestive of a severe Type I hypersensitivity or anaphylactic or anaphylactoid reaction, with painful desquamation or mucosal

involvement suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis, or with other life-threatening complications.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Assessments that require blood, draws should be monitored closely to ensure that no more than 2.5% of the total blood volume is taken at one time or that no more than 5% of the total blood volume is taken over a 30-day period (total blood volume is defined as 80 mL/kg). Institutions should use micro sampling systems to minimize the amount of blood drawn when able. In situations where the total amount will exceed the amount stated above, clinical laboratory assessments should be prioritized. Any remaining blood should be sent for PK analysis followed by biomarker and PD analyses.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (WBC count, hemoglobin, platelet count, 3-cell differential count [absolute neutrophils, monocytes, and lymphocytes])
- Serum chemistry (sodium, potassium, magnesium, chloride, bicarbonate (or total carbon dioxide), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin [if abnormal, fractionate sample for direct and indirect], alkaline phosphatase, CPK, ALT, AST, uric acid, LDH)
- Urinalysis (specific gravity, glucose, protein, blood) in children >3 years of age.

  Creatinine clearance as clinically indicated (If radioisotope glomerular filtration rate is routinely performed at the institution to measure patients' creatinine clearance, this test can be used to assess renal function at screening, per the eligibility criteria. Otherwise, serum creatinine is sufficient to document renal function at screening).
- Pregnancy test

  All post-menarcheal females will undergo pregnancy tests within 1 week prior to the start of each treatment cycle. A serum pregnancy test must be performed at screening (prior to Cycle 1). Urine or serum pregnancy tests will be performed prior to all subsequent cycles.
- Coagulation (INR, aPTT, PT)

Samples for the following research laboratory tests will be sent to one or several central laboratories for analysis:

- Plasma samples for PK analysis (see Central Laboratory Manual)

The following samples will be sent to a central laboratory, the Sponsor, or a designee for analysis:

- Plasma samples for exploratory research on candidate biomarkers, including but not limited to *BRAF* mutations, *BRAF* fusions, *RAS* mutations, *NF1*, and other candidate biomarkers (including somatic mutations of the tumor)

- Availability of tumor tissue at study enrollment is mandatory. Archival and/or fresh primary tumor tissue samples are required for exploratory research on candidate biomarkers, including but not limited to p-MEK, p-ERK, Ki67, *BRAF* mutations, *BRAF* fusions, *RAS* mutations, and *NF1.*

  Submission of bone biopsy specimens is strongly discouraged due to complications in the assessment of such tissue, but they may be submitted if no other tissue is available.

  For patients with archival samples: Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks or at least 15 freshly cut, unstained, serial slides (blocks preferred), with an associated pathology report, are required for study entry. The specimen should be of good tissue quality and to have sufficient viable tumor content as determined by the institutional pathologist. Patients with fewer than 15 slides available may be eligible for study entry following discussion with the Medical Monitor. The tumor specimen and associated pathology report must be confirmed to be available prior to patient participation in any study-specific screening procedures and must be shipped within 30 days of first dosing.

- Patients will be encouraged to submit all available FFPE tumor specimens from prior surgeries and biopsies performed as part of routine medical care. If a patient has multiple archival specimens available but only wishes to submit one sample, the specimen obtained closest to the start of treatment should be used, with the exception that non-bone specimens are preferred over bone biopsy specimens.

  Archival tumor blocks will be returned to the sites at the end of the study or upon site request.

- Patients without archival samples must be willing to undergo a core or excisional biopsy prior to enrollment. Fine-needle aspiration, brush biopsy, and lavage samples are not acceptable.

- A whole blood sample for molecular analysis of mutations and single-nucleotide polymorphisms (SNPs) is required ONLY for patients who consent to submitting optional on-study tissue (tissue submission described in Section 4.5.10). This sample may be used for the analysis of novel mutations detected in tumor tissue in order to verify the somatic nature of this mutation and SNPs that might be associated with safety, efficacy, or PK of the drug. This sample is not collected if patients have not consented to the optional on-study biopsy.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

These samples will be destroyed when the final clinical study report has been completed, with the following exception:

- Any remaining samples collected for PK analysis, biomarker assays, and ATA assays may be used for exploratory biomarker profiling, identification, and PD assay development purposes and for additional safety assessments (e.g., ATA assay) as appropriate. The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the date of final closure of the clinical database unless the patient gives specific consent for the remainder of the samples to be stored for optional exploratory research. If the patient provides consent for optional exploratory research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

4.5.10 Acceptability Survey

To better understand the acceptability of the cobimetinib formulations, a survey will be administered immediately following administration of cobimetinib on Day 8 of Cycle 1. It would be advisable that patients rinse their mouths prior to taking the medication and complete the survey before any rinsing or water.

For patients who have not yet developed the cognitive ability to provide detailed feedback on the acceptability of a medication, the parent or guardian will complete the Acceptability Survey based on their observation of their child's reaction and facial expression following the medication intake. Patients able to provide feedback will complete the survey with reading support from their parents or the clinical staff as needed. Study staff and patient's caregiver possibly present during the assessment should remain neutral. If a patient is having difficulty with selecting a score, patients may be asked the interview question first and then redirected to complete the assessment score. Parents or caregivers will be asked about their ease of experience of administering the suspension at home.

The survey will document specific aspects of the acceptability of each of the cobimetinib formulations, including swallowability and palatability (Kozarewicz 2014). The survey is required regardless of whether the patient is taking tablets or suspension.

4.5.11 Samples for Roche Clinical Repository

4.5.11.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and

analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board (IRB) or Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to cobimetinib or solid tumors:

- Fresh tissue from on-study biopsies and residual tissue from non-study related procedures, from the primary tumor location, metastatic site, or site of local recurrence or advancement will be collected for analyses that may include DNA or RNA extraction. Samples should be obtained at the following timepoints: prior to drug initiation; during the week before Cycle 3 of drug; and at the time of disease progression (if applicable). Patients may choose to consent to any or all of these timepoints.

    For fresh tissue biopsies, a minimum of three fresh tissue cores should be acquired using an 18-gauge needle. If not feasible, one or two cores may be acceptable after discussion with the Medical Monitor.

Patients consenting to the optional on-study biopsies will also be required to provide a mandatory whole blood sample listed under the main informed consent form.

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4.

4.5.11.4 Confidentiality

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.11.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. *After withdrawal of consent, any*

remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. *If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:*

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study GO29665 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29665.

4.5.11.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study (or be withdrawn by their parents or caregivers, if the patient is a minor) at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent (or withdrawal of consent by their parents or caregivers, if the patient is a minor) at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study procedures (e.g., dosing instructions, study visits)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients in the dose-escalation stage who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be replaced except as noted in Section 3.1.1. Patients in the expansion stage who discontinue from the study will not be replaced.

4.6.2 Study Drug Discontinuation

Patients must discontinue study drug if they experience any of the following:

- Disease progression as determined by the investigator using mINRC, RANO criteria for HGG, RANO criteria for LGG, or RECIST v1.1, as appropriate. In cases where any doubt regarding disease progression exists, the patient should remain under close observation (e.g., every 4 weeks) and further radiographic assessments should be performed to document either stability or progression. If subsequent evaluations confirm that the patient is experiencing progression, the date of progressive disease should be the time at which the potential progression was first noted. Should such uncertainty occur during the treatment period, the patient may continue with the study treatment until the next scheduled efficacy assessment.
- Unacceptable toxicity despite per-protocol dose reductions or treatment interruptions
- Pregnancy
- Withdrawal of consent

Patients who discontinue study drug for any reason will be asked to return to the clinic for a study drug discontinuation visit and undergo follow-up assessments (see the schedule of assessments in Appendix 1). If treatment with another anti-cancer treatment is scheduled to begin less than 30 days after the last dose of cobimetinib, assessments at this visit should be performed before the patient starts the other treatment, if possible. Patients who discontinue for reasons other than progressive disease should continue follow-up assessments, including tumor assessments, using the same schedule of assessments as on treatment until radiographic documentation of progressive disease, start of another treatment, or withdrawal of consent. The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients in the dose-escalation stage who discontinue study drug prior to completing the DLT assessment window for reasons other than a DLT will be replaced except as noted in Section 3.1.1. Patients in the expansion stage who discontinue study drug will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is discontinued.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with cobimetinib in completed and ongoing studies. The anticipated important safety risks of cobimetinib are outlined below. Please refer to the cobimetinib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1). In addition, patients will undergo safety monitoring during the study as described in Section 4.5, Section 5, and the schedule of assessments (see Appendix 1).

An Internal Monitoring Committee and an Scientific Oversight Committee will monitor patient safety throughout the study. The Internal Monitoring Committee will provide a recommendation on the dose to be taken forward into the expansion stage after completion of the dose-escalation stage (see Section 3.1.3 for details).

Finally, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, have been provided (see Section 5.1.1). These guidelines apply to patients in the dose-escalation and expansion stages. However, the guidelines are not intended to replace clinical judgment or dictate care of individual patients.

5.1.1 Management of Specific Adverse Events

Guidelines for managing specific adverse events are provided in Table 2. Asymptomatic declines in left ventricular ejection fraction should be managed according to the algorithm presented in Table 3 in Section 5.1.2.1.

If dose reduction is indicated for an individual patient, the dose should be reduced to the next lower dose level, with dose defined in Appendix 10. The dose regimen of adult patients (≥ 18 years of age) treated with the adult-recommended daily dose of 60 mg will be reduced by one 20 mg tablet (i.e., from 60 mg to 40 mg). If the patient is treated at the lowest defined dose level, the dose should be reduced by 25%. Note that the need for dose reduction below the minimum doses for administration in this study (specified in Appendix 10) is considered unacceptable toxicity and requires study drug discontinuation. For patients taking tablets, study drug should be discontinued if required weekly dose after reduction is < 60 mg/week. For patients taking suspension, study drug should be discontinued if required dose after reduction is < 4.8 mg (1 mL) daily. Dose re-escalation is not allowed.

Table 2 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Grade ≥2 diarrhea	Grade ≥3 diarrhea • If Grade ≥3 diarrhea occurs despite adequate supportive care, do not administer cobimetinib until recovery to Grade ≤1. • Following recovery, resume cobimetinib at a dose corresponding to a reduction of one dose level. • If patient experiences two episodes of Grade ≥3 diarrhea despite adequate supportive care, discontinue cobimetinib permanently. Grade 2 diarrhea • If Grade 2 diarrhea persists for ≥10 days despite adequate supportive care, do not administer cobimetinib until recovery to Grade ≤1. • Following recovery, resume cobimetinib at a reduced dose after consulting with the Medical Monitor.
Any rash with concurrent signs or symptoms strongly suggestive of a severe Type I hypersensitivity or anaphylactic or anaphylactoid reaction, with painful desquamation or mucosal involvement suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis, or with other life-threatening complications	• Discontinue cobimetinib permanently. • Immediately consult a dermatologist.
Skin lesion suspicious for SCC/BCC	• Do not administer cobimetinib. • Immediately consult a dermatologist. • Biopsy suspicious lesions. If lesion is benign, resume cobimetinib; if lesion consistent with SCC or BCC, do not resume cobimetinib.

Table 2 Guidelines for Management of Specific Adverse Events (cont.)

