STUDY TITLE: COBI-AVM STUDY – A PHASE 2 STUDY TO ASSESS THE SAFETY AND EFFICACY OF COBIMETINIB IN EXTRACRANIAL ARTERIOVENOUS MALFORMATIONS (AVM)

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ABBREVIATIONS

ACH	Arkansas Children's Hospital
ACRI	Arkansas Children's Research Institute
AE	Adverse Events
AESI	AEs of Special Interest
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AVM	Arteriovenous Malformations
AZD6244	Selumetinib (MEK inhibitor)
AZD8055	mTOR Kinase Inhibitor
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CK-MB	Creatine Kinase-Myocardial Band
CNS	Central Nervous System
COBI	Cobimetinib
CPK	Creatinine Phosphokinase
CR	Complete Response
CRF	Case Report Form
CSSCR	Central Serous Chorioretinopathy
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Case Transmission Verification
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
e.g.	(*exempli gratia*) For Example
EOT	End of Treatment
FDA	US Food and Drug Administration
FS	Fractional Shortening
g	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
GGT	Gamma-Glutamyl Transferase
hCG	Human Chorionic Gonadotropin
H&E	Hematoxylin and Eosin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IND	Investigational New Drug
IRB	Institutional Review Board
kg	Kilogram
LVEF	Left Ventricular Ejection Fraction
LVSF	Left Ventricular Systolic Function

MAP	Mitogen Activated Protein (MAP)
MAPK	Mitogen Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAP Extracellular Signal-Regulated Kinase 1
mg	Milligram
MOO	Manual of Operation
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
MUGA	Multiple-Gated Acquisition
NCI	National Cancer Institute
NRS-11	Numeric Rating Scale-11
ORRA	Office of Research Regulatory Affairs
OS	Overall Survival
PD	Progressive Disease
pERK	Plasma Extracellular Signal-Regulated Kinase
PFS	Progression-Free Survival
PI	Principal Investigator or Co-Principal Investigator
PI3K	Phosphatidylinositol 3-Kinase
PII	Pain Interference Index
PO4	Phosphate
PO	(*Per Os*) By Mouth
PR	Partial Response
PROMIS	Patient-Reported Outcomes Measurement Information System
QD	(*Quaque Die*) Once Daily
RAS	Rat Sarcoma gene
REDCap	Research Electronic Data Capture
RP2D	Recommended Phase 2 Dose
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SD	Stable Disease
SoC	Standard of Care
STIAMP	Suspected Transmission of Infectious Agent via a Medicinal Product
TEAE	Treatment-Emergent Adverse Event
TTP	Time to Progression
TTR	Time to Response
UAMS	University of Arkansas for Medical Sciences
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others

1. PROTOCOL SUMMARY

This trial is an open-label, single-site, Phase 2 study to evaluate the safety and efficacy of cobimetinib in extracranial arteriovenous malformations (AVM). Mitogen-activated protein kinase (MAPK) pathway activation has been reported in extracranial AVM. It will include children and adults with extracranial AVM. Cobimetinib will be given orally at the recommended phase 2 dose (RP2D). Safety monitoring will continue such that the study dose may be decreased based on frequencies of dose modifications, and/or discontinuation of cobimetinib due to adverse events (AEs). Response and disease progression will be assessed after 6 cycles, the end of the study after 12 cycles, and for 1 year following. Subjects will be followed for clinical and survival data a total of 2 years from the start of study entry or until subject withdrawal criteria have been met.

1.1 Study Population

Up to 17 subjects, children and adults with extracranial AVM will be recruited from Arkansas Children's Hospital (ACH) and University of Arkansas for Medical Sciences (UAMS).

1.2 Summary of Inclusion Criteria

Male or female patients, 2 years to 80 years of age, with volumetrically measurable extracranial AVM, the ability to take enteral medication, Karnofsky or Lansky performance status of ≥ 50% (as applicable), and adequate hematologic, cardiac, renal and liver function.

1.3 Summary of Exclusion Criteria

Patients with intracranial or metrically unmeasurable AVM, concomitant treatment (CYP3A4 inducers/inhibitors, chemotherapy, immunotherapy, targeted therapy, biological therapy, hematopoietic growth factor, hormonal therapy, corticosteroid therapy or other investigational therapy), active malignancy or secondary malignancy, current infection, HIV, significant ophthalmologic, cardiovascular, or malabsorptive disorders/conditions; or female patients who are pregnant or lactating. See eligibility criteria.

1.4 Experimental Design Schema

Cobimetinib will be administered at a maximal dose of 60 mg daily for 21 days on, then 7 days off, in a 28-day treatment cycle for 12 cycles (approximately 12 months). AVM evaluations will occur at baseline, Cycle 1, Day 1 (photographs only) the beginning of Cycle 7, the End of Treatment, and every 6 months during Long-Term Follow-Up. For subjects who cannot swallow pills, oral suspension will be used.

Table 1: Cobimetinib Schedule - (maximum 60 mg per dose)	
Days 1-21	0.8 mg/kg/dose orally daily (tablet) 1 mg/kg/dose orally daily (oral suspension)
Days 22-28	No therapy administered
Day 28	End of Cycle

2. BACKGROUND

2.1 Background/Rationale

Arteriovenous malformations (AVM) are congenital vascular anomalies that consist of abnormal connections between feeding arteries and veins.[1] They can occur anywhere in the body and cause progressive destruction to surrounding tissues, resulting in ulceration, bleeding, pain, and disfigurement.[2,3] These high flow vascular lesions also lead to severe, devastating functional and life-threatening consequences with heart failure, bleeding, and high mortality rates.[4] Due to the high-flow arterial component, AVMs are the most difficult to manage vascular anomalies.[5] Non-surgical treatment options are limited and have poor efficacy overall, leaving patients without good curative options.[6] Surgical excision of AVM is possible only for select patients, and comes with many risks, including severe hemorrhage, permanent nerve damage, systemic coagulopathy, disfigurement, pulmonary embolism, and recurrence.[7,8] Due to the infiltrative nature of AVM, normal tissue must be removed along with the malformation and patients are too often left with significant functional impairments, amputations, and the need for extensive reconstructive surgery.[9-11]

In the search of targets for alternative systemic therapies, research has identified underlying somatic mutations in AVM tissue in mitogen activated protein kinase 1 (MAP2K1), the gene that encodes MAP-extracellular signal-regulated kinase 1 (MEK1).[12,13] These mutations increase MEK1 activity and have also been found in cancers.[14-16] MEK1, a protein product of the MAP2K1 gene, is involved in the RAS/MAPK pathway and controls cellular process and development.[17] Several studies support potential efficacy of targeted MEK1 inhibition in tumors with MAP2K1 mutations.[18-22] Given the success of MEK1 inhibition with neoplasms housing these mutations, it is thought that MEK1 inhibitors may have clinical benefit in patients with extracranial AVMs with RAS/MAPK mutations. This study will test the potential toxicity and efficacy of cobimetinib, which targets MEK activation without paradoxical activation of the MAPK pathways in healthy cells. In addition, information about quality of life associated with cobimetinib treatment will be explored.

Cobimetinib is currently approved by the US Food and Drug Administration (FDA) as part of drug combination with vemurafenib for metastatic melanoma. Overall, the drug is well tolerated and the most common (≥ 20%) treatment-emergent adverse events (TEAEs) were diarrhea, photosensitivity, nausea, pyrexia, and vomiting. Phase I/II studies of the safety and pharmacokinetics of cobimetinib in pediatric and young adult subjects are ongoing.

2.2 Preclinical Studies

1. Antitumor Activity

There are several pre-clinical studies demonstrating efficacy of MEK inhibitors in pediatrics tumors with known RAS-ERK pathway aberrations. The MEK/ERK inhibitor U0126 has shown to inhibit growth of rhabdomyosarcoma both as a single agent *in vivo* and *in vitro* as well as in combination with dual PI3K/mTOR inhibitor PI103.[23] In addition, *in vitro* and *in vivo* synergy has also been seen between inhibitors of TORC1/2 (AZD8055), and MEK (AZD6244) in embryonal rhabdomyosarcoma.[24] Pre-clinical data also support potential activity for MEK inhibitors against neuroblastoma with MAPK gene mutations.[25] Lastly, NF-1 deficiency has shown to be predictive of sensitivity to MEK inhibitors *in vitro* in glioblastoma multiforme.[26] In preclinical studies, some MAP2K1 mutations are sensitive to MEK inhibition.[27,28]

2. Nonclinical Pharmacology

Nonclinical data show that cobimetinib is a potent and highly selective inhibitor of MEK1/2, resulting in inhibition of cellular phosphorylation of ERK1/2 and anti-proliferative activity in a variety of human tumor cell lines and tumor xenograft models. Cobimetinib accumulates in tumor xenografts and remains at high concentration in the tumor after plasma concentrations have declined.