Event	Action to Be Taken
Grade ≥ 3 rash that does not meet above criteria	• Consult a dermatologist. • Do not administer cobimetinib until recovery to Grade ≤ 2. • Following recovery, resume cobimetinib at a dose corresponding to a reduction of one dose level. • If patient experiences two episodes of Grade ≥ 3 rash, discontinue cobimetinib. • If Grade ≥ 3 rash persists for > 10 days despite adequate supportive care, discontinue cobimetinib permanently.
Retinopathy or Grade ≥ 2 visual disorders	• Do not administer cobimetinib. • Consult ophthalmologist, who should perform complete ophthalmologic examination that includes visual acuity testing, IOP measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy with dilation, and SD-OCT. • Resume cobimetinib if no evidence of retinopathy and either visual disorder has recovered to Grade ≤ 1 or visual disorder is attributable to underlying disease (i.e., optic glioma). Diagnosis of serous retinopathy • Do not administer cobimetinib until retinopathy has resolved (or in patients who were symptomatic at presentation, recovered to Grade ≤ 1). • When retinopathy resolves, resume cobimetinib at the next lower dose per the dose-escalation scheme, or if at or below lowest dose level, reduce dose by 25% (Section 3.1.1.2). • If retinopathy recurs, discontinue cobimetinib permanently. Diagnosis of retinal vein occlusion or Grade 3+ retinal detachment • Permanently discontinue cobimetinib
Grade ≥ 3 ALT or AST elevations	ALT or AST elevation of ≥ 5 × ULN • Do not administer cobimetinib until recovery to < 3 × ULN. • Following recovery, resume cobimetinib at a dose corresponding to a reduction of one dose level. ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN or clinical jaundice • Discontinue cobimetinib permanently.

Table 2 Guidelines for Management of Specific Adverse Events (cont.)

Event	Action to Be Taken
Grade ≥ 3 rash that does not meet above criteria	• Consult a dermatologist. • Do not administer cobimetinib until recovery to Grade ≤ 2. • Following recovery, resume cobimetinib at a dose corresponding to a reduction of one dose level. • If patient experiences two episodes of Grade ≥ 3 rash, discontinue cobimetinib. • If Grade ≥ 3 rash persists for > 10 days despite adequate supportive care, discontinue cobimetinib permanently.
Left ventricular dysfunction	
Symptomatic congestive heart failure	• Discontinue cobimetinib permanently.
Asymptomatic LVEF decrease	• Consult algorithm Table 3 in Section 5.1.2.1. • Patients who require dose reduction should have LVEF measurements at 2, 4, 10, and 16 weeks after diagnosis or as clinically indicated.
Cerebral hemorrhage (all grades)	• Permanently discontinue cobimetinib.
Grade 2 hemorrhage (excluding cerebral hemorrhage)	• Interrupt cobimetinib treatment until recovery to Grade ≤ 1, then contact Medical Monitor prior to restarting. **Do not resume cobimetinib without approval of Medical Monitor and careful benefit-risk assessment.** • There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment.
Grade ≥ 3 hemorrhage	• Permanently discontinue cobimetinib.
Rhabdomyolysis and CPK elevations	
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib treatment. If severity is improved by at least one grade (note rhabdomyolysis can be graded using the scale provided in Table 4 in Section 5.3.3) within 4 weeks, restart cobimetinib at a dose corresponding to a reduction of one dose level, if clinically indicated. If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, permanently discontinue cobimetinib treatment.

Table 2 Guidelines for Management of Specific Adverse Events (cont.)

Event	Action to Be Taken
Asymptomatic CPK elevations:	• Grade ≤3: cobimetinib dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤3 CPK elevations. • Grade 4: Interrupt cobimetinib treatment. If improved to Grade ≤3 within 4 weeks, restart cobimetinib at a dose corresponding to a reduction of one dose level, if clinically indicated. If CPK elevations do not improve to Grade ≤ 3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment.
Other Grade ≥ 3 non-hematologic toxicities or Grade 4 hematologic toxicities considered to be related to cobimetinib	• Do not administer cobimetinib until recovery to Grade ≤ 1. • Following recovery, resume cobimetinib at a dose corresponding to a reduction of one dose level. • If patient experiences two episodes of the toxicity, discontinue cobimetinib permanently. • If toxicity persists for > 14 days despite adequate supportive care, discontinue cobimetinib permanently.

BCC = basal cell carcinoma; IOP = intraocular pressure; LVEF = left ventricular ejection fraction; SCC = squamous cell carcinoma; SD-OCT = spectral domain optical coherence tomography; ULN = upper limit of normal.

5.1.2 Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from this Phase III Study GO28141 (cobimetinib plus vemurafenib), Phase Ib Study NO25395 (cobimetinib plus vemurafenib), and Phase I Study MEK4592g (cobimetinib monotherapy). For further information regarding clinical safety, please refer to the current cobimetinib Investigator's Brochure.

5.1.2.1 Important Identified Risks Associated with Cobimetinib

Hemorrhage Events

Hemorrhage including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III Study GO28141, Grade 1–4 hemorrhagic events were reported in 13% of patients treated with cobimetinib plus vemurafenib, and in 7.3% of patients treated with placebo plus vemurafenib. Higher frequencies in the cobimetinib plus vemurafenib arm were observed for cerebral hemorrhage (1% vs. 0%). The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3 and 4 hemorrhage events were reported in 1.2% of patients receiving cobimetinib plus vemurafenib and 0.8% of patients receiving placebo plus vemurafenib.

Serious and severe bleeding has been reported in both the clinical-trial and postmarketing setting. These events occurred in patients with additional risk factors for bleeding, such as central nervous system metastasis, and/or in patients who use concomitant medications that increased the risk of bleeding (including antiplatelet or anticoagulant therapy). Intracerebral events were predominantly associated with brain metastases in patients on therapy with cobimetinib and vemurafenib for metastatic melanoma.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Instructions for dose modification for hemorrhage events are included in Table 2 in Section 5.1.1.

Any Grade ≥2 hemorrhagic event will be considered a dose-limiting toxicity on this study, except intracranial hemorrhagic events, which are considered a dose-limiting toxicity regardless of their grading. For Grade 2 extracranial hemorrhagic events, investigator should not administer study drug until toxicity resolves to Grade ≤1. Dose reductions or discontinuations should be implemented per Table 2 in Section 5.1.2. For hemorrhagic events of Grade ≥3, or for any intracranial hemorrhage, study drug should be permanently discontinued.

Ocular Toxicity (Serous Retinopathy)

Serous retinopathy (fluid accumulation within the layers of the retina is a known adverse drug reaction for cobimetinib (Infante et al. 2012; Schoenberger et al. 2013; Larkin et al. 2014). Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment, and retinopathy. Serous retinopathy events may also be asymptomatic. In Study MEK4592g, visual disturbances associated with accumulation of fluid between the layers of the retina were reported as related to cobimetinib. In some cases, patients had subretinal fluid observed incidentally on ophthalmologic examination without visual symptoms. Some patients have been able to resume cobimetinib at the same dose or at a reduced dose. One dose-limiting toxicity of Grade 3 blurred vision was reported at 125 mg, and all other visual disturbances (including blurred vision and seeing flashing lights) were Grade 1 or 2. Serous retinopathy has been characterized in the Phase III Study GO28141. The study incorporated prospective serial ophthalmic examinations for all enrolled patients. Serous retinopathy was reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (25.5% vs. 2.8%, respectively), and approximately half the events were asymptomatic Grade 1 events. Few patients treated with cobimetinib plus vemurafenib experienced Grade ≥3 ocular events (2.8%); the majority of these were managed with dose modification of both cobimetinib and vemurafenib.

To address potential ocular toxicity, all patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmologic examinations at specified timepoints throughout the study (see Appendix 1). Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.5.6.

Guidelines for management of patients who develop Grade ≥2 visual disorders or retinopathy are provided in Table 2 in Section 5.1.1.

Cardiac Toxicity

Decrease in cardiac function has been identified as an adverse event that falls under "Warnings and Precautions" for adult use of cobimetinib. Study GO28141 demonstrated a decrease in cardiac function in 7% of cobimetinib plus vemurafenib-treated patients versus 3% of vemurafenib-treated patients. Most cases were asymptomatic. Symptoms consistently improved following treatment discontinuation, treatment interruption, or dose reduction in the cobimetinib arm, while improvement was inconsistent in the vemurafenib arm. There has been no in vitro or nonclinical evidence of decreased cardiac function with cobimetinib administration.

As there is no biomarker that can accurately identify early decreased cardiac function in children, cardiac function will be assessed through echocardiograms performed at specified timepoints throughout the study (see Appendix 1). This is particularly important in pediatric patients who have been treated with an anthracycline analogue, and even more so in pediatric patients who have had chest radiotherapy in addition to anthracycline treatment, both of which increase the risk of cardiac dysfunction.

Guidelines for the management of symptomatic reduction in left ventricular ejection fraction are provided in Table 3.

Table 3 Guidelines for Management of Asymptomatic Reduction in Left Ventricular Ejection Fraction

Patient	LVEF Value	Recommended Cobimetinib Dose Modification	LVEF Value Following Treatment Break	Recommended Cobimetinib Daily Dose
Asymptomatic	≥ 50% (or 40%–49% and < 10% absolute decrease from baseline)	Continue at current dose	N/A	N/A
	< 40% (or 40%–49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	< 10% absolute decrease from baseline	1st occurrence: reduce by 1 dose level
				2nd occurrence: reduce by additional dose level
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation

LVEF = left ventricular ejection fraction; FS = fractional shortening.

Note: Investigators may substitute FS for LVEF in algorithm above as follows:

- FS ≥ 28% equivalent to LVEF 50%
- FS 25%–27.9% equivalent to LVEF 40%–49%
- FS < 25% equivalent to LVEF < 40%

Patients who require dose reduction should have LVEF measurements at 2, 4, 10, and 16 weeks after diagnosis. Patients with symptomatic heart failure must discontinue study drug.

Rhabdomyolysis and CPK Elevations

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when combined with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III Study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥ 3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥ 3 events).

CPK will be monitored at baseline, on Cycle 1 Days, 1, 8, 15, and 21; then on Day 1 of each subsequent cycle (monthly), and at study drug discontinuation as indicated in Appendix 1, or as clinically indicated. Instructions for dose modification for elevated CPK and rhabdomyolysis are included in Table 2 in Section 5.1.1.

Photosensitivity

No evidence of phototoxicity has been observed with cobimetinib as a single agent. However, photosensitivity was observed on the GO28141 trial with a higher frequency in the cobimetinib plus vemurafenib arm vs. placebo plus vemurafenib arm (46% vs. 35%, respectively). The majority of events were Grades 1 or 2, with Grade ≥3 events occurring in 4% of patients in the cobimetinib plus vemurafenib arm versus 0% in the placebo plus vemurafenib arm. There were no apparent trends in the time of onset of Grade ≥3 events. Grade ≥3 photosensitivity events in the cobimetinib plus vemurafenib arm were treated with primary topical medication in conjunction with interruption of study agents. Grade≥3 photosensitivity on this trial will be treated as any other Grade ≥3 non-hematologic toxicity as outlined in Table 2 in Section 5.1.1.

Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered non-serious and low-severity grade. In the Phase III Study GO28141, pneumonitis events were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (1.6% vs. 0.4%, all grades). There were no reported Grade ≥3 events in either study arm. Serious events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib. Pneumonitis is an expected adverse drug reaction for cobimetinib.

5.1.2.2 Potential Risks Associated with Cobimetinib

Liver Laboratory Abnormalities and Severe Hepatotoxicity

Liver laboratory abnormalities can occur when cobimetinib is used with vemurafenib, and when vemurafenib is used as a single agent.

Liver laboratory test abnormalities, including increases in ALT, AST, and alkaline phosphatase, have been reported as adverse events and serious adverse events in patients treated with cobimetinib plus vemurafenib.

In the Phase III Study GO28141, liver laboratory test abnormalities reported as Grade ≥3 adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (20.5% vs. 15.1%, respectively).

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms, the majority of Grade ≥3 liver laboratory test abnormalities resolved.

No Grade ≥3 liver laboratory test elevations were reported in the cobimetinib monotherapy Study MEK4952g, with the exception of 1 case of Grade 3 bilirubin increase.

Impaired Female Fertility

There is a potential for effects on fertility and embryo-fetal toxicity based on results from nonclinical studies.

While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea, seminal vesicle and epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. These changes were reversible upon discontinuation of cobimetinib administration.

Teratogenicity and Developmental Toxicity

In a dedicated embryo-fetal toxicity study, cobimetinib produced fetal toxicity (resorptions and reductions in fetal weight), and teratogenicity (malformations of the great vessels and skull) at similar systemic exposures to those observed in adult patients administered the 60 mg dose.

See Section 4.1.1 for contraceptive requirements for study.

5.1.2.3 Other Risks Associated with Cobimetinib

Skin Toxicity

Skin rash, including erythema and maculopapules, is a known and expected dose-limiting toxicity of MEK inhibitors (LoRusso et al. 2007; Adjei et al. 2008; LoRusso et al. 2010) and can be monitored and managed clinically. Skin toxicities of rash, including dermatitis acneiform, rash pruritic, rash generalize, dermatitis, exfoliative rash, rash erythematous, and rash maculopapular, were reported frequently in studies where cobimetinib was used as a single agent or in combination with other drugs.
In Study MEK4592g with use of cobimetinib as a single agent, the incidence of rash regardless of attribution was reported to be 52.6%.

In the Phase III Study GO28141, combined rash events of all types and grades were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (71.7% vs. 66.7%, respectively), although Grade ≥3 events (approximately 16% of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (39% all grades, 5.9% Grade ≥3, 1.6% serious adverse events) and rash maculopapular (14.6% all grades, 6.3% Grade ≥3, 1.2% serious adverse events).

Generally, Grade ≥3 rash events were effectively managed with dose modification guidelines. In Study GO28141, approximately 90% of Grade ≥3 rash events resolved in both arms.

Patients will undergo dermatologic examinations at specified timepoints throughout the study (see Appendix 1). Patients who develop mild to moderate skin toxicity may be treated with concomitant medications (e.g., topical agents or oral antibiotics) at the discretion of the investigator. Skin toxicity should be managed according to institutional guidelines.

Guidelines for management of patients who develop Grade ≥3 rash are provided in Table 2 in Section 5.1.1.

Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult cancer patients.

In the Phase III Study GO28141, a randomized, placebo-controlled trial comparing cobimetinib plus vemurafenib versus placebo plus vemurafenib in adult patients with advanced BRAF V600-mutated melanoma, diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in 59.9% of patients and Grade 3 or 4 events were reported in 6.5% of patients treated with cobimetinib plus vemurafenib versus 30.9% and 0.8% in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported in 1.2% of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III Study GO28141, nausea and vomiting events were reported more frequently in the cobimetinib plus vemurafenib arm than the placebo plus vemurafenib arm (nausea 39.0% vs. 23.8%; vomiting 21.3% vs. 12.1%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea 0.8%, vomiting 1.2%).

In the Phase I single agent study MEK4592g, all grades of nausea and vomiting were reported as 33.9% for both, with 0.9% reported for Grade ≥3 nausea and none reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care.

Patients and their parents should be instructed to promptly contact the investigators if the patient develops diarrhea. Investigators should treat diarrhea and intervene promptly for patients who appear to be at increased risk of development of significant

dehydration, electrolyte imbalances, and/or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

Guidelines for management of patients who develop Grade ≥2 diarrhea are provided in Table 2 in Section 5.1.1.

Cutaneous Squamous Cell and Basal Cell Carcinoma

Cutaneous squamous cell carcinoma has been reported at high frequency with use of BRAF inhibitors, including vemurafenib, but co-administration of cobimetinib with vemurafenib was associated with lower frequency of squamous cell carcinoma on the GO28141 trial (3% in cobimetinib/vemurafenib-treated patients vs. 11% in placebo/vemurafenib-treated patients). Basal cell carcinoma occurred at higher frequency on the GO28141 trial in the cobimetinib/vemurafenib arm compared to placebo/vemurafenib arm (4% vs. 2%, respectively). Specific management of lesions suspicious for cutaneous squamous cell carcinoma or basal cell carcinoma is outlined in Table 2 in Section 5.1.1.

Hypersensitivity

There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to cobimetinib as monotherapy or when used with other agents. These have appeared to be isolated reports, and in some cases, occurred in patients with histories of drug allergies. Therefore, the relationship of cobimetinib to these events is unclear.

In the Phase III study GO28141, Grade 3 hypersensitivity events were reported in 3 patients in the cobimetinib and vemurafenib arm compared with no such events in the placebo plus vemurafenib arm. All events required hospitalization and treatment with steroids.

Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE

criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest, regardless of seriousness, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, serous retinopathy, or CSCR
- Any grade retinal vein occlusion
- Rhabdomyolysis or Grade ≥3 CPK elevation
- Any grade hemorrhage event *(except Grade 1 epistaxis per CTCAE v4.0 criteria)*
- *Any* grade cerebral hemorrhage
- Any new malignancy, including cutaneous squamous cell and basal cell carcinoma
- Grade ≥3 rash
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (as defined in Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Symptomatic heart failure or Grade ≥2 LVEF reduction

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.1.1, are required to be reported by the investigator to the Sponsor

immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures, such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting age-appropriate self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living for adults refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Age appropriate developmental milestones, however, should be taken into account when assessing instrumental activities of pediatric patients.

[b] Examples of self-care activities for adults daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden. Age-appropriate developmental milestones, however, should be taken into account when assessing self-care activities of pediatric patients.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol–specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of underlying disease should be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

During survival follow-up, deaths attributed to progression of underlying disease should be recorded only on the Study Discontinuation eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Cancer

Events that are clearly consistent with the expected pattern of disease evolution should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on mINRC, RANO criteria for HGG, RANO criteria for LGG, or RECIST v1.1, as appropriate. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of underlying disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of underlying disease

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of cobimetinib are available.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest, regardless of seriousness (see Section 5.4.2 for further details)
- DLTs (immediate reporting during the DLT assessment window; see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Alternate Telephone:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest, and Dose-Limiting Toxicities

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 30 days after the last dose of study drug. DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the last dose of study drug. The Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of study drug. The Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. Follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, using the Adverse Event eCRF via the electronica data capture (EDC) system, unless EDC is no longer available; in which case, they should be faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Cobimetinib Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase I/II, multicenter, open-label, dose-escalation, study designed to evaluate the safety, tolerability, PK, and preliminary efficacy of cobimetinib in pediatric and young adult patients with solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable. The primary analysis will be conducted after enrollment has been completed and all enrolled patients have been followed for at least 12 months.

6.1 DETERMINATION OF SAMPLE SIZE

For the dose-escalation stage, the sample size is based on the dose-escalation rules described in the study design section of this document. Explicit power and Type I error considerations were not factored into the design, as the dose-escalation stage was designed to obtain preliminary safety and PK information for the study drug.

To make a preliminary assessment of the efficacy of the study drug, two phases of response assessment are planned for the expansion stage: an initial response assessment and an additional response assessment. Taking into account historical control ORRs for each pediatric tumor type, the minimum number of patients in the initial

response assessment and the minimum number of responders needed for advancement to the additional response assessment were calculated and are presented by tumor type in Table 6. The selection of tumor type cohorts for additional response assessment, as well as the number of patients needed for the additional response assessment, will also take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information. Similar consideration will be given to other rare pediatric tumor types that are enrolled in the study and not included in Table 6. No formal hypothesis testing is planned in this study.

Table 6 Sample Size and Responder Requirements for Initial Response Assessment

Tumor Type (relapsed/refractory)	Historical Control Overall Response Rate (%)	Initial Response Assessment	
		Minimum No. of Patients Enrolled	Minimum No. of Responders Needed for Tumor Type Cohort Expansion
Melanoma	20%	10	3
Neuroblastoma	18%	10	3
Rhabdomyosarcoma	10%	10	2
Non-rhabdomyosarcoma soft tissue sarcoma	10%	10	2
High-grade glioma [a]	12%	10	2
Low-grade glioma [b]	20%	10	3

[a] Gururangan et al. 2010; Warren et al. 2012; Fouladi et al. 2013; MacDonald et al. 2013.

[b] Packer et al. 2009; Bouffet et al. 2012; Yalon et al. 2013.

Overall, approximately 70 patients will be enrolled in the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment will be tabulated by study site. Patient disposition and reasons for discontinuations will be summarized for all enrolled patients. In addition, major protocol deviations will be summarized.

Patient demographics and baseline characteristics, including age, sex, race, medical history, and prior cancer treatment, will be summarized overall and by tumor type cohort. Descriptive statistics (mean, median, standard deviation, 25 ^{h} percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

6.3 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as patients who receive any amount of study drug. Subgroup safety analyses by tumor type cohort will also be conducted as appropriate.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All adverse events, serious adverse events, adverse events leading to death, DLTs, adverse events of special interest, and adverse events leading to study treatment discontinuation, that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events), will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Laboratory toxicities will be summarized by NCI CTCAE grade.

6.4 PHARMACOKINETIC ANALYSES

Plasma samples for determination of cobimetinib concentration will be collected prior to dosing and at 2, 4, 6, and 24 hours after dosing on Days 1 and 21 of Cycle 1, and within 4 hours prior to dosing on Day 1 of Cycle 2. The sampling will allow determination of the total exposure (AUC_{0-24} after a single dose and at steady state), C_{max}, T_{max}, and accumulation ratio. Mean and individual concentration-time graphs will be plotted, and PK parameters will be reported using descriptive statistics (e.g., mean, standard deviation, coefficient of variation, median, minimum, and maximum). Other PK parameters such as steady-state concentration, steady-state concentration at the end of a dosing interval, CL/F, and $t_{1/2}$ may be determined as data allow. After a minimum of 20 patients have completed Cycle 1, an interim PK and safety analysis will be conducted.

In addition, cobimetinib plasma concentration–time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a population PK analysis approach.

Additional analyses may be conducted as warranted by the data.

6.5 EFFICACY ANALYSES

All efficacy analyses will be performed on safety-evaluable population, which is defined as patients who receive any amount of study drug.

6.5.1 Primary Efficacy Endpoints

The co-primary endpoints for efficacy are ORR and PFS.

An objective response is defined as a complete or partial response on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, RANO criteria for patients with LGG, and RECIST v1.1 for patients with other tumors. ORR is the percentage of patients who are determined to have an objective response. Patients with no post-baseline tumor assessments will be counted as non-responders. ORR and

corresponding 95% exact confidence interval (CI), using the Blyth-Still-Casella method, will be summarized overall and by tumor type cohort.

PFS is defined as the time from initiation of study drug to the first documented occurrence of disease progression, as determined by the investigator, or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the date of the last tumor assessment at which the patient was known to be progression-free or, if no tumor assessment is performed after the baseline visit, at the date of initiation of study drug. The Kaplan-Meier approach will be used to estimate median PFS. The 95% CI of the median PFS will be estimated using Brookmeyer and Crowley method. Subgroup analysis of PFS by tumor type cohort will be conducted as appropriate.

6.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are DOR and OS.

For patients who achieve an objective response, DOR is defined as the time from the first tumor assessment that supports the patient's objective response to the time of disease progression, as determined by the investigator, or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the date of the last tumor assessment at which the patient was known to be progression-free or, if no tumor assessment is performed after the baseline visit, at the date of initiation of study drug. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be estimated using Brookmeyer and Crowley method. Subgroup analysis of DOR by tumor type cohort will be conducted as appropriate.

OS is defined as the time from initiation of study drug to death from any cause. Patients who are alive at the data cutoff date will be censored at the date the patient was last known to be alive. The Kaplan-Meier approach will be used to estimate median OS. The 95% CI of the median OS will be estimated using Brookmeyer and Crowley method. Subgroup analysis of OS by tumor type cohort will be conducted as appropriate.

6.6 EXPLORATORY ANALYSES

6.6.1 Biomarker Analyses

Levels of potential PD biomarkers (including but not limited to p-MEK, p-ERK, and Ki67) will be measured in tumor tissue collected at baseline, on treatment, and at the time of disease progression. These samples will be analyzed for changes in biomarker levels in response to exposure to cobimetinib.