The inhibition of ERK1 phosphorylation by cobimetinib correlates more closely with concentrations of cobimetinib in tumor tissues than in plasma; in general, there is a good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models.

The findings of *in vitro* and *in vivo* nonclinical safety pharmacology studies indicated a low potential for cardiovascular, neurobehavioral, or respiratory function in subjects.

3. Pharmacokinetics and Drug Metabolism in Animals

Nonclinical and *in vitro* metabolic profiling studies suggest that cobimetinib is a substrate for CYP3A4 and UGT2B7-mediated metabolism in human liver microsomes and recombinant enzymes; cobimetinib is an inhibitor of isozymes CYP2D6 and CYP3A4 *in vitro*. Cobimetinib is approximately 95% bound to human plasma proteins. The pharmacokinetics of cobimetinib has been characterized in multiple species including mice, rats, dogs, and monkeys as detailed below.

4. Animal Toxicology

The nonclinical toxicity of cobimetinib was characterized in single-dose and repeat-dose studies in rats and dogs, repeat-dose toxicity study in juvenile rats, reproductive and developmental studies in rats, genotoxicity studies including *in vitro* bacterial and mammalian genotoxicity bioassays and *in vivo* micronucleus assay in rats, and *in vitro* (3T3 mouse fibroblasts) and *in vivo* (pigmented rats) phototoxicity studies.

The nonclinical safety assessment for cobimetinib identified degenerative effects in multiple tissues that are clinically manageable and the potential for reproductive toxicity at therapeutically relevant exposures. It was not phototoxic or genotoxic *in vitro* or *in vivo*. When considered together with the clinical safety database and the intended treatment population, the results of the nonclinical toxicity program provide a safety profile that supports the use of cobimetinib in the treatment of cancers.

2.3 Adult Studies

1. Phase 1 Studies using Cobimetinib as Monotherapy

a. Study MEK4592g

As of the data cutoff date of 11 June 2013, 115 subjects were treated across all study Stages in Study MEK4592g, including 45 subjects treated with cobimetinib 60mg 21/7 QD (once daily) (Table 2).

b. Demographics and Baseline Characteristics

The population was comprised of subjects with diverse advanced solid tumors (Table 2). The median age in all subjects (n = 115) was 60 years (range: 25-82 years of age). Approximately one-half of all subjects (49.6%) were male, and the majority of all subjects (87%) were white. The mean number of prior chemotherapy and targeted regimens was 4.4 (range: 0-13) for all subjects. ECOG performance status was 1 (symptomatic, fully ambulatory) in 73.9% of all subjects. Overall, 14 subjects

(12.2%), including 7 who received cobimetinib 60 mg 21/7, had melanoma. Other tumor types treated on-study included colorectal cancer (37 subjects total), pancreatic cancer (7 subjects total) and other tumor types (57 subjects total).

c. Clinical Efficacy

The clinical efficacy of cobimetinib has been assessed in subjects with cancer in the study listed in **Table 2**.

Table 2: Clinical Studies of Cobimetinib

Study No.	Phase	n[a]	Subject Population
MEK4592g (single agent)	I	115 (in Stages I, IA, II, IIA, & III)	Phase I population with solid tumors including subjects with RAS/RAF mutant cancers during dose expansion

[a] *Indicates total subjects accrued on study and is not representative of an efficacy-evaluable population.*

d. Efficacy with Monotherapy Cobimetinib

Assessment of responses was an exploratory endpoint in Study MEK4592g. Best overall response was assessed for 74 of 97 subjects in Stages I, IA, II and IIA of the study who had measurable lesions and at least 1 post-baseline tumor assessment. Overall, 6 subjects (all of whom had melanoma; 6.2%) had a confirmed partial response (PR), 28 subjects (28.9%) had stable disease (SD), and 40 subjects (41.2%) had PD. Twenty-three subjects had non-measurable lesions or measurable lesions with no post-baseline tumor assessments.

In Stage III of Study MEK4592g, 18 subjects were accrued. Best overall response was assessed for 14 of 18 subjects in Stage III with measurable lesions and at least 1 post-baseline tumor assessment. Overall, 4 subjects (22.2%) had SD as their best overall response, 8 subjects (44.4%) had disease progression and 2 subjects (11.1%) had unconfirmed tumor response.

e. Dose-Limiting Toxicities (DLT)

Four DLTs were observed in Stage I (21/7 dosing schedule) of Study MEK4592g. At the 40-mg dose level, a DLT of Grade 4 hepatic encephalopathy and Grade 3 elevated ammonia was reported in a subject with pre-existing liver metastases. At the 60-mg dose level, a DLT of Grade 3 rash was reported that improved with skin toxicity management and drug holiday. At the 80-mg dose level, two DLTs were reported: 1 subject with Grade 3 diarrhea despite treatment with anti-diarrheal medications and 1 subject with Grade 3 rash.

Two DLTs were observed in Stage IA (14/14 dosing schedule) both at the 125-mg dose level. One subject had a Grade 3 rash and another had a Grade 3 blurred vision associated with neurosensory detachment of the retina.

f. Adverse Events (AEs)

TEAEs refer to AEs with onset on or after the date of first dose of cobimetinib. An overview of TEAEs, regardless of relationship to cobimetinib, with frequency 10% or greater in all subjects in Study MEK4592g is presented in **Table 3**. These are listed by System Organ Class and Preferred Term from MedDRA (Medical Dictionary for Regulatory Activities) v16.0. AEs are listed by frequency, representing adverse drug reactions (ADRs) for cobimetinib.

All subjects in Study MEK4592g experienced an AE. The most frequent AEs were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea (33.9%), vomiting (33.9% each), and edema peripheral (28.7%). Other events that occurred in ≥ 10% of subjects included anemia, abdominal pain constipation, hypokalemia, decreased appetite, headache, dizziness, back pain, increased aspartate aminotransferase (AST), dermatitis acneiform, pruritus, and dry skin. Amongst the subjects who received cobimetinib 60 mg 21/7, the most frequent TEAEs were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea (31.1%), edema peripheral (31.1%), and vomiting (28.9%).

Table 4 summarizes the Grade 3 or higher TEAEs affecting 2 or more of all subjects in study MEK4592g (n = 115) and of those who received cobimetinib 60mg 21/7 (n = 45). Amongst all cobimetinib-treated subjects, 5 subjects (4.3%) experienced a Grade 4 AE, and 53 subjects (46.1%) experienced a Grade 3 AE. The most frequent Grade 3 and Grade 4 AEs were hyponatremia (9.6%), fatigue (8.7%), anemia (7.8%), diarrhea (6.1%), and hypokalemia (6.1%). Grade 5 AEs, which in Study MEK4592g included disease progression reported as an AE, are discussed separately below.

Table 3: TEAEs Regardless of Relationship to Cobimetinib in ≥ 10% of Subjects in Study MEK4592g[1,2]

MedDRA System Organ Class and Preferred Term	60mg QD 21/7[3] (n = 45)	All subjects[4] (n = 115)
Subjects with at least one AE, n (%)	***45 (100)***	***115 (100)***
Blood & lymphatic system disorders	*9*	*26*
Anemia	8 (17.8)	21 (18.3)
Gastrointestinal disorders	*43*	*109*
Diarrhea	29 (64.4)	77 (67.0)
Nausea	14 (31.1)	39 (33.9)
Vomiting	13 (28.9)	39 (33.9)
Abdominal pain	6 (13.3)	28 (24.3)
Constipation	10 (22.2)	24 (20.9)
Stomatitis	4 (8.9)	14 (12.2)
General disorders & administration site conditions	*29*	*82*
Fatigue	22 (48.9)	58 (50.4)
Edema peripheral	14 (31.1)	33 (28.7)
Infections & infestations	*10*	*35*
Urinary tract infection	5 (11.1)	14 (12.2)
Investigations	*19*	*36*
Aspartate aminotransferase increased	5 (11.1)	12 (10.4)
Metabolism & nutrition disorders	*25*	*65*
Decreased appetite	11 (24.4)	27 (23.5)
Dehydration	10 (22.2)	27 (23.5)
Hypokalemia	5 (11.1)	14 (12.2)
Hyponatremia	4 (8.9)	12 (10.4)
Musculoskeletal & connective tissue disorders	*13*	*36*
Back pain	5 (11.1)	13 (11.3)
Nervous system disorders	*17*	*42*
Dizziness	7 (15.6)	21 (18.3)
Headache	3 (6.7)	14 (12.2)
Skin & subcutaneous tissue disorders	*35*	*84*
Rash	24 (53.3)	57 (49.6)
Dry skin	4 (8.9)	16 (13.9)
Dermatitis acneiform	8 (17.8)	13 (11.3)
Pruritus	4 (8.9)	13 (11.3)

1 Modified from Study MEK4592g Summary of Clinical Safety; Data cutoff: 11JUN2013
2 At each level of subject summarization, a subject is counted once if the subject experienced ≥ 1 events.
3 Subjects who received the proposed cobimetinib commercial dosing regimen (60 mg QD 21/7) (pooled from Stages I, IA, II, IIA & III).
4 Subjects who received cobimetinib on all schedules and doses (pooled from Stages I, IA, II, IIA & III).