Plasma and archival tumor tissue samples will be collected at baseline and analyzed for non-inherited and inherited biomarkers (including but not limited to *BRAF* mutations, *BRAF* fusions, *RAS* mutations, and *NF1* mutations) that may be correlated with

response or resistance to MEK inhibition or with severity of adverse effects associated with MEK inhibition.

A modified ORR will be used for LGG and is defined as the percentage of patients with measurable disease who have a complete, partial, or minor response on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RANO criteria for LGG.

ORR for LGG will also be assessed using RECIST v1.1 and is defined as the percentage of patients with measurable disease who have a complete or partial response for on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator.

Diffusion activity and metabolic activity before and after cobimetinib treatment will be analyzed in available tumor MRI scans and PET scans, respectively.

6.6.2 Acceptability Survey

Analyses will be descriptive, enumerating the number of patients that selected each answer choice. Analyses will be conducted separately for patients receiving suspension and patients receiving tablets.

6.7 INTERIM ANALYSES

6.7.1 Planned Interim Analyses

Interim efficacy analyses will be conducted whenever a tumor type cohort has enrolled the 10 patients required for initial response assessment and patients have been followed for approximately 12 months.

6.7.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and IWRS data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor or its representatives direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug Application (IND) will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient and/or the patient's legally authorized representative(s) before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients and/or the patient's legally authorized representative(s) must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative(s). All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal

Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored by Roche and managed with the support of a contract research organization, which will provide clinical monitoring, sample management, and project management support. Approximately 70 patients are expected be enrolled in this study, at approximately 30 investigative sites in Europe and North America. If an efficacy signal is observed during the first expansion step for the initial response assessment, up to an additional 30 patients per cohort may be enrolled in the second expansion step for the additional response assessment. Patients will be enrolled through the study groups Innovative Therapies for Children with Cancer (ITCC) and Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC). Patients will be enrolled using an IWRS.

Central facilities will be used for certain study assessments (i.e., PK and biomarker analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be obtained. An IMC will monitor patient safety throughout the

study and provide a recommendation on the dose to be taken forward into the expansion stage after completion of the dose-escalation stage.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Adjei AA, Cohen RB, Franklin W, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogenactivated protein kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol 2008;26:2139–46.

Amidon GL, Lennernäs H, Shah VP, et al. A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research 1995;12:413-420.

Barretina J, Taylor, BS, Banerji S, et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat Genet 2010;42:715–21.

Barretina J, Caponigro G, Stransky N, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. Nature 2012;483(7391):603–7.

Bartelink IH, Rademaker CMA, Schobben AFAM, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharamcokinet 2006;45:1077–97.

Bautista F, Paci A, Minard-Colin V, et al. Vemurafenib in pediatric patients with $BRAF^{V600E}$ mutated high-grade gliomas. Pediatr Blood Cancer 2014;61:1101–3.

Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. Cancer. 2006 Oct 1; 107(7 Suppl):1645–55.

Bouffet E, Jakacki R, Goldman S, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 2012;30:1358–63.

Choo EF, Belvin M, Boggs J, et al. Preclinical disposition of GDC-0973 and prospective and retrospective analysis of human dose and efficacy predictions. Drug Metab Dispos 2012;40:919–27.

Choo EF, Ly J, Chan J, et al. Role of P-glycoprotein on the brain penetration and brain pharmacodynamic activity of the MEK inhibitor cobimetinib. Mol Pharm 2014;11:4199–207.

Dodd RD, Mito JK, Eward WC, et al. NF1 deletion generates multiple subtypes of soft-tissue sarcoma that respond to MEK inhibition. Mol Cancer Ther 2013;12:1906–17.

Doussau A, Asselain B, Le Deley MC, et al. Dose-finding designs in pediatric phase I clinical trials: Comparison by simulations in a realistic timeline framework. Contemporary Clinical Trials 2012;33:657-65.

Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003;3:11–22.

Dummer R, Goldinger SM, Turtschi CP, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. Eur J Cancer 2014;50:611–21.

Eleveld TF, Oldridge DA, Bernard V, et al. Relapsed neuroblastomas show frequent RAS-MAPK pathway mutations. Nature Genetics, epub ahead of print 29 June 2015.

Food and Drug Administration. The biopharmaceutics classification system (BCS) guidance [resource on the Internet]. 2009 [updated 2009 Apr 1; cited 2015 Apr 30]. Available from: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128219.htm.

Forshew T, Tatevossian RG, Lawson AR, et al. Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. J Pathol 2009;218:172–81.

Fouladi M, Stewart CF, Blaney SM, et al. A molecular biology and phase II trial of lapatinib in children with refractory CNS malignancies: a pediatric brain tumor consortium study. J Neurooncol 2013;114:173–9.

Gajjar A, Pfister SM, Taylor MD, et al. Molecular insights into pediatric brain tumors have the potential to transform therapy. Clin Cancer Res 2014;20(22):5630-5640.

Gururangan S, Chi SN, Poussaint TY, et al. Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a pediatric brain tumor consortium study. J Clin Oncol 2010;28:3069–75.

Han D, Spengler BA, Ross RA Increased wild-type N-ras activation by neurofibromin down-regulation increases human neuroblastoma stem cell malignancy. Genes Cancer 2011;2:1034–43.

Holdhoff M, Grossman SA. Controversies in the adjuvant therapy of high-grade gliomas. The Oncologist 2011;16:351–8.

Hölzel M, Huang S, Koster J, et al. NF1 is a tumor suppressor in neuroblastoma that determines retinoic acid response and disease outcome. Cell 2010;142:218–29.

Infante JR, Fecher LA, Falchook GS, et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:773–81.

Jacob K, Albrecht S, Sollier C, et al. Duplication of 7q34 is specific to juvenile pilocytic astrocytomas and a hallmark of cerebellar and optic pathway tumours. Br J Cancer 2009;101:722–33.

Jessen WJ, Miller SJ, Jousma E, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. J Clin Invest 2013;123:340–7. doi:10.1172/JCI60578.

Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases [review]. Science 2002;298:1911–12.

Jongmans MC, van der Burgt I, Hoogerbrugge PM, et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. Eur J Hum Genet 2011;19:870–74.

Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology - drug disposition, action, and therapy in infants and children. New Engl J Med 2003;349:1157–67.

Kinsler VA, Thomas AC, Ishida M, et al. Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in Codon 61 of NRAS. J Invest Dermatol 2013;133:2229–36.

Kolb EA, Gorlick R, Houghton PJ, et al. Initial testing (stage 1) of AZD6244 (ARRY-142886) by the pediatric preclinical testing program. Pediatr Blood Cancer 2010;55:668–77.

Kozarewicz P.Regulatory perspectives on acceptability testing of dosage forms in children. Int J Pharm 2014;469(2):245–8.

Larkin J., Ascierto PA, Dreno B., et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867–76.

Lee DP, Skolnik JM, Adamson PC. Pediatric phase I trials in oncology: An analysis of study conduct efficiency. J Clin Oncol 2005;23:8431–41.

LoRusso PA, Krishnamurthi SS, Rinehart JJ, et al. Clinical aspects of a Phase I study of PD-0325901, a selective oral MEK inhibitor, in patients with advanced cancer [abstract]. Mol Cancer Ther 2007;6:3649s (abstract B113).

LoRusso PM, Krishnamurthi SS, Rinehart JJ, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral MAPK/ERK kinase inhibitor PD-0325901 in patients with advanced cancers. Clin Cancer Res 2010;16:1924–37.

Lu C, Zhang J, Nagahawatte P, et al. The Genomic Landscape of Childhood and Adolescent Melanoma. J Invest Dermatol 2014 [epub ahead of print].

MacDonald TJ, Vezina G, Stewart CF, et al. Phase II study of cilegitide in the treatment of refractory or relapsed high-grade gliomas in children: a report from the Children's Oncology Group. Neurooncol 2013;15:1438–44.

Marampon F, Bossi G, Ciccarelli C, et al. MEK/ERK inhibitor U0126 affects in vitro and in vivo growth of embryonal rhabdomyosarcoma. Mol Cancer Ther 2009;8:543–51.

Mittapalli RK, Vaidhyanathan S, Sane R, et al. Impact of P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) on the brain distribution of a novel BRAF inhibitor: vemurafenib (PLX4032). J Pharmacol Exp Ther 2012;342:33-40.

Morrison H, Sperka T, Manent J, et al. Merlin/neurofibromatosis type 2 suppresses growth by inhibiting the activation of Ras and Rac. Cancer Res 2007;67(2):520–27.

Neff BA, Voss SG, Schmitt WR, et al. Inhibition of MEK pathway in vestibular schwannoma cell culture. Laryngoscope 2012;122:2269–78.

Oldridge D, McDaniel L, Attiyeh E, et al. (2014). High-risk neuroblastoma genomic plasticity allows for significant clonal evolution under the selective pressure of chemotherapy. Paper presented at the Advances in Neuroblastoma Research Congress 2014, Cologne, Germany.

Packer RJ, Jakacki R, Horn M, et al. Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan. Pediatr Blood Cancer 2009;52:791–5.

Paoletti X, Geoerger B, Doz F, et al. A comparative analysis of paediatric dose-finding trials of molecularly targeted agent with adults' trials. Eur J Cancer 2013;49:2392–402.

Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet 2013;14:355–69.

Renshaw J, Taylor KR, Bishop R, et al. Dual blockade of the PI3K/AKT/mTOR (AZD8055) and RAS/MEK/ERK (AZD6244) pathways synergistically inhibits rhabdomyosarcoma cell growth in vitro and in vivo. Clin Cancer Res 2013;19:5940–51.

Roberts PJ, Der CJ. Targeting the RAF-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer [review]. Oncogene 2007;26:3291–310.

Robinson GW, Orr BA, Gajjar A. Complete clinical regression of a BRAF V600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy. BMC Cancer 2014;14:258.

Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol 2011;121:97–405.

Schoenberger SD, Kim SJ. Bilateral Multifocal Central Serous-Like Chorioretinopathy due to MEK Inhibition for Metastatic Cutaneous Melanoma. Case Rep Ophthalmol Med 2013;2013:673–796.

See WL, Tan IL, Mukherjee J, et al. Sensitivity of glioblastomas to clinically available MEK inhibitors is defined by neurofibromin 1 deficiency. Cancer Res 2012;72(13):3350-3359.

Shern JF, Chen L, Chmielecki J, et al. Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer Discov 2014;4:216–31.

Sievert AJ, Jackson EM, Gai X, et al. Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density single-nucleotide polymorphism-based genotype arrays results in a novel BRAF fusion gene. Brain Pathol 2009;19:449–58.

Sievert AJ, Lang SS, Boucher KL, et al. Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. Proc Natl Acad Sci USA, 2013;110:5957–62.

Skolnik JM, Barrett JS, Jayaraman B, et al. Shortening the timeline of pediatric phase I trials: The rolling six design. J Clin Oncol 2008;26(2):190–195.

Strother D. Atypical teratoid rhabdoid tumors of childhood: diagnosis, treatment and challenges. Expert Rev Anticancer Therapy 2005;5:907–15.

Vujic I, Sanlorenzo M, Posch C, et al. Metformin and trametinib have synergistic effects on cell viability and tumor growth in NRAS mutant cancer. Oncotarget 2015;6(2):969-978.

Warren KE, Gururangan S, Geyer JR, et al. A Phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high grade gliomas and brainstem gliomas: a pediatric brain tumor consortium study. J Neurooncol 2012;106:643–9.

Weingart MF, Roth JJ, Hutt-Cabezas M, et al. Disrupting LIN28 in atypical teratoid rhabdoid tumors reveals the importance of the mitogen activated protein kinase pathway as a therapeutic target. Oncotarget 2015;6(5):3165–77.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.

Wu G, Diaz AK, Paugh BS, et al.; St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome, P. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet 2014;46:444–50.