Table 4: Grade 3 or Greater TEAEs in Study MEK4592g[1,2]

MedDRA System Organ Class and Preferred Term	60mg QD 21/7[3] (n = 45)	All Subjects[4] (n = 115)
Subjects with at least one ≥ Grade 3 AE, n (%)	***26 (57.8)***	***75 (65.2)***
Blood & lymphatic system disorders	*2*	*11*
Anemia	2 (4.4)	9 (7.8)
Leukopenia	1 (2.2)	2 (1.7)
Lymphopenia	1 (2.2)	2 (1.7)
Cardiac disorders	*1*	*4*
Cardio-respiratory arrest	0	2 (1.7)
Gastrointestinal disorders	*9*	*26*
Diarrhea	0	7 (6.1)
Abdominal pain	3 (6.7)	5 (4.3)
Gastrointestinal hemorrhage	0	2 (1.7)
Ileus	1 (2.2)	2 (1.7)
Intestinal obstruction	1 (2.2)	2 (1.7)
General disorders & administration site conditions	*6*	*13*
Fatigue	6 (13.3)	10 (8.7)
Chest pain	0	2 (1.7)
Hepatobiliary disorders	*1*	*4*
Bile duct obstruction	0	3 (2.6)
Infections & infestations	*2*	*6*
Urinary tract infection	2 (4.4)	3 (2.6)
Pneumonia	0	2 (1.7)
Investigations	*7*	*14*
Aspartate aminotransferase increased	1 (2.2)	3 (2.6)
Blood creatinine phosphokinase (CPK) increased	2 (4.4)	3 (2.6)
Electrocardiogram QT prolonged	2 (4.4)	3 (2.6)
Gamma-Glutamyl Transferase increased	1 (2.2)	3 (2.6)
Alanine aminotransferase increased	0	2 (1.7)
Blood bilirubin increased	1 (2.2)	2 (1.7)
Blood lactate dehydrogenase increased	1 (2.2)	2 (1.7)
Metabolism & nutrition disorders	*7*	*21*
Hyponatremia	4 (8.9)	11 (9.6)
Hypokalemia	2 (4.4)	7 (6.1)
Dehydration	2 (4.4)	5 (4.3)
Hypophosphatemia	0	3 (2.6)
Neoplasms benign, malignant & unspecified (including cysts & polyps)	*4*	*7*
Malignant neoplasm progression	1 (2.2)	2 (1.7%)
Nervous system disorders	*1*	*7*
Syncope	0	5 (4.3%)
Respiratory, thoracic & mediastinal disorders	*7*	*10*
Respiratory arrest	3 (6.7)	3 (2.6%)
Skin & subcutaneous tissue disorders	*2*	*8*
Rash	0	5 (4.3%)
Vascular disorders	3	10
Hypertension	2 (4.4)	4 (3.5%)
Deep vein thrombosis	1 (2.2)	3 (2.6%)

1 Modified from Study MEK4592g Summary of Clinical Safety; Data cutoff: 11JUN2013
2 At each level of subject summarization, a subject is counted once if the subject experienced ≥ 1 events.
3 Subjects who received the proposed cobimetinib commercial dosing regimen (60 mg QD 21/7) (pooled from Stages I, IA, II, IIA & III).
4 Subjects who received cobimetinib on all schedules and doses (pooled from Stages I, IA, II, IIA & III).

g. Serious Adverse Events (SAEs)

A total of 49 subjects (42.6%) experienced an SAE. The most common types of SAE were GI disorders (n = 17), but there were no trends in specific preferred terms. The GI SAEs, such as intestinal obstructions and GI hemorrhages, occurred in subjects with GI malignancies. SAEs reported for more than 2 subjects among all subjects in the study were anemia, bile duct obstruction, dehydration, syncope, and respiratory arrest (3 subjects each [2.6%]).

h. Deaths

Study MEK4592g accrued a subject population with metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. In addition, in Study MEK4592g disease progression was reported as an AE (Grade 5) instead of an outcome measure.

As of the clinical-data cutoff date (11 June 2013), a total of 29 subjects (25.2%) had died, including 11 subjects in the cobimetinib 60 mg QD 21/7 group.

A total of 14 deaths were reported for subjects treated in Stage I of the study. With the exception of 1 subject who died of cardiopulmonary arrest secondary to PD, all Stage I deaths occurred because of PD. No death was considered by the investigator to be related to cobimetinib.

During Stage IA, II, and IIA of the study, 12 deaths were reported, all of which occurred ≤ 30 days after the last dose of cobimetinib. Of these, 2 deaths were considered by the investigator to be possibly related to cobimetinib. In both cases, the investigator considered the metastatic cancer to be a contributing etiologic factor to the subject's death.

Three deaths were reported in Stage III of this study. None was assessed by the investigator as treatment related. Other contributing etiologic factors to the deaths included the subjects' underlying diseases and malignant tumor progression.

An additional 6 subjects continued in study MEK4592g beyond the data cutoff date of 11 June 2013 and were summarized in the final CSR (16 December 2014). There were no deaths reported. No new safety trends were observed for cobimetinib in the data reviewed for the final CSR, and the safety findings were consistent with those observed in the previous CSRs for Study MEK4592g.

2.4 Pediatric Studies (subjects < 18 years old)

A Phase I/II Multicenter, open-label, dose-escalation study (NCT02639546) was conducted to evaluate the safety and pharmacokinetics of cobimetinib in pediatric and young adult subjects with previously treated solid tumors. The MTD for pediatric subjects receiving cobimetinib oral suspension is 1 mg/kg/dose PO daily for 21 days of a 28-day cycle, which was declared on June 22, 2018. A separate dose escalation was performed for the tablet formulation with an MTD of 0.8 mg/kg. An expansion cohort was opened for subjects with low-grade gliomas and known RAS/RAF/MEK/ERK pathway activation, and is currently closed to enrollment but open until follow up is completed with results pending.

3. OBJECTIVES AND ENDPOINTS

3.1 Specific Hypothesis

Subjects with extracranial AVM with MAPK pathway mutations will experience an objective response when treated with cobimetinib.

Table 5: Level of Response Based on Volumetric Data Analysis	
Complete Response (CR)	Complete resolution of the target AVM
Partial Response (PR)	≥ 20% reduction in the volume of the target AVM
Stable Disease (SD)	< 20% increase or < 20% decrease in the volume of the target AVM
Progressive Disease (PD)	≥ 20% increase in the volume of the target AVM

3.2 Primary Objective

1. To determine the overall response rate to cobimetinib in children and adults who have extracranial AVM that is measurable by volumetric magnetic resonance imaging (MRI/MRA or Computed Tomography (CT)/Computed Tomography Angiography (CTA)).

3.3 Secondary Objectives

1. To determine the clinical and radiologic response rates of subjects with extracranial AVM to cobimetinib
2. To estimate progression free survival (PFS) in subjects with extracranial AVM treated with cobimetinib
3. To identify the nature and severity of AEs in subjects with extracranial AVM treated with cobimetinib

3.4 Exploratory Objectives

1. To determine if identifiable MAP kinase alterations correlate with response to therapy
2. To determine the ability of pre-therapy plasma biomarkers to predict response to therapy
3. To determine the ability of serial plasma biomarkers to measure response to therapy

3.5 Primary Endpoints

1. Complete response (CR) or partial response (PR) rate compared to Baseline. Partial response is defined as a ≥ 20% reduction in target extracranial AVM volume.
2. Response will be determined by a blinded review of volumetric MRI/MRA or CT/CTA.

3.6 Secondary Endpoints

1. Duration of response (DOR) for subjects who meet criteria for objective response rate. Response will be determined by a blinded review of volumetric MRI/MRA or CT/CTA.
2. Time to response (TTR) defined as the time between first dose and the first date of objective response. Response will be determined by a blinded review of volumetric MRI and phase contrast magnetic resonance angiography (MRA) – 4D flow or CT and computed tomography angiography (CTA).
3. Time to progression (TTP) defined as the time from the first dose to the date of a ≥ 20% increase in AVM volume measure from Baseline. Evidence of progression or AVM growth will be determined by a blinded review of volumetric MRI/MRA or CT/CTA.
4. Comparison of AVM response to levels of plasma extracellular-signal-regulated kinase (pERK) and biomarkers indicative of inhibition of downstream targets of MAP2K1 (e.g., ERK phosphorylation). Biomarkers will be measured in blood and tissue.

5. PFS, defined as the time in months from the first dose to the date of a ≥ 20% increase in AVM volume from Baseline or death. Evidence of progression or AVM growth will be determined by a blinded review of volumetric MRI/MRA or CT/CTA.
6. Change from Baseline in AVM-associated disfigurement using standardized photography and/or clinical exam reviewed by physicians familiar with the condition, centrally reviewed. For subjects with extracranial AVMs visible and amenable to photography, changes in visible AVM aspects will be evaluated by reviewer.
7. Incidence of treatment-emergent AEs (TEAEs) with a 28-Day Post-Treatment Safety Follow-Up after discontinuation to a maximum of 13 months. AEs will be assessed according to toxicities graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
8. Change from Baseline in pain as measured by the Numeric Rating Scale-11 (NRS-11).
9. Change from Baseline in pain as measured by the Pain Interference Index (PII).
10. Change from Baseline in physical functional status as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS): physical function, mobility, and upper extremity short forms (8a and 8b).

4. PATIENT ELIGIBILITY

Up to 17 subjects, children and adults, age 2 years to 80 years, with extracranial AVM will be recruited from ACH and UAMS Clinics.

4.1 Inclusion Criteria

1. Age at study entry

- 2 years to 80 years of age

2. Diagnosis and Disease Status

- Extracranial AVM with volumetric measurable disease
  - AVM Tissue from a prior biopsy along with the corresponding pathology report will be required for histologic diagnosis and biomarker testing. If not available, a biopsy will be performed per standard of care (SoC).
    - If the diagnosis of the AVM is clinically and radiologically evident and the PI determines that the risk of the biopsy poses too much risk to the subject (e.g. risk of excessive bleeding), the biopsy may be exceptionally waived after notifying the Medical Monitor and Sponsor.

3. Able to take an enteral dose and formulation of medication

- Patient must be able to take an enteral dose and formulation of medication. Study medication is only available as an oral suspension or tablet to be taken by mouth.

4. Performance Level (See Appendix B)

- Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50% for patients ≤ 16 years of age

5. Organ Function Requirements:

a. <u>Adequate Hematologic Function Defined as:</u>

- ANC ≥ 0.75 x 109/L (unsupported/without growth factor stimulant in past 7 days)
- Platelet count ≥ 75 x 109/L (unsupported/without transfusion in past 7 days)
- Hemoglobin ≥ 8 g/dL (unsupported/without transfusion in past 7 days)

b. Adequate Renal Function Defined as:

- Calculated creatinine clearance (or radioisotope GFR) ≥ 70 mL/min/1.73m^2 or serum creatinine based on age/gender as follows:

Table 6: Maximum Serum Creatinine (mg/dL)		
Age	**Male**	**Female**
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

c. Adequate Liver Function Defined as:

- AST and ALT ≤ 2.5x upper limit of normal (ULN) for age
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age

d. Adequate Cardiac Function Defined as:

- Fractional shortening (FS) of ≥ 30% or ejection fraction of ≥ 50% by echocardiogram (ECHO) at Baseline, as determined by echocardiography within 21 days prior to study entry.

6. Pregnancy/Birth Control

- Female patients of childbearing potential (FOCBP) require a negative urine or serum pregnancy test at Baseline, within one week (7 days) prior to the start of each cycle, at the End of Treatment (EOT) visit, the 28-Day Post-Treatment Safety Follow-Up (Safety Follow-Up) visit and the Long-Term Follow-Up (LTFU) visit 1.
- FOCBP and female partners of male patients who are pregnant or could become pregnant (i.e., females childbearing potential) must agree to follow the contraceptive requirements using two forms of effective contraceptive methods (one of which must be a barrier method) for the duration of the study treatment and for at least 3 months after the last dose of cobimetinib to avoid pregnancy and/or potential adverse effects on a developing embryo. Agreement to true abstinence (not periodic abstinence or withdrawal method) is an acceptable method of birth control.
- Patients must also agree not to donate eggs (female patients) or sperm (male patients) during this study and for at least 3 months after the last dose of cobimetinib.

4.2 Exclusion Criteria

1. Diagnosis and Disease Status

- Intracranial or metrically unmeasurable AVM

2. Prior and Concomitant Use of Drugs with CYP3A4 inducing/inhibiting activity

- Patients taking strong inducers or inhibitors of CYP3A4 within 14 days prior to study entry, including but not limited to erythromycin, clarithromycin, ketoconazole, azithromycin, itraconazole, grapefruit juice, or St. John's Wort. Appendix A includes a list of other known CYP3A4 inducers and inhibitors that should be discontinued at least 14 days prior to initiation of cobimetinib and avoided during study participation, if reasonable alternatives exist.

3. Prior Therapy Restrictions

- Completion of previous chemotherapy, immunotherapy, or targeted therapy for extracranial AVM with resolution of all associated toxicity to ≤ Grade 1 (except for alopecia and ototoxicity, which do not need to be resolved ≤ Grade 1) at least 28 days prior to study entry (except if otherwise specified below). Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to study entry. If, after the required timeframe, the laboratory eligibility criteria are met, the patient is considered to have recovered adequately.
- Treatment with a long-acting hematopoietic growth factor within 14 days prior to initiation of cobimetinib or a short-acting hematopoietic growth factor within 7 days prior to study entry
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives), immunotherapy, biologic therapy, investigational therapy, or herbal cancer therapy within 28 days or < 5 half-lives, whichever is longer, prior to study entry.
- Corticosteroid therapy < 0.5 mg/kg/day averaged during the month prior to study entry is permissible but must be discontinued 14 days prior to study entry.

4. Exclusions for other illness

- Active malignancy or history of secondary malignancy
- History of severe hypersensitivity reactions to components of cobimetinib
- Refractory nausea and vomiting, malabsorption, external biliary shunt
- Patients who have a known active infection (excluding documented fungal infection of the nail beds) within 28 days prior to study entry that has not completely resolved.
- Major surgical procedure or significant traumatic injury within 28 days prior to study entry, or anticipation of the need for major surgical procedure during the course of the study. Placement of a vascular access device or minor surgery is permitted within 14 days of study entry (provided the wound has healed).
- History of significant bowel resection that would preclude adequate absorption or other significant malabsorptive disease
- History of pneumonitis
- Ophthalmologic considerations: Patients with known significant ophthalmologic conditions or known risk factors for retinal vein occlusion are not eligible. Specifically, patients with a history of retinal vein occlusion (RVO), retinal detachment, retinal pathology on ophthalmologic exam, retinopathy of prematurity, central serous chorioretinopathy (CSSCR), neovascular retinopathy, intraocular pressure > 21 mmHg, and predisposing factors to RVO (e.g., uncontrolled hypertension, diabetes, or hyperlipidemia, coagulopathy) will be excluded.
- Any other disease, metabolic or psychological dysfunction, physical examination or clinical laboratory finding giving reasonable suspicion of a disease or condition that in the opinion of the Investigator's judgement contraindicates use of an investigational drug or places the patient at unacceptable risk from treatment complications.
- History of clinically significant cardiac dysfunction, including the following:
  - Clinically significant cardiac arrhythmias or unstable arrhythmia including bradyarryhthmias and/or patients who require anti-arrhythmic therapy (with the exception of beta-blockers or digoxin). Patients with controlled atrial fibrillation are not excluded.
  - Unstable angina, or new-onset angina within 3 months prior to initiation of cobimetinib,

  - Symptomatic congestive heart failure, defined as New York Heart Association Class II or higher,
  - Myocardial infarction within 3 months prior to initiation of cobimetinib.
- Known chronic human immunodeficiency virus (HIV)
- History of ≥ Grade 2 central nervous system (CNS) hemorrhage or history of any CNS hemorrhage within 28 days of study entry
- Female patients who are pregnant or lactating. Pregnant or lactating women will not be enrolled in this study because there is no available information regarding human fetal or teratogenic toxicities.
- Patient has received treatment with investigational therapy within 4 weeks prior to initiation of cobimetinib.