Yalon M, Rood B, MacDonald TJ, et al. A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade glioma. Pediatr Blood Cancer 2013;60:71–6.

Zhang J, Wu G, Miller CP, et al.; St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome, P. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet 2013;45:602–12.

Appendix 1
Schedule of Assessments

	Screening [a]	Treatment Period									Follow-Up Period	
		Cycle 1						Cycle 2	Cycle 3	Cycles 4+	Study Drug Discont. [b]	Long-Term Follow-Up [c]
Day	–28 to –1	1	2	8	15	21	22	1	1	1		
Window (days)			0	±3	±3	3	[v]	±3	±3	±3	±3	±14 Yr 1, then ±30
Informed consent [d]	x											
Archival or fresh tumor tissue [e]	x											
Medical history and demographics [f]	x											
Serum or urine pregnancy test [g]	x							x	x	x		
Vital signs [h]	x	x [i]		x	x			x	x	x	x	
Physical examination [j]	x	x [i]		x	x			x	x	x	x	
Weight [k]	x							x	x	x	x	x
Height, head circumference, Tanner staging	x [l]									x [l]	x [l]	x [l]
Lansky or Karnofsky Performance Status [m]	x	x [i]		x	x			x	x	x	x	
Hematology [n]	x [o]	x [i]		x	x	x		x	x	x	x	
Chemistry [p]	x [o]	x [i]		x	x	x		x	x	x	x	
Urinalysis [q]	x [o]										x	
Coagulation (INR, aPTT, PT)	x											
Tumor assessments [r]	x							x [s]		x [s]		
Plasma samples for biomarkers [t]		x [u]						x [t]		x [t]	x	
PK plasma sample		x [v]	x [v]			x [v]	x [v]	x [v]				

Appendix 1
Schedule of Assessments (cont.)

	Screening [a]	Treatment Period									Follow-Up Period	
		Cycle 1						Cycle 2	Cycle 3	Cycles 4+	Study Drug Discont. [b]	Long-Term Follow-Up [c]
Day	–28 to –1	1	2	8	15	21	22	1	1	1		
Window (days)			0	±3	±3	±3	[v]	±3	±3	±3	±3	±14 Yr 1, then ±30
Concomitant medications	x[w]	x[w]		x	x	x		x	x	x	x[w]	
Adverse events	x	x		x	x	x		x	x	x	x	
Cobimetinib administration		x[x]	x[x]	x[x]	x[x]	x[x]		x[x]	x[x]	x[x]		
Study drug compliance				x	x	x		x	x	x	x	
Acceptability survey				x[y]								
12-lead ECG	x											
Echocardiogram	x							x[z]		x[z]	x	
Ophthalmologic examination [aa]	x			x[bb]	x[bb]			x[bb]	x[bb]	x[bb]	x[cc]	
Dermatologic examination (full body)	x							x[dd]		x[dd]		x
Survival assessment												x
Optional RCR tumor tissue sample [ee]		x						x			x	
Blood sample for molecular analysis [ff]		x										

CT = computed tomography; discont. = discontinuation; eCRF = electronic Case Report Form; MRI = magnetic resonance imaging; OCT = optical coherence tomography; PK = pharmacokinetic; RCR = Roche Clinical Repository.

Notes: All assessments should be performed within 3 days of the scheduled visit (excluding Day 1 of Cycle 1), unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Cycles are 28 days in length.

Appendix 1
Schedule of Assessments (cont.)

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event or a pregnancy).

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug will return to the clinic for a study drug discontinuation visit 30 (±3) days after the last dose of study drug. If treatment with another anti-cancer treatment is scheduled to begin less than 30 days after the last dose of cobimetinib, assessments at this visit should be performed before the patient starts the other treatment, if possible.

[c] Long term follow-up information will be collected every 3 months during the first 2 years (Years 1 and 2), every 6 months during Year 3, and yearly until study termination by Sponsor, death, loss to follow-up, or withdrawal of consent, whichever occurs first. Timing of visits will be determined by date of study drug discontinuation. More information is required for some patients as noted in Section 4.6.2.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] A tumor specimen and associated pathology report must be confirmed to be available prior to patient participation in any study-specific screening procedures and must be shipped within 30 days of first dosing. Specimens must be adequate for biomarker testing even though the results will not be used to determine eligibility. See Section 4.5.9 for details on sample collection.

[f] Medical history includes clinically significant diseases, major surgeries, cancer history (including prior cancer therapies and procedures), menstrual history, fertility history, and puberty history. Demographic data will include age, sex, and self-reported race/ethnicity.

[g] All females of childbearing potential will undergo pregnancy tests within 1 week prior to the start of each treatment cycle. A serum pregnancy test must be performed at screening (prior to Cycle 1). Urine or serum pregnancy tests will be performed prior to all subsequent cycles.

[h] Includes respiratory rate, pulse rate, systolic and diastolic blood pressures, oxygen saturation, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record abnormalities on the Adverse Event eCRF.

[i] Assessments performed within 96 hours prior to Day 1 of Cycle 1 do not need to be repeated on Day 1.

[j] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. When age appropriate, patients will be asked specifically about vision changes. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] In Cycle 1, weight recorded during the screening period is acceptable. For subsequent cycles, weight must be recorded within 3 days prior to Day 1 dose.

[l] See Section 4.5.3 for required assessments, depending on age and Tanner stage.

Appendix 1
Schedule of Assessments (cont.)

[m] Perform Lansky Performance Status for patients < 16 years of age (Appendix 7) and Karnofsky Performance Status for patients ≥ 16 years of age (Appendix 8).

[n] Hematology includes WBC count, hemoglobin, platelet count, 3-cell differential count (absolute neutrophils, monocytes, and lymphocytes).

[o] Screening laboratory assessments should be obtained within 14 days prior to Day 1 of Cycle 1.

[p] Chemistry includes sodium, potassium, magnesium, chloride, bicarbonate (or total carbon dioxide), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin (if abnormal, fractionate sample for direct and indirect), alkaline phosphatase, CPK, ALT, AST, uric acid, LDH.

[q] Urinalysis includes specific gravity, glucose, protein, and blood in patients > 3 years of age. If radioisotope glomerular filtration rate is routinely performed at the institution to measure patients' creatinine clearance, this test can be used to assess renal function at screening. Otherwise, serum creatinine is sufficient to document renal function at screening.

[r] The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). To the extent that is feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits. Urine catecholamine levels (homovanillic acid, vanillylmandelic acid) are required for patients with neuroblastoma at the time of tumor evaluation. See Section 4.5.5 for detailed information on tumor and response evaluations.

[s] Tumor assessments must be performed during the last week of the even-numbered cycles (i.e., at the end of Cycles 2, 4, 6, 8, etc., prior to the start of treatment in the next cycle). *For patients who have not met study criteria for progressive disease after 12 cycles, tumor assessments must be performed at the end of even-numbered cycles for the first 12 cycles, then cycles 16, 20, 24, and every 6 cycles thereafter.* At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected. An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation.

[t] Plasma samples for biomarkers *should* be collected *on Day 1 of Cycle 1 and* during the last week of the even-numbered cycles (i.e., at the end of Cycles 2, 4, 6, 8, etc., prior to the start of treatment in the next cycle) and at the time of disease progression *± 3 days. After the first 12 cycles of treatment, plasma for biomarkers should* be collected *every 4 cycles of treatment (*at *end of Cycles: 16, 20, 24) and every 6 cycles thereafter.*

[u] Ensure that samples are obtained prior to receipt of study drug.

[v] See Appendix 2 for detailed schedule. The PK sampling at Cycle 1 Day 22 should occur 24 hours after the last dose intake of the Cycle 1 Day 21 visit.

[w] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug until 30 days after the last dose of study drug.

[x] Patients will take cobimetinib orally according to the instructions in Appendix 10 on Days 1–21 of each 28-day treatment cycle until disease

progression as determined by the investigator, death, unacceptable toxicity, or patient or investigator decision to discontinue treatment. Patients will be weighed at the beginning of each cycle, and the dose will be adjusted as needed.

[y] Performed immediately after dosing (Appendix 9).

[z] Echocardiograms should be performed at Cycle 2 and every third cycle thereafter (i.e., Cycles 5, 8, 11, etc.)

[aa] Ophthalmologic examinations will include age-specific visual acuity testing *(should be reported in Snellen units)*, intraocular pressure measurements, slit-lamp ophthalmoscopy, and spectral domain OCT at all scheduled timepoints. Indirect ophthalmoscopy and color fundus photography will be performed at screening and (if performed) at study drug discontinuation. If spectral domain OCT is not available, time-domain OCT may be performed. In patients who are unable to successfully complete OCT scans due to underlying visual impairment from non-retinal causes (such as brain tumor), color fundus photography and indirect ophthalmoscopy should be performed instead of OCT at each scheduled ophthalmologic evaluation. Fluorescein angiography will be performed for identified OCT serous fluid accumulation or edema and thereafter based upon clinical findings. Binocular indirect ophthalmoscopy will be performed any time fluorescein angiography is performed.

[bb] During treatment, ophthalmologic examinations should be performed on Cycle 1 Days 8 and 15 and at the start of every subsequent cycle*; for patients who have completed 6 cycles of cobimetinib therapy and who have not developed serous retinopathy, retinal detachment, or other adverse events involving the retina, ophthalmologic evaluations will be performed at Cycles 8, 10, 12, 16, 20, 24, and every 6 cycles thereafter*.

[cc] Ophthalmologic examination is not required if performed within the previous 12 weeks and there were no clinically significant findings or changes identified in the prior examination.

[dd] During treatment, dermatologic examinations will be performed at Cycle 2 and every third cycle thereafter (i.e., Cycles 5, 8, 11, etc.).

[ee] Optional RCR tumor tissue samples will be collected prior to drug initiation, during the last week of Cycle 2 (i.e., prior to the start of treatment in Cycle 3) and at the time of disease progression or treatment discontinuation. Samples may be collected at the time of scheduled tumor assessments.

[ff] *Blood* sample is required *for exploratory research for patients who consented to the optional on-study biopsy.*

Appendix 2
Schedule of Pharmacokinetic and Pharmacodynamic Assessments

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Prior to the dose	Plasma PK sample for cobimetinib + Plasma PD biomarker sample
	2 hr (±30 min) after the dose	Plasma PK sample for cobimetinib
	4 hr (±30 min) after the dose	Plasma PK sample for cobimetinib
	6 hr (±30 min) after the dose	Plasma PK sample for cobimetinib
	24 hr (±1 hr) after the dose, prior to dose on Day 2 of Cycle 1	Plasma PK sample for cobimetinib
Cycle 1, Day 21	Prior to the dose	Plasma PK sample for cobimetinib
	2 hr (±30 min) after the dose	Plasma PK sample for cobimetinib
	4 hr (±30 min) after the dose	Plasma PK sample for cobimetinib
	6 hr (±30 min) after the dose	Plasma PK sample for cobimetinib
	24 hr (±1 hr) after the dose	Plasma PK sample for cobimetinib
Cycle 2, Day 1	Prior to the dose (within 4 hr prior)	Plasma PK sample for cobimetinib
Cycle 2 (and every 2 cycles thereafter), Days 22–28	Samples should be collected on the day of scheduled tumor assessments.	Plasma PD biomarker sample
Study drug discontinuation	Any time during visit	Plasma PD biomarker sample

hr = hour; min = minute; PD = pharmacodynamics; PK = pharmacokinetic.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within 3 days of the scheduled date.

Appendix 3
Modified International Neuroblastoma Response Criteria

Below response assessment is modified from the original INRC publication in 1993.

DEFINITION OF MEASURABLE (EVALUABLE) DISEASE ON CT/MRI SCAN

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With a spiral computed tomography (CT) scan, lesions must be at least 10 mm. The investigator will identify up to 10 measurable target lesions to be followed for response. Note that bone lesions will be considered as non-target lesions for evaluation of CT/magnetic resonance imaging (MRI) response since they will be evaluated with MIBG scans.

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. Serial measurements of lesions are to be done with CT or MRI. The same method of assessment used to characterize each identified and reported lesion at baseline should be used during follow-up.

RESPONSE CRITERIA FOR MEASURABLE DISEASE ON CT/MRI SCAN

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement. The response of the CT/MRI lesions will be defined as outlined below:

- Complete response (CR): Disappearance of all target and non-target CT/MRI lesions
- Very good partial response (VGPR): Greater than 90% decrease of the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry; non-target CT/MRI lesions stable to smaller in size
- Partial response (PR): At least a 30% decrease in the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry; non-target CT/MRI lesions stable to smaller in size
- Progressive disease (PD): At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement since the treatment started, or a new site of tumor; non-target CT/MRI lesions stable, smaller, or increased in size
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started; no new sites of disease

Appendix 3
International Neuroblastoma Response Criteria (cont.)

RESPONSE CRITERIA FOR MORPHOLOGIC BONE MARROW DISEASE

Only those patients with morphologic evidence of neuroblastoma by routine H and E staining (neuron-specific enolase [NSE] staining only is not evaluable) will be evaluable to assess bone marrow response.

- CR: No tumor cells detectable by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 3 weeks apart after study entry.
- PD: Tumor seen on morphology on two consecutive bone marrows done at least 3 weeks apart in patients who had no tumor in bone marrow at study entry

  Patient may be declared to have PD in bone marrow after only one diagnostic bone marrow at the discretion of the treating physician

  Patients who enter study with bone marrow tumor by morphology will be considered to have PD if there is a minimum of 25% tumor in the marrow by morphology and a doubling in the amount of tumor in the marrow compared with the level present at study entry. For example, a patient entering with 5% tumor in marrow by morphology must increase to $>$25% tumor to have PD; a patient entering with 30% tumor must increase to $>$60% tumor.
- SD: Persistence of an amount of tumor in the bone marrow by morphology that does not meet criteria for either CR or PD

  Patients who clear morphologic tumor but have immunocytologic tumor will be called SD.

RESPONSE CRITERIA FOR MIBG-POSITIVE LESIONS

All patients with known MIBG-avid lesions will be evaluable for MIBG response following the first course of therapy. The following criteria will be used to report MIBG response:

- CR: Complete resolution of all MIBG-positive lesions
- PR: Resolution of at least one MIBG-positive lesion, with persistence of other MIBG positive lesions
- SD: No change in MIBG scan in number of positive lesions (includes patients who have same number of positive lesions but decreased intensity)
- PD: Development of new MIBG-positive lesions

Appendix 3
International Neuroblastoma Response Criteria (cont.)

DEFINITION OF OVERALL RESPONSE FOR EACH PATIENT WITH NEUROBLASTOMA

The International Neuroblastoma Response Criteria were developed to define responses in patients being treated with frontline therapy from diagnosis.[1] These criteria were utilized as a basis for the following response criteria, which integrate response at all sites defined as measurable in this study, including CT/MRI lesions that meet RECIST, MIBG-positive lesions, and bone marrow disease. These criteria will be used to define the overall response for each patient.

- CR: Disappearance of all target lesions; no evidence of tumor at any site (chest, abdomen, liver, bone, bone marrow, nodes, etc.); homovanillic acid (HVA) and vanillylmandelic acid (VMA) normal
- VGPR: Greater than 90% decrease of the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry; all preexisting bone lesions with CR by MIBG; MIBG scan can be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI; CR in bone marrow; no new sites of tumor; HVA/VMA normal
- PR: At least a 30% decrease in the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry; bone marrow with CR; MIBG with either PR or CR in bone lesions; MIBG may be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI; HVA/VMA may still be elevated.
- PD: Any one of the following:

  At least a 20% increase in the disease measurement for CT/MRI target lesions, taking as reference the smallest disease measurement recorded since the start of treatment

  Appearance of one or more new lesions or new sites of tumor

  PD as defined above for either bone marrow or MIBG lesions
- SD: Stable disease by either CT/MRI lesion, bone marrow, or MIBG criteria; no new lesions; no new sites of disease

The overall response as assessed at any particular timepoint based on the various disease sites is summarized in the table below.

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[1] Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11:1466–77.

Appendix 3
International Neuroblastoma Response Criteria (cont.)

Table 1 Overall Response at Any Timepoint

CT/MRI Lesions	MIBG Lesions	Bone Marrow	Catechols	Overall Response
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
CR	CR	CR	Normal	CR
VGPR	CR in bone lesions ; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Normal	VGPR
PR	PR/CR in bone lesions; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Any	PR
SD	SD	SD	Any	SD
SD/PR/VGPR/CR	SD	SD/CR	Any	SD
SD/PR/VGPR/CR	SD/PR/CR	SD	Any	SD

CR = complete response; CT = computed tomography; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

Appendix 4
Response Assessment in Neuro-Oncology Criteria for High-Grade Glioma

Response	Criteria
Complete response	Requires **all** of the following: • Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks • No new lesions • Stable or improved non-enhancing (T2/FLAIR) lesions • Patients must be off corticosteroids (or on physiological replacement doses only) • Clinical status is stable or improved
Partial response	Requires **all** of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks • No progression of nonmeasurable T1 enhancing disease • No new lesions • Stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease
Stable disease	Requires **all** of the following: • Patient does not qualify for complete response, partial response, or progression • Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: 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 corticosteroids 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.

Appendix 4
Response Assessment in Neuro-Oncology Criteria for High-Grade Glioma (cont.)

Response	Criteria
Progression	Defined by **any** of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (of no decrease) or best response, on a stable or increasing dose of corticosteroids • Significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of steroids compared with baseline scan or best response after initiation of therapy, not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, seizures, postoperative changes, or other treatment effects) • Presence of any new lesions • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or decreases in corticosteroid dose • Failure to return for evaluation due to death or deteriorating condition • Clear progression of nonmeasurable disease

FLAIR = fluid-attenuated inversion recovery.

Note: Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.

Appendix 5
Response Assessment in Neuro-Oncology Criteria for Low-Grade Glioma

Response	Criteria
Complete response	Requires all of the following criteria compared with the baseline scan: • Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely) • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • Patients must be off corticosteroids or only on physiological replacement doses • Patients should be stable or improved clinically
Partial response	Requires all of the following criteria compared with the baseline scan: • ≥ 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Minor response	Requires the following criteria compared with baseline: • A decrease of the area of non-enhancing lesion on T2 or FLAIR magnetic resonance imaging between 25% and 50% compared with baseline • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Stable disease	Is present if the changes do not qualify for complete, partial, or minor response, or progression and requires: • Stable area of non-enhancing abnormalities on T2 or FLAIR imaging • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically

Appendix 5
Response Assessment in Neuro-Oncology Criteria for Low-Grade Glioma (cont.)

Response	Criteria
Progression	Defined by any of the following: • Development of new lesions or increase of enhancement (radiological evidence of malignant transformation) • A 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events • Definite clinical deterioration not attributable to other causes apart from the tumor or decrease in corticosteroid dose • Failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders

FLAIR = fluid-attenuated inversion recovery; RANO=Response Assessment in Neuro-Oncology.

Note: Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[2] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[3]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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[2] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.
[3] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

< 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it

would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

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

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint (Table 3). If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 7
Lansky Performance Status Scale (Patients < 16 Years of Age)

Score	Description
100	Fully active; normal
90	Minor restrictions in physically strenuous activity
80	Active but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed

Appendix 8
Karnofsky Performance Status Scale (Patients ≥ 16 Years of Age)

Score	Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated; death not imminent
20	Very sick; hospitalization indicated; death not imminent
10	Moribund; fatal processes progressing rapidly

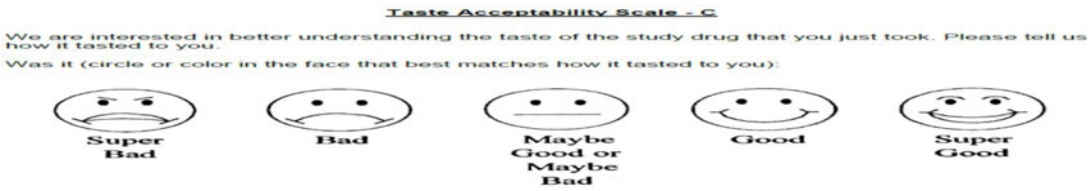
Appendix 9
Acceptability Survey for Patients

Instructions: Please answer the questions below to help us understand your experience with the study medication (cobimetinib). For questions with a face, indicate which of the faces best matches how you felt about the medication.

For children who cannot read yet, parents or caregiver, please help us understand your child's experience with the medication. Invite your child to look at the cartoon, ask him or her the questions, and record his or her answer. If your child cannot answer the question, please leave the question blank.

For children who cannot answer for themselves, parents or caregiver, please go directly to questions 7 and 8.

1. How much did you like the taste of the medication?



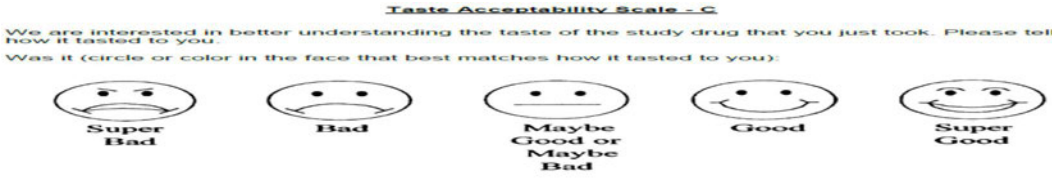
☐	☐	☐	☐	☐
Really Bad	Bad	Not sure	Good	Really Good

2. What was the taste of the medication?
   - ☐ Bitter
   - ☐ Sweet
   - ☐ Sour
   - ☐ Salty
3. How much did you like the feeling of the medication in your mouth?

☐	☐	☐	☐	☐
Really Bad	Bad	Not sure	Good	Really Good

Appendix 9
Acceptability Survey for Patients (cont.)

4. How difficult was it to swallow the medication?



☐	☐	☐	☐	☐
Really Bad	Bad	Not sure	Good	Really Good

5. After the medication was not in your mouth anymore, could you still taste the medication?

   ☐ Yes

   ☐ No

6. What was the taste you had in your mouth after the medication was gone?

   ☐ Bitter

   ☐ Sweet

   ☐ Sour

   ☐ Salty

For parent or caregiver of children who cannot answer for themselves:

7. At any time did you have a problem in giving the medication to your child because he or she refused to take it?

   ☐ Yes

   ☐ No

8. At any time did you have a problem in giving the planned dose of the medication to your child because he or she threw it up?

   ☐ Yes

   ☐ No

Appendix 9
Acceptability Survey for Patients (cont.)

Additional questions for participants receiving the SUSPENSION:

Instructions: Please answer the questions below to help us understand your experience giving the study medication (cobimetinib) at home.

9. Which size medication dispenser (syringe) did you use to administer the medication?

   ☐ 3-mL

   ☐ 10-mL

10. How many times did you have to fill the medication dispenser (syringe) to administer the prescribed dose of the medication?