5. INVESTIGATIONAL DRUG

Cobimetinib fumarate is a kinase inhibitor indicated for the treatment of unresectable or metastatic melanoma a with BRAF V600E or V600K mutation (not for wild-type BRAF mutations). This fumarate salt appears as a white to off-white solid and exhibits a pH -dependent solubility.

Cobimetinib IDP will be supplied in two formulations:
- Tablet: 20 mg, round film-coated, immediate-release tablets
- Oral Suspension: 250 mg, multi-dose container of powder for oral suspension

Cobimetinib will be administered at a maximal dose of 60 mg daily for 21 days on, then 7 days off, in a 28-Day treatment cycle for 12 cycles (approximately 12 months). Cobimetinib should be taken once daily at approximately the same time each day, and no later than 4 hours after the scheduled time. Cobimetinib can be taken with or without a meal. **Cobimetinib tablets should never be chewed, cut, or crushed.** Therapy may continue for up to 12 cycles provided the subject meets the criteria for starting subsequent cycles and does not meet any of the criteria for cobimetinib discontinuation. At least 7 days off cobimetinib (within +7 days) is required prior to starting a new treatment cycle.

Table 1: Cobimetinib Schedule - (maximum 60 mg per dose)	
Days 1-21	0.8 mg/kg/dose orally daily (tablet) 1 mg/kg/dose orally daily (oral suspension)
Days 22-28	No therapy administered
Day 28	End of Cycle

Adult dosing (≥ 18 years old) will be 60 mg orally once daily (tablet formulation).

Due to different MTDs for suspension and tablet in the pediatric population, pediatric subjects (< 18 years old), < 75kg, will be required to take the oral suspension. Pediatric dosing will be 1 mg/kg/dose (maximum 60 mg per dose) orally once daily (oral suspension formulation). An exception may be made if the pediatric subject's weight is ≥ 75kg. In this case, the pediatric subject may be prescribed tablets (maximum 60 mg per dose) instead of the oral suspension.

For subjects who cannot swallow pills (regardless of weight/age), the oral suspension will be used.

Cobimetinib is manufactured for and distributed by Genentech USA, Inc. (San Francisco, CA, USA). It will be provided to the ACH Research Pharmacy and stored at 2°C-25°C. Please refer to the Cobimetinib Investigator's Brochure (COBI IB) for preparation and storage condition details.

6. TREATMENT PLAN

6.1 Registration, Enrollment, and Screening

Subjects may be recruited from ACH or UAMS clinics (e.g., Vascular Anomalies, ENT, Hematology, or Interventional Radiology) who see patients with vascular anomalies. Potential subjects at ACH or UAMS may be identified by their clinical providers or delegated study staff during routine clinic visits or medical record review. Existing patients at ACH or UAMS identified during record review who potentially qualify for the study may be contacted by delegated study staff via phone or email. Delegated study staff from ACH or UAMS will present the study to all potential subjects. Potential subjects who learn of the study from outside sources (e.g. ClinicalTrials.gov) may also contact the study team regarding participation in the study. For non-ACH patients, medical records will be requested using an approved process for obtaining protected health care information. All consenting and study evaluations/assessments will be performed at ACH.

All potential subjects and parents/legally authorized representatives (LARs) of minor subjects must sign the informed consent form (ICF) approved by the Institutional Review Board (IRB) prior to any study-specific screening procedures being performed. All consented subjects will be registered on the study, assigned a study-specific ID, and screened for study eligibility. All screening evaluations must be completed and verified by the investigator. All subjects who sign an ICF are enrolled in the study. The ***enrollment*** is the date the subject signs the ICF. The ***study entry*** is defined as the time the subject is determined to be eligible for study participation and scheduled for study treatment.

Subjects who meet all eligibility criteria will then be entered into the study and scheduled for protocol therapy. Subjects will begin cobimetinib upon successful completion of screening tests (i.e. safety assessments). Protocol therapy must be started no later than 5 calendar days after the date of study entry. Subjects who do not meet eligibility criteria or fail to be started on cobimetinib for any reason will be considered a screen failure. Screen failures will be replaced and therefore will not be counted towards study accrual.

All clinical and laboratory studies to determine eligibility (Baseline screening evaluations) must be performed within 21 calendar days prior to study entry, unless otherwise indicated. If AVM tissue is not available from a prior biopsy, an AVM biopsy must be performed at Baseline per SoC (unless determined by the PIs the biopsy poses too much risk to the subject). If a subject has a laboratory result(s) that does not meet eligibility criteria, the screening period may be extended an additional 21 days and the test(s) repeated. The test(s) may be repeated as soon as the investigator believes the re-test result(s) is likely to be within the acceptable range to meet eligibility criteria. In this case, the subject will not be required to sign another ICF, and the original assigned subject ID will be retained.

Conversely, if the laboratory test(s) cannot be performed in the 21-day extended screening period, the re-test(s) does not meet eligibility criteria, or other eligibility criteria are no longer met, the subject will be a screen failure and must be withdrawn from the study. However, the subject may be considered for re-enrollment if eligibility criteria are met in the future.

During the screening period, laboratory values used to assess eligibility must be no older than 7 days at the start of therapy (Cycle 1, Day 1). Laboratory tests need not be repeated if therapy starts within 7 days of obtaining labs to assess eligibility. Cardiac evaluations must be obtained within 21 days prior to study entry. Imaging studies must be obtained within 45 days prior to study entry (repeat AVM imaging if necessary).

Clarification in timing when counting days: For example, please note that if the subject's last day of prior therapy is September 1st, the protocol requires waiting at least 7 days inclusive for that type of prior therapy; therefore, that subject cannot be enrolled until September 9th.

Important note: All clinical and laboratory data required for determining eligibility of a subject enrolled on this trial must be available in the subject's medical or research record which will serve as the source document for verification at the time of monitoring visits or audits.

6.2 Treatment Period

The *Treatment Period* is defined as the time of the first cobimetinib administration (Cycle 1, Day 1) until cobimetinib discontinuation (End of Treatment (EOT) visit). Study evaluations/assessments will be performed at the times specified in the Schedule of Events. Evaluations/assessments should be completed prior to dosing on the visit day unless otherwise specified. Pregnancy tests are to be performed within 7 days prior to each protocol-specified timepoint. With the exception of Cycle 1, laboratory tests should be administered within ±3 days of the protocol-specified day. Cycle 1 bi-weekly assessments and laboratory tests must be performed within ±1 day of the protocol-specified day. Other study evaluations/assessments are to be performed within ±7 days of the protocol-specified day.

Subjects will be given diaries to record the cobimetinib doses with the date/time of each dose and missed doses. The date/time of missed doses should be recorded, including vomited doses with approximate time after ingestion. These diaries will be used to track compliance with study treatment. Diaries and empty cobimetinib containers will be collected at the completion of each cycle.

6.3 Patient Reported Outcomes (PROs)

The change from Baseline in pain and physical functions will be measured with three patient-reported outcome (PRO) questionnaires recommended as a core outcome measures for clinical trials in children and adults with Neurofibromatosis 1: the NRS-11 for pain intensity, the PII for pain interference, and the PROMIS for physical functioning.[30]

Paper PROs will be completed by subjects ≥ 6 years and, if required, parent proxy (subjects ≥ 5 to ≤ 17 years) prior to all other study assessments at the required visits to minimize subject bias. The age-specific PRO will be determined at Screening/Baseline. The subject must be administered the same age-specific PRO at all required visits, regardless of the age at the time of administration. The same parent/LAR should be administered the Parent Proxy PRO throughout the study.

1. Numerical Rating Scale-11 (NRS-11)

The NRS-11 is a self-report segmented 11-point numeric scale that assesses pain severity over the past 24 hours. Subjects ≥ 8 years of age will be administered the NRS-11 as a self-report, which takes < 1 minute. Subjects are asked to select the one number from 0 to 10 that best describes their worst pain over the past 24 hours for target tumor pain with 0 representing "no pain" and 10 representing "worst pain you can imagine".

2. Pain Interference Index (PII)

The PII assesses self-reported consequences of pain on relevant aspects of one's life, including pain interference with activities, spending time with family/friends, mood, sleep, and attention, over the past 7 days. The PII is universal rather than disease-specific. Subjects ≥ 6 years of age will complete a self-report PII (PROMIS® Item Bank v1.1 - Pain

Interference - Short Form 8a). Parents/LARs of subjects ≥ 6 to ≤ 17 years of age will complete the Parent Proxy PII in parallel (PROMIS® Parent Proxy Item Bank v2.0 - Pain Interference - Short Form 8a).

3. Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS for physical functioning forms measure self-reported capability rather than actual performance of physical activities, including the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living (ADLs), such as running errands. The PROMIS Physical Function - Mobility Short Forms measure self-reported activities of physical mobility such as getting out of bed or a chair to activities such as running. The PROMIS Physical Function - Upper Extremity Short Forms measure self-reported activities that require use of the upper extremity including shoulder, arm, and hand activities. Examples include writing, using buttons, or opening containers. A single Physical Function capability score is obtained from each short form.

All subjects ≥ 18 years will complete the self-report PROMIS® Item Bank v2.0 - Physical Function - Short Form 8b, regardless of target AVM location.

Subjects ≥ 8 to ≤ 17 years will complete the self-report PROMIS pediatric short forms specific to the morbid target AVM location. The parents/LARs will also complete the corresponding PROMIS parent proxy short forms. Subjects with upper extremity AVM will use the PROMIS® Pediatric Item Bank v2.0 - Upper Extremity - Short Form 8a in parallel with the PROMIS® Parent Proxy Item Bank v2.0 - Upper Extremity - Short Form 8a. Subjects with lower extremity AVM will self-report use the PROMIS® Pediatric Item Bank v2.0 - Mobility - Short Form 8a in parallel with the PROMIS® Parent Proxy Item Bankv2.0 - Mobility - Short Form 8a.

For subjects ≥ 5 to ≤ 7 years, only the parents/LARs will complete the PROMIS parent proxy short form specific to the location of the target AVM.

Table 7: Patient Reported Outcomes

Age (years)	NRS-11	PII		PROMIS	
	Self-Report	Self-Report	Parent Proxy	Self-Report	Parent Proxy
≤ 4	N/A				
5					X
≥ 6- to ≤ 7		X	X		X
≥ 8 to ≤ 17	X	X	X	X	X
≥ 18	X	X		X	

6.4 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the subject has at least SD and has again met laboratory parameters as defined in the eligibility section. If a lab value is outside the limits of eligibility, or laboratory values are older than 6 days, then the following labs must be re-tested within 48 hours prior to initiating therapy: complete blood count (CBC) with differential, bilirubin, AST, ALT, and serum creatinine. If the re-test is outside the limits of eligibility, the cobimetinib will be discontinued. Subjects who have discontinued cobimetinib are to be followed for a total of one year (12 months) from the last dose of cobimetinib or until subject withdrawal criteria have been met (see below).

6.5 End of Treatment (EOT) Visit

All subjects discontinuing cobimetinib, regardless of reason, should undergo treatment discontinuation procedures and evaluation as soon as possible after the decision to discontinue cobimetinib has been made. These include laboratory tests (CBC with differential, creatinine, ALT, AST, bilirubin, alkaline phosphatase, calcium, magnesium, phosphate, albumin, CPK), pregnancy test (serum or urine), AVM disease evaluation, ECHO, skin exam, ophthalmology exam, concomitant medication review, and collection/assessment of AEs (see Schedule of Events).

6.6 Follow-Up Period

1. 28-Day Post-Treatment Safety Follow-Up Visit (Safety Follow-Up)

Subjects will return for a Safety Follow-Up visit 28 days (±5 days) after the EOT for laboratory test (CBC with differential, creatinine, ALT, AST, bilirubin, alkaline phosphatase, calcium, magnesium, phosphate, albumin, CPK), pregnancy test (serum or urine), ECHO, ophthalmology exam, concomitant medication review, and collection/assessment of AEs (see Schedule of Events).

2. Long-Term Follow-Up (LTFU)

After cobimetinib discontinuation, all subjects will be followed every 3 months (±14 days) from the EOT Visit for blood samples (annually), AVM disease evaluation (every 6 months), skin exam, ophthalmology exam (LTFU Visit 1 and as clinically indicated), drug-related AEs, Overall Survival (OS), PFS, and start of any new anticancer therapies. A pregnancy test (serum or urine) will also be required at the first LTFU visit. LTFU will not stop due to initiation of a new anticancer treatment. Follow-up will continue every 3 months for up to 12 months after the last study dose (i.e., 3, 6, 9, and 12 months), unless the subject/parent withdraws consent/assent, the subject becomes lost to follow-up, or subject death.

In addition, subjects who discontinue cobimetinib prior to disease progression will require AVM disease evaluation as described below, using appropriate imaging modality or other indicated study every 6 months from cobimetinib discontinuation for 12 months after the last study dose, or until subject/parent withdraws consent/assent, subject becomes lost to follow up, or subject death, whichever occurs first. Survival/LTFU may be conducted by clinic visits, by record review (including public records) and/or telephone contact with the subject, family, or treating physician.

7. DOSE-LIMITING TOXICITIES AND DOSE MODIFICATIONS

7.1 Grading of AEs

Toxicities and AEs will be graded according to the NCI CTCAE v5.0. A copy can be downloaded from the Cancer Therapy Evaluation Program (CTEP) website (http://ctep.cancer.gov). All appropriate treatment areas will have access to the CTCAE v5.0.

Dose modifications, delays, and discontinuation of cobimetinib (study treatment) should be made based on the guidelines provided below (Table 8). *Dose modification* is a change in dosing, generally a reduction, from the starting dose of cobimetinib. *Dose delay* means temporarily stopping cobimetinib (i.e. holding the dose of cobimetinib) with or without a subsequent dose modification for a specified time period based on the specific toxicity. *Discontinuation* means permanently stopping cobimetinib. The dose modification guidelines are not intended to replace clinical judgment or dictate care of individual subjects. Should a

subject be dose-reduced and the reason for the reduction resolves, re-challenging with the previous dose level is allowable after approval by the Medical Monitor.

Table 8: Recommended Tablet Dose Levels for Dose Reductions	
Dose Reduction	**Cobimetinib**
Starting Dose	0.8 mg/kg daily (max dose 60 mg), 21 days on, 7 days off
Dose Level 1	0.6 mg/kg daily (max dose 40 mg), 21 days on, 7 days off
Dose Level 2	0.4 mg/kg daily (max dose 20 mg), 21 days on, 7 days off
Dose Level 3	Discontinue Therapy

Table 9: Recommended Oral Suspension Dose Levels for Dose Reductions	
Dose Reduction	**Cobimetinib**
Starting Dose	1 mg/kg daily (max dose 60 mg), 21 days on, 7 days off
Dose Level 1	0.8 mg/kg daily (max dose 40 mg), 21 days on, 7 days off
Dose Level 2	0.6 mg/kg daily (max dose 20 mg), 21 days on, 7 days off
Dose Level 3	Discontinue Therapy

7.2 Skin Toxicity

In the Phase I single-agent study (MEK4592g), reported rash events included rash (49.6% all grades, 4.3% ≥ Grade 3) and maculopapular rash (1.7% all grades, 0.9% ≥ Grade 3). No evidence of phototoxicity was observed with cobimetinib as a single agent.

The appearance of rash and other dermatologic events should be closely monitored. Subjects who develop mild-to-moderate skin toxicity may be treated with concomitant medications (e.g., topical agents, including topical steroids, or oral antibiotics) at the investigator's discretion. Skin toxicity should be managed per institutional guidelines.

1. Dose Modification Guidelines for Rash (≥ Grade 3)

The appearance of rash must be characterized as acneiform or non-acneiform. No change in cobimetinib dosing will be implemented for Grade ≤ 2 rash unless deemed intolerable by the investigator. Subjects will receive maximal supportive care per institutional guidelines.

2. Acneiform Rash

If acneiform rash ≥ Grade 3 occurs, hold dose until recovery to Grade ≤ 2 and reduce cobimetinib by 1 dose level, then restart cobimetinib on same schedule.