    ☐ Once

    ☐ More than once

11. How easy or difficult was it to fill the medication dispenser (syringe) from the bottle?

    ☐ Very easy

    ☐ Somewhat easy

    ☐ Somewhat difficult

    ☐ Very difficult

Thank You

Appendix 10
Dosing Tables for Cobimetinib

DOSE LEVEL 1 = 0.6 MG/KG/DAY, 20 MG TABLETS

Cumulative weekly dose = 4.2 mg/kg/week

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose for 7 days	Cumulative Weekly Dose (mg/wk)
20.0–21.4	1 tab 4 d/wk, 0 tab 3 d/wk	80
21.5–26.1	1 tab 5 d/wk, 0 tab 2 d/wk	100
26.2–30.9	1 tab 6 d/wk, 0 tab 1 d/wk	120
31.0–35.7	1 tab daily	140
35.8–40.4	2 tab 1 d/wk, 1 tab 6 d/wk	160
40.5–45.2	2 tab 2 d/wk, 1 tab 5 d/wk	180
45.3–50.0	2 tab 3 d/wk, 1 tab 4 d/wk	200
50.1–54.7	2 tab 4 d/wk, 1 tab 3 d/wk	220
54.8–59.5	2 tab 5 d/wk, 1 tab 2 d/wk	240
59.6–64.2	2 tab 6 d/wk, 1 tab 1 d/wk	260
64.3–69.0	2 tab daily	280
69.1–73.8	3 tab 1 d/wk, 2 tab 6 d/wk	300
73.9–78.5	3 tab 2 d/wk, 2 tab 5 d/wk	320
78.6–83.3	3 tab 3 d/wk, 2 tab 4 d/wk	340
83.4–88.0	3 tab 4 d/wk, 2 tab 3 d/wk	360
88.1–92.8	3 tab 5 d/wk, 2 tab 2 d/wk	380
92.9–97.6	3 tab 6 d/wk, 2 tab 1 d/wk	400
97.7–102.3	3 tab daily	420
102.4–107.1	4 tab 1 d/wk, 3 tab 6 d/wk	440
107.2–111.9	4 tab 2 d/wk, 3 tab 5 d/wk	460
112.0–116.6	4 tab 3 d/wk, 3 tab 4 d/wk	480
116.7–121.4	4 tab 4 d/wk, 3 tab 3 d/wk	500
121.5–126.1	4 tab 5 d/wk, 3 tab 2 d/wk	520
126.2–130.9	4 tab 6 d/wk, 3 tab 1 d/wk	540
131.0–135.7	4 tab daily	560
> 135.7	Contact Medical Monitor	

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL = 0.6 MG/KG/DAY, SUSPENSION (4.8 MG/ML)

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)	Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)
<7.6	Call Medical Monitor		38.0–41.9	5	168.0
7.6–8.3	1.0	33.6	42.0–45.9	5.5	184.8
8.4–9.1	1.1	37.0	46.0–49.9	6	201.6
9.2–9.9	1.2	40.3	50.0–53.9	6.5	218.4
10.0–10.7	1.3	43.7	54.0–57.9	7	235.2
10.8–11.5	1.4	47.0	58.0–61.9	7.5	252.0
11.6–12.3	1.5	50.4	62.0–65.9	8	268.8
12.4–13.1	1.6	53.8	66.0–69.9	8.5	285.6
13.2–13.9	1.7	57.1	70.0–73.9	9	302.4
14.0–14.7	1.8	60.5	74.0–77.9	9.5	319.2
14.8–15.5	1.9	63.8	78.0–81.9	10	336.0
15.6–16.7	2.0	67.2	82.0–85.9	10.5	352.8
16.8–18.3	2.2	73.9	86.0–89.9	11	369.6
18.4–19.9	2.4	80.6	90.0–93.9	11.5	386.4
20.0–21.5	2.6	87.4	94.0–97.9	12	403.2
21.6–23.1	2.8	94.1	98.0–101.9	12.5	420.0
23.2–25.9	3.0	100.8	102.0–105.9	13	436.8
26.0–29.9	3.5	117.6	106.0–109.9	13.5	453.6
30.0–33.9	4	134.4	110.0–113.9	14	470.4
34.0–37.9	4.5	151.2	114.0–117.9	14.5	487.2
			118.0–121.9	15	504.0
			122.0–125.9	15.5	520.8
			126.0–129.9	16	537.6
			130.0–133.9	16.5	554.4
			>133.9	Call Medical Monitor	

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL 2 = 0.8 MG/KG/DAY, 20 MG TABLETS

Cumulative weekly dose = 5.6 mg/kg/week (wk).

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose for 7 days	Cumulative Weekly Dose (mg/wk)
20.0–23.2	1 tablet (tab) 6 d/wk, 0 tab 1 d/wk	120
23.3–26.7	1 tab daily	140
26.8–30.3	2 tab 1 d/wk, 1 tab 6 d/wk	160
30.4–33.9	2 tab 2 d/wk, 1 tab 5 d/wk	180
34.0–37.5	2 tab 3 d/wk, 1 tab 4 d/wk	200
37.6–41.0	2 tab 4 d/wk, 1 tab 3 d/wk	220
41.1–44.6	2 tab 5 d/wk, 1 tab 2 d/wk	240
44.7–48.2	2 tab 6 d/wk, 1 tab 1 d/wk	260
48.3–51.7	2 tab daily	280
51.8–55.3	3 tab 1 d/wk, 2 tab 6 d/wk	300
55.4–58.9	3 tab 2 d/wk, 2 tab 5 d/wk	320
59.0–62.5	3 tab 3 d/wk, 2 tab 4 d/wk	340
62.6–66.0	3 tab 4 d/wk, 2 tab 3 d/wk	360
66.1–69.6	3 tab 5 d/wk, 2 tab 2 d/wk	380
69.7–73.2	3 tab 6 d/wk, 2 tab 1 d/wk	400
73.3–76.7	3 tab daily	420
76.8–80.3	4 tab 1 d/wk, 3 tab 6 d/wk	440
80.4–83.9	4 tab 2 d/wk, 3 tab 5 d/wk	460
84.0–87.5	4 tab 3 d/wk, 3 tab 4 d/wk	480
87.6–91.0	4 tab 4 d/wk, 3 tab 3 d/wk	500
91.1–94.6	4 tab 5 d/wk, 3 tab 2 d/wk	520
94.7–98.2	4 tab 6 d/wk, 3 tab 1 d/wk	540
98.3–101.7	4 tab daily	560
101.8–105.3	5 tab 1 d/wk, 4 tab 6 d/wk	580
105.4–108.9	5 tab 2 d/wk, 4 tab 5 d/wk	600
109.0–112.5	5 tab 3 d/wk, 4 tab 4 d/wk	620
112.6–116.0	5 tab 4 d/wk, 4 tab 3 d/wk	640
116.1–119.6	5 tab 5 d/wk, 4 tab 2 d/wk	660
119.7–123.2	5 tab 6 d/wk, 4 tab 1 d/wk	680
123.3–126.7	5 tab daily	700
> 126.8	Contact Medical Monitor	

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL 2 = 0.8 MG/KG/DAY, SUSPENSION (4.8 MG/ML)

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)	Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)
<5.7	Call Medical Monitor		34.5–37.4	6	201.6
5.7–6.2	1.0	33.6	37.5–40.4	6.5	218.4
6.3–6.8	1.1	37.0	40.5–43.4	7	235.2
6.9–7.4	1.2	40.3	43.5–46.4	7.5	252.0
7.5–8.0	1.3	43.7	46.5–49.4	8	268.8
8.1–8.6	1.4	47.0	49.5–52.4	8.5	285.6
8.7–9.2	1.5	50.4	52.5–55.4	9	302.4
9.3–9.8	1.6	53.8	55.5–58.4	9.5	319.2
9.9–10.4	1.7	57.1	58.5–61.4	10	336.0
10.5–11.0	1.8	60.5	61.5–64.4	10.5	352.8
11.1–11.6	1.9	63.8	64.5–67.4	11	369.6
11.7–12.5	2.0	67.2	67.5–70.4	11.5	386.4
12.6–13.7	2.2	73.9	70.5–73.4	12	403.2
13.8–14.9	2.4	80.6	73.5–76.4	12.5	420.0
15.0–16.1	2.6	87.4	76.5–79.4	13	436.8
16.2–17.3	2.8	94.1	79.5–82.4	13.5	453.6
17.4–19.4	3.0	100.8	82.5–85.4	14	470.4
19.5-22.4	3.5	117.6	85.5–88.4	14.5	487.2
22.5–25.4	4	134.4	88.5–91.4	15	504.0
25.5–28.4	4.5	151.2	91.5–94.4	15.5	520.8
28.5–31.4	5	168.0	94.5–97.4	16	537.6
31.5–34.4	5.5	184.8	97.5–100.4	16.5	554.4
			100.5–103.4	17	571.2
			103.5–106.4	17.5	588.0
			106.5–109.4	18	604.8
			109.5–112.4	18.5	621.6
			>112.4	Call Medical Monitor	

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL 3 = 1 MG/KG/DAY, 20 MG TABLETS

Cumulative weekly dose = 7 mg/kg/week

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose for 7 days	Cumulative Weekly Dose (mg/wk)
20.0–21.4	1 tab daily	140
21.5–24.2	2 tab 1 d/wk, 1 tab 6 d/wk	160
24.3–27.1	2 tab 2 d/wk, 1 tab 5 d/wk	180
27.2–30.0	2 tab 3 d/wk, 1 tab 4 d/wk	200
30.1–32.8	2 tab 4 d/wk, 1 tab 3 d/wk	220
32.9–35.7	2 tab 5 d/wk, 1 tab 2 d/wk	240
35.8–38.5	2 tab 6 d/wk, 1 tab 1 d/wk	260
38.6–41.4	2 tab daily	280
41.5–44.2	3 tab 1 d/wk, 2 tab 6 d/wk	300
44.3–47.1	3 tab 2 d/wk, 2 tab 5 d/wk	320
47.2–50.0	3 tab 3 d/wk, 2 tab 4 d/wk	340
50.1–52.8	3 tab 4 d/wk, 2 tab 3 d/wk	360
52.9–55.7	3 tab 5 d/wk, 2 tab 2 d/wk	380
55.8–58.5	3 tab 6 d/wk, 2 tab 1 d/wk	400
58.6–61.4 [a]	3 tab daily	420
61.5–64.2	4 tab 1 d/wk, 3 tab 6 d/wk	440
64.3–67.1	4 tab 2 d/wk, 3 tab 5 d/wk	460
67.2–70.0	4 tab 3 d/wk, 3 tab 4 d/wk	480
70.1–72.8	4 tab 4 d/wk, 3 tab 3 d/wk	500
72.9–75.7	4 tab 5 d/wk, 3 tab 2 d/wk	520
75.8–78.5	4 tab 6 d/wk, 3 tab 1 d/wk	540
78.6–81.4	4 tab daily	560
81.5–84.2	5 tab 1 d/wk, 4 tab 6 d/wk	580
84.3–87.1	5 tab 2 d/wk, 4 tab 5 d/wk	600
87.2–90.0	5 tab 3 d/wk, 4 tab 4 d/wk	620
90.1–92.8	5 tab 4 d/wk, 4 tab 3 d/wk	640
92.9–95.7	5 tab 5 d/wk, 4 tab 2 d/wk	660
95.8–98.5	5 tab 6 d/wk, 4 tab 1 d/wk	680
98.6–101.4	5 tab daily	700
101.5–104.2	6 tab 1 d/wk, 5 tab 6 d/wk	720
104.3–107.1	6 tab 2 d/wk, 5 tab 5 d/wk	740
107.2–110.0	6 tab 3 d/wk, 5 tab 4 d/wk	760
110.1–112.8	6 tab 4 d/wk, 5 tab 3 d/wk	780
112.9–115.7	6 tab 5 d/wk, 5 tab 2 d/wk	800
115.8–118.5	6 tab 6 d/wk, 5 tab 1 d/wk	820
118.6–121.4	6 tab daily	840

[a] For patients > 60 kg, contact Medical Monitor.