If acneiform rash ≥ Grade 3 recurs, then further reduce cobimetinib by another dose level (i.e. 20 mg once daily). If acneiform rash ≥ Grade 3 recurs despite second dose reduction, then discontinue cobimetinib.

If acneiform rash does not improve to ≤ Grade 3 within 28 days despite adequate supportive care, discontinue cobimetinib.

3. Non-acneiform or maculopapular rash

Cobimetinib dosing may continue without dose reduction.

7.3 Gastrointestinal Toxicity

1. Nausea and Vomiting

Nausea and vomiting were reported in the Phase I clinical trial (MEK4952g) with cobimetinib at the single-agent MTD of 60 mg on a 21/7 dosing schedule.

If a subject vomits after the dose, that dose should not be repeated. Instances where doses are missed because of vomiting should be recorded including date/time dose was vomited with approximate timeframe after ingestion. Nausea and vomiting should be managed according to institutional guidelines with adherence to recommendations on drugs to be avoided (see Section 8 below) while taking cobimetinib. Subjects should be monitored for symptoms of clinically significant volume depletion/dehydration and decreased oral intake.

2. Diarrhea

In the Phase I single-agent study (MEK4592g), diarrhea of any grade was reported in 67.0% of subjects, 6.1% of subjects experienced Grade 3 diarrhea, and no Grade 4 or 5 events were reported as of the data cutoff date. Serious events of diarrhea were reported in 1.7% of subjects. In the majority of cases, diarrhea was effectively managed with antidiarrheal agents and supportive care.

Diarrhea should be managed according to institutional guidelines. Subjects should receive supportive care as clinically indicated and be monitored for symptoms of clinically significant volume depletion/dehydration and decreased oral intake.

3. Dose Modification Guidelines for Diarrhea ≥ Grade 3

No change in cobimetinib dosing will be implemented for ≤ Grade 2 diarrhea unless deemed intolerable by investigator. Subjects should receive maximal supportive care.

If ≥ Grade 3 diarrhea occurs despite adequate supportive care, then hold cobimetinib.

If diarrhea improves to ≤ Grade 1 within 28 days, reduce cobimetinib by 1 dose level and then restart cobimetinib. If cobimetinib is held mid-cycle, cobimetinib may be restarted on the same schedule (cycle/day held) or a different schedule for that cycle, as determined by the investigator to be in the subject's best interest.

If diarrhea does not improve to ≤ Grade 1 within 28 days, then discontinue cobimetinib.

If the diarrhea ≥ Grade 3 recurs despite supportive care and dose reductions of 2 dose levels (i.e. 20 mg once daily), then discontinue cobimetinib.

4. Other Gastrointestinal Events

In single-agent cobimetinib studies in adults, other gastrointestinal (GI) events reported have included events of GI inflammation (reported as mucosal inflammation, mucositis, stomatitis, colitis, and GI ulceration), GI obstruction, and/or GI perforation.

Gastrointestinal toxicities will be managed according to institutional guidelines, with the exception of fluconazole for stomatitis, which will be replaced with a non-interacting agent. During the study, subjects are to receive supportive care as clinically indicated.

7.4 Ocular Toxicities

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed with MEK inhibitors, including cobimetinib. The majority of events in cobimetinib-treated subjects were reported as chorioretinopathy or retinal detachment. In MEK4592g, with ocular examinations prescribed for subjects reporting visual disturbances, 2.6% of subjects experienced serous retinopathy events, all of which were Grade 1 or 2.

Subjects with neurosensory detachment of the retina typically present with visual disturbances such as blurred vision, seeing spots, and photophobia; however, some subjects have been asymptomatic. Most of these cases have been reversible and most subjects were able to continue treatment at the same or reduced dose.

To address the potential ocular toxicity, subjects with a history of RVO or glaucoma, visible retinal pathology, intraocular pressure > 21 mmHg, and predisposing factors to RVO (e.g., uncontrolled hypertension, diabetes, or hyperlipidemia, coagulopathy) will be excluded. Subjects will be asked about any vision changes at each physical examination. All new subjects will have complete ophthalmologic examinations performed and interpreted by a qualified ophthalmologist, including visual acuity testing and all ophthalmologic evaluations per discretion of ophthalmologist to ensure evaluation of retina and visual function which may include intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. These complete ophthalmologic examinations will be performed at baseline, day 15 of cycle 1 (+/- 1 day), prior to the start of cycle 2, 4, 6, 9 and at EOT, Safety Follow-Up, LTFU Visit 1, and as clinically indicated if subjects note any visual disturbances.

Providers should be advised that subjects < 3 years of age are likely to require examination under anesthesia for successful evaluation.

For subjects reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, then hold cobimetinib until visual symptoms improve to ≤ Grade 1 per dose modification guidelines below.

1. Dose Modification Guidelines for Visual Symptoms (≥ Grade 2)

If ≥ Grade 2 visual AE occurs, then hold cobimetinib.

Consult ophthalmology and undergo complete ophthalmologic examination, which includes age- specific visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography.

If retinal vein occlusion (RVO) is diagnosed, then discontinue cobimetinib and start RVO treatment per institutional guidelines.

If neurosensory retinal detachment is diagnosed, hold cobimetinib until symptoms improve to ≤ Grade 1, and then reduce cobimetinib by 1 dose level. If visual symptoms ≥ Grade 2 recur despite dose reduction, then discontinue cobimetinib.

If RVO and neurosensory retinal detachment are not identified:

- If visual symptoms improve to ≤ Grade 1 within 28 days, then restart current cobimetinib dose and schedule.

- If visual symptoms do not improve to ≤ Grade 1 within 28 days, then discontinue cobimetinib.
- If visual symptoms ≥ Grade 2 recur, then reduce cobimetinib by 1 dose level.
- If visual symptoms ≥ Grade 2 recur despite dose reduction, then discontinue cobimetinib.

7.5 Liver Laboratory Abnormalities

In MEK4592g, there were no reported AEs or SAEs for clinically significant Grade 4 elevations in liver laboratory tests, and no subjects experienced findings suggestive of drug-induced liver injury or liver failure. Subjects must have adequate liver function, as manifested by measurements of total bilirubin, alkaline phosphatase (ALP), and hepatic transaminases, to be eligible for this study. Subjects with diseases that affect liver function should be excluded. Hepatic parameters should be assessed prior to each cycle of the study regimen.

1. Dose Modification Guidelines for Liver Laboratory Abnormalities

- If ≤ Grade 3 AE occurs, then continue current cobimetinib dose and schedule.
- If Grade 4 AE occurs, then hold cobimetinib.
- If the AE improves to ≤ Grade 1 within 28 days, then reduce cobimetinib by 1 dose level and restart cobimetinib on same schedule.
- If the AE does not improves to ≤ Grade 1 within 28 days, then discontinue cobimetinib.
- If Grade 4 AE recurs (a second time), then discontinue cobimetinib.

No dose modification is required for isolated GGT elevation in the absence of clinically significant above baseline grade in AST, ALT, ALP, and bilirubin.

7.6 Hypersensitivity

Cobimetinib is contraindicated in subjects with known hypersensitivity to cobimetinib or any of its ingredients. There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with subjects who have been exposed to cobimetinib monotherapy. These have appeared to be isolated reports, and in some cases occurred in subjects with histories of drug allergies. In reported cases occurring in subjects exposed to cobimetinib, signs, and symptoms of hypersensitivity or anaphylaxis improved or resolved after treatment with steroids and/or other medications as clinically indicated.

In study GO28141 involving cobimetinib in combination with vemurafenib, Grade 3 hypersensitivity events were reported for 3 patients in the cobimetinib plus 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 subjects who are suspected of experiencing a hypersensitivity reaction. Suspected hypersensitivity events in cobimetinib-treated subjects should be managed according to institutional guidelines, and subjects are to receive clinically indicated supportive care as well as diagnostic workups as indicated.

7.7 Cardiac Effects

In MEK4692g, there were no events in this risk category reported. A single case of symptomatic Grade 3 dilated cardiomyopathy has been reported in the Phase Ib trial (N025395) involving cobimetinib in combination with vemurafenib. No Grade 4 of 5 events of reduction in LVEF have been reported in single-agent cobimetinib clinical studies as of the data cutoff dates for the current investigational brochure. Decrease in left ventricular

ejection fraction (LVEF) from baseline has been reported in subjects receiving MEK inhibitors other than cobimetinib.