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL 3=1 MG/KG/DAY, SUSPENSION (4.8 MG/ML)

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)	Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)
<4.6	Call Medical Monitor		44.4–46.7	9.5	319.2
4.6–5.0	1.0	33.6	46.8–49.1	10	336.0
5.1–5.5	1.1	37.0	49.2–51.5	10.5	352.8
5.6–5.9	1.2	40.3	51.6–53.9	11	369.6
6.0–6.4	1.3	43.7	54.0–56.3	11.5	386.4
6.5–6.9	1.4	47.0	56.4–58.7	12	403.2
7.0–7.4	1.5	50.4	58.8–61.1[a]	12.5	420.0
7.5–7.9	1.6	53.8	61.2–63.5	13	436.8
8.0–8.3	1.7	57.1	63.6–65.9	13.5	453.6
8.4–8.8	1.8	60.5	66.0–68.3	14	470.4
8.9–9.3	1.9	63.8	68.4–70.7	14.5	487.2
9.4–10.0	2.0	67.2	70.8–73.1	15	504.0
10.1–11.0	2.2	73.9	73.2–75.5	15.5	520.8
11.1–11.9	2.4	80.6	75.6–77.9	16	537.6
12.0–12.9	2.6	87.4	78.0–80.3	16.5	554.4
13.0–13.9	2.8	94.1	80.4–82.7	17	571.2
14.0–15.5	3.0	100.8	82.8–85.1	17.5	588.0
15.6–17.9	3.5	117.6	85.2–87.5	18	604.8
18.0–20.3	4	134.4	87.6–89.9	18.5	621.6
20.4–22.7	4.5	151.2	90.0–92.3	19	638.4
22.8–25.1	5	168.0	92.4–94.7	19.5	655.2
25.2–27.5	5.5	184.8	94.8–97.1	20	672.0
27.6–29.9	6	201.6	97.2–99.5	20.5	688.8
30.0–32.3	6.5	218.4	99.6–101.9	21	705.6
32.4–34.7	7	235.2	102.0–104.3	21.5	722.4
34.8–37.1	7.5	252.0	104.4–106.7	22	739.2
37.2–39.5	8	268.8	106.8–109.1	22.5	756.0
39.6–41.9	8.5	285.6	109.2–111.5	23	772.8
42.0–44.3	9	302.4	111.6–113.9	23.5	789.6
			114.0–116.3	24	806.4

[a] For patients >60 kg, contact Medical Monitor.

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL 4 = 1.33 MG/KG/DAY, 20 MG TABLETS

Cumulative weekly dose = 9.31 mg/kg/week

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose for 7 days	Cumulative Weekly Dose (mg/wk)
20.0–20.4	2 tab 2 d/wk, 1 tab 5 d/wk	180
20.5–22.5	2 tab 3 d/wk, 1 tab 4 d/wk	200
22.6–24.7	2 tab 4 d/wk, 1 tab 3 d/wk	220
24.8–26.8	2 tab 5 d/wk, 1 tab 2 d/wk	240
26.9–29.0	2 tab 6 d/wk, 1 tab 1 d/wk	260
29.1–31.1	2 tab daily	280
31.2–33.2	3 tab 1 d/wk, 2 tab 6 d/wk	300
33.3–35.4	3 tab 2 d/wk, 2 tab 5 d/wk	320
35.5–37.5	3 tab 3 d/wk, 2 tab 4 d/wk	340
37.6–39.7	3 tab 4 d/wk, 2 tab 3 d/wk	360
39.8–41.8	3 tab 5 d/wk, 2 tab 2 d/wk	380
41.9–44.0	3 tab 6 d/wk, 2 tab 1 d/wk	400
44.1–46.1	3 tab daily	420
46.2–48.3	4 tab 1 d/wk, 3 tab 6 d/wk	440
48.4–50.4	4 tab 2 d/wk, 3 tab 5 d/wk	460
50.5–52.6	4 tab 3 d/wk, 3 tab 4 d/wk	480
52.7–54.7	4 tab 4 d/wk, 3 tab 3 d/wk	500
54.8–56.9	4 tab 5 d/wk, 3 tab 2 d/wk	520
57.0–59.0	4 tab 6 d/wk, 3 tab 1 d/wk	540
59.1–61.2[a]	4 tab daily	560
61.3–63.3	5 tab 1 d/wk, 4 tab 6 d/wk	580
63.4–65.5	5 tab 2 d/wk, 4 tab 5 d/wk	600
65.6–67.6	5 tab 3 d/wk, 4 tab 4 d/wk	620
67.7–69.8	5 tab 4 d/wk, 4 tab 3 d/wk	640
69.9–71.9	5 tab 5 d/wk, 4 tab 2 d/wk	660
72.0–74.1	5 tab 6 d/wk, 4 tab 1 d/wk	680
74.2–76.2	5 tab daily	700
76.3–78.4	6 tab 1 d/wk, 5 tab 6 d/wk	720
78.5–80.5	6 tab 2 d/wk, 5 tab 5 d/wk	740
80.6–82.7	6 tab 3 d/wk, 5 tab 4 d/wk	760
82.8–84.8	6 tab 4 d/wk, 5 tab 3 d/wk	780
84.9–87.0	6 tab 5 d/wk, 5 tab 2 d/wk	800
87.1–89.1	6 tab 6 d/wk, 5 tab 1 d/wk	820
89.2–91.2	6 tab daily	840

[a] For patients >60 kg, contact Medical Monitor.

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL 4 = 1.33 MG/KG/DAY, SUSPENSION (4.8 MG/ML)

Doses to be administered on Days 1–21 of cycle; do not administer on Days 22–28.

Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)	Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)
<4.9	Call Medical Monitor		37.0–38.7	10.5	352.8
4.9–5.2	1.4	47.0	38.8–40.6	11	369.6
5.3–5.5	1.5	50.4	40.7–42.4	11.5	386.4
5.6–5.9	1.6	53.8	42.5–44.2	12	403.2
6.0–6.3	1.7	57.1	44.3–46.0	12.5	420.0
6.4–6.6	1.8	60.5	46.1–47.8	13	436.8
6.7–7.0	1.9	63.8	47.9–49.6	13.5	453.6
7.1–7.5	2.0	67.2	49.7–51.4	14	470.4
7.6–8.3	2.2	73.9	51.6–53.2	14.5	487.2
8.4–9.0	2.4	80.6	53.2–55.0	15	504.0
9.1–9.7	2.6	87.4	55.1–56.8	15.5	520.8
9.8–10.4	2.8	94.1	56.9–58.6	16	537.6
10.5–11.7	3.0	100.8	58.7–60.4 [a]	16.5	554.4
11.8–13.5	3.5	117.6	60.5–62.2	17	571.2
13.6–15.3	4	134.4	62.3–64.0	17.5	588.0
15.4–17.1	4.5	151.2	64.1–65.8	18	604.8
17.2–18.9	5	168.0	65.9–67.6	18.5	621.6
19.0–20.7	5.5	184.8	67.7–69.4	19	638.4
20.8–22.5	6	201.6	69.5–71.2	19.5	655.2
22.6–24.3	6.5	218.4	71.3–73.0	20	672.0
24.4–26.1	7	235.2	73.1–74.8	20.5	688.8
26.2–27.9	7.5	252.0	74.9–76.6	21	705.6
28.0–29.7	8	268.8	76.7–78.4	21.5	722.4
29.8–31.5	8.5	285.6	78.5–80.3	22	739.2
31.6–33.3	9	302.4	80.4–82.1	22.5	756.0
33.4–35.1	9.5	319.2	82.2–83.9	23	772.8
35.2–36.9	10	336.0	84.0–85.7	23.5	789.6
			85.8–87.5	24	806.4

[a] For patients >60 kg, contact Medical Monitor.

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL −1 (MINUS ONE) = 0.45 MG/KG/DAY, 20 MG TABLETS

Cumulative weekly dose = 4.2 mg/kg/week

Doses to be administered on Days 1−21 of cycle; do not administer on Days 22−28.

Weight (kg)	Daily Dose for 7 days	Cumulative Weekly Dose (mg/wk)
20−22.2	1 tab 3 d/wk, 0 tab 4 d/wk	60
22.3−28.5	1 tab 4 d/wk, 0 tab 3 d/wk	80
28.6−34.9	1 tab 5 d/wk, 0 tab 2 d/wk	100
35.0−41.2	1 tab 6 d/wk, 0 tab 1 d/wk	120
41.3−47.6	1 tab daily	140
47.7−53.9	2 tab 1 d/wk, 1 tab 6 d/wk	160
54.0−60.3	2 tab 2 d/wk, 1 tab 5 d/wk	180
60.4-66.6	2 tab 3 d/wk, 1 tab 4 d/wk	200
66.7−73.0	2 tab 4 d/wk, 1 tab 3 d/wk	220
73.1−79.3	2 tab 5 d/wk, 1 tab 2 d/wk	240
79.4−85.7	2 tab 6 d/wk, 1 tab 1 d/wk	260
85.8−92.0	2 tab daily	280
92.1−98.4	3 tab 1 d/wk, 2 tab 6 d/wk	300
98.5−104.7	3 tab 2 d/wk, 2 tab 5 d/wk	320
104.8−111.1	3 tab 3 d/wk, 2 tab 4 d/wk	340
111.2−117.4	3 tab 4 d/wk, 2 tab 3 d/wk	360
117.5−123.8	3 tab 5 d/wk, 2 tab 2 d/wk	380
123.9−130.1	3 tab 6 d/wk, 2 tab 1 d/wk	400
130.2−136.5	3 tab daily	420
> 136.5	Contact Medical Monitor	

Appendix 10
Dosing Tables for Cobimetinib (cont.)

DOSE LEVEL −1 (MINUS ONE) = 0.45 MG/KG/DAY, SUSPENSIN (4.8 MG/ML)

Doses to be administered on Days 1−21 of cycle; do not administer on Days 22−28.

Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)	Weight (kg)	Daily Dose (mL)	Cumulative Weekly Dose (mg)
<10.2	Call Medical Monitor		50.7−55.9	5	168.0
10.2−11.1	1.0	33.6	56.0−61.3	5.5	184.8
11.2−12.2	1.1	37.0	61.4−66.6	6	201.6
12.3−13.3	1.2	40.3	66.7−71.9	6.5	218.4
13.4−14.3	1.3	43.7	72.0−77.3	7	235.2
14.4−15.4	1.4	47.0	77.4−82.6	7.5	252.0
15.5−16.5	1.5	50.4	82.7−87.9	8	268.8
16.6−17.5	1.6	53.8	88.0−93.3	8.5	285.6
17.6−18.6	1.7	57.1	93.4−98.6	9	302.4
18.7−19.7	1.8	60.5	98.7−103.9	9.5	319.2
19.8−20.7	1.9	63.8	104.0−109.3	10	336.0
20.8−22.3	2.0	67.2	109.4−114.6	10.5	352.8
22.4−24.5	2.2	73.9	114.7−119.9	11	369.6
24.6−26.6	2.4	80.6	120.0−125.3	11.5	386.4
26.7−28.7	2.6	87.4	125.4−130.6	12	403.2
28.8−30.9	2.8	94.1	>130.6	Call Medical Monitor	
31.0−34.6	3.0	100.8			
34.7−39.9	3.5	117.6			
40.0−45.3	4	134.4			
45.4−50.6	4.5	151.2			

Appendix 11
List of Moderate and Strong CYP3A Inducers and Inhibitors That Are to Be Excluded in Dose Escalation Patients When Determining MTD

Based on in vitro studies, cobimetinib is a substrate of CYP3A. Cobimetinib exposures were significantly increased in presence of a strong CYP3A inhibitor (itraconazole) in healthy subjects. Hence, strong and moderate inhibitors or inducers of CYP3A are excluded in this study.

CYP3A STRONG INHIBITORS

- Clarithromycin
- Conivaptan
- Indinavir
- Ketoconazole
- Nefazodone
- Posaconazole
- Ritonavir
- Telaprevir
- Voriconazole

CYP3A MODERATE INHIBITORS

- Aprepitant
- Atazanavir
- Ciprofloxacin
- Darunavir
- Diltiazem
- Dronedarone
- Erythromycin
- Fluconazole
- Fosamprenavir
- Grapefruit Juice
- Imatinib
- Verapamil
- Diltiazem

CYP3A STRONG INDUCERS

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- St. John's Wort

CYP3A MODERATE INDUCERS

- Bosentan
- Efavirenz
- Etravirine
- Modafinil