LVEF will be evaluated before initiation of treatment to establish Baseline values, then subsequently on Day 1 of Cycles 2, 4, 6, 8, 10, 12, EOT, and Safety Follow-Up (at a minimum), and as clinically indicated until treatment discontinuation. Subjects with Baseline LVEF lower than 50% will be excluded. Decrease in LVEF from Baseline can be managed using treatment delays, dose reduction, or treatment discontinuation. After treatment delays for decreases in LVEF, all subjects restarting treatment with a dose reduction of cobimetinib should have LVEF measurements taken at approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated until treatment discontinuation.

1. Dose Modifications for Reduction in Cardiac Function

Subjects who require dose reduction of cobimetinib should have LVEF or LVSF measurements at 2, 4, 10, and 16 weeks after diagnosis of decreased LVEF or FS. Subjects with symptomatic heart failure must discontinue cobimetinib.

Table 10: Dose Modifications for subjects with LVEF decreased from Baseline

Subject	LVEF value	Cobimetinib dose	LVEF value following treatment	Cobimetinib dose
Asymptomatic	50% (or 40 - 49% and < 10% absolute decrease from Baseline)	Continue current dose	N/A	N/A
	< 40% (or 40 - 49% and 10% absolute decrease from Baseline)	Hold treatment for 2 weeks	< 10% absolute decrease from Baseline	1st occurrence Reduce to 40mg
				2nd occurrence Reduce to 20mg
				3rd occurrence Discontinuation
			< 40% (or 10% absolute decrease from Baseline)	Discontinuation
Symptomatic	N/A	Hold treatment for 4 weeks	Asymptomatic and/or < 10% absolute decrease from Baseline	1st occurrence Reduce to 40mg
				2nd occurrence Reduce to 20mg
				3rd occurrence Discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from Baseline)	Discontinuation
			Symptomatic regardless of LVEF	

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%

7.8 Creatinine Phosphokinase (CPK) Elevation

Elevations in CPK have been observed in subjects receiving cobimetinib monotherapy. These events were not associated with rhabdomyolysis or myocardial injury. One event of rhabdomyolysis was reported in the Phase III Study G028141 (cobimetinib + vemurafenib), and rhabdomyolysis has been reported in post marketing experience. In Study G028141, CPK elevations was reported as an AE more frequently in subjects treated with cobimetinib + vemurafenib (32.4% all grades, 11.3% ≥ Grade 3) than with placebo + vemurafenib (8.1% all grades, 0% ≥ Grade 3).

Events of CPK elevation in cobimetinib-treated subjects should be monitored and managed according to institutional guidelines, and subjects are to receive maximal supportive care as well as diagnostic workups as clinically indicated.

1. Dose Modification Guidelines for CPK Elevation

Rule out cardiac cause (check electrocardiogram (ECG), serum cardiac troponin, and CK-MB fraction) and rule out rhabdomyolysis (clinical examination, serum creatinine, serum CPK, potassium, calcium, phosphorus, uric acid, albumin; and urine myoglobin). Consider discontinuation of cobimetinib if there is evidence of clinically significant cardiac injury or rhabdomyolysis. Assess subject for history of strenuous physical activity, blunt trauma, or recent intramuscular injections.

For asymptomatic Grade 3 CPK elevations that are deemed not clinically significant, continue current cobimetinib dose and schedule. Recheck CPK at least once a week. If CPK remains ≤ Grade 3, continue current cobimetinib dose and schedule.

For asymptomatic Grade 4 CPK elevations that are deemed not clinically significant, hold cobimetinib and recheck CPK within 3 days. If CPK improves to ≤ Grade 3, then reduce cobimetinib by 1 dose level and restart on the same schedule.

If Grade 4 CPK elevation recurs after dose reduction, then discontinue cobimetinib.

7.9 Other Grade 3 or 4 Non-Hematologic AEs Related to Cobimetinib

If ≥ Grade 3 related non-hematologic AE occurs, then hold cobimetinib.

If the AE improves to ≤ Grade 1 within 28 days, then reduce cobimetinib by 1 dose level and restart cobimetinib on the same schedule.

If the AE does not improve to ≤ Grade 1 within 28 days, or a Grade 3 or 4 AE recurs (a second time), then discontinue cobimetinib.

7.10 Special Patient Populations

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 subjects administered the 60-mg dose. In combination with embryo lethality observed in mice deficient in MEK-I due to reduced vascularization in the labyrinthine region of the placenta[31], inhibition of MEK by cobimetinib in humans is a potential risk for the developing fetus. Therefore, cobimetinib should not be administered to pregnant women, and women of childbearing potential should use effective birth control. FOCBP may be included in initial trials, provided they have a negative pregnancy test within 7 days prior to the start of each cycle and agree to use two forms of effective contraception while in the study.

It is not known whether cobimetinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious ADRs in nursing infants, cobimetinib should not be administered to nursing mothers.

Female subjects who become pregnant will discontinue cobimetinib. Female partners of male subjects receiving cobimetinib or within 90 days after the last dose and females subjects who become pregnant will be counseled on the risks of the pregnancy and possible effects of cobimetinib on the fetus. All efforts will be made to follow any pregnancies occurring in female subjects or female partners of males subjects during study participation and for at least 3 months following the last dose of cobimetinib.

Female subjects must not donate eggs during this study and for at least 3 months after the last dose of cobimetinib. Male subjects must not donate sperm during this study and for at least 3 months after your last dose of cobimetinib.

8. SUPPORTIVE CARE AND CONCOMITANT THERAPY GUIDELINES

8.1 Antimicrobial prophylaxis

Prophylaxis is not required or recommended as part of this study but is permissible per provider discretion.

8.2 Growth factor for neutropenia

We do not recommend routine use of G-CSF (filgrastim) in subjects with neutropenia. However, there may be clinical situations, which warrant consideration of its use, and this will be at the discretion of the treating provider. If G-CSF is utilized, subjects must be off this medication for at least 48 hours prior to initiation of the next cycle of cobimetinib.

8.3 Concomitant Therapy Restrictions

Cobimetinib is a substrate of CYP3A and thus has the potential to interact with inducers or inhibitors of CYP3A, therefore patients who are currently receiving such drugs are not eligible. Patients may be eligible if such therapies are discontinued at least 14 days prior to initiation of cobimetinib. Moderate to strong inhibitors or inducers of these enzymes should not be given while on study therapy (See Appendix A).

Strong inducers or inhibitors of CYP3A4 (including, but not limited to, St. John's wort and grapefruit juice) should not be given within 14 days prior to initiation of cobimetinib. See Appendix A for a list of agents.

Corticosteroid administration other than that prescribed on therapy is NOT permissible unless medically indicated (such as intractable nausea/vomiting unresponsive to all other antiemetic options). Hydrocortisone is permitted if indicated due to medical concern for adrenal insufficiency. Any steroid use other than hydrocortisone should be reported prior to start of steroid therapy to the PI with indication for use provided. Medical Monitor will approve or disapprove continuation on study with concurrent use of steroid medication after documentation is provided.

9. SCHEDULE OF EVENTS

	Eligibility/ Screening/ Baseline[1]	Cycle 1	Subsequent Cycles (Cycles 2-12)	End of Treatment Visit (±7 days)	28-Day Post-Treatment Safety Follow-Up Visit (±5 days)	Long-Term Follow-up (±14 days)
History/Physical Exam[2]/Vital Signs	X	Bi-weekly	X	X	X	
Cobimetinib		X	X			
Quality of Life Assessments[3]	X		X	X	X	
Karnofsky/Lansky Performance Status[4]	X			X	X	
Pregnancy Test[5]	X	X	X	X	X	X
Lab Tests[6, 7]	X	Bi-weekly	X	X	X	
Urinalysis	X			X	X	
AVM Disease Evaluation/Photographs[8]	X	X	X	X		X
AVM Tissue[9]	X					
Biomarker Blood Samples[10]	X		X	X		X
ECHO[11]	X		X	X	X	
Skin Examination/Evaluation[12]	X		X	X	X	X
Ophthalmologic Examination[13]	X	X	X	X	X	X
Concomitant medications[14]	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Disease Progression and Survival[15]						X
Dispense/review subject diary[16]		X	X	X		

[1] Subject must sign the ICF prior to screening/baseline. AVM imaging will be done within 45 days prior to study entry; labs within 7 days prior to study entry; and all other screening/baseline evaluations within 21 days prior to study entry.
[2] Physical Exam is to include height and weight at Baseline, prior to start of each Cycle treatment, at EOT, and Safety Follow-Up.
[3] Quality of Life Assessments include NRS-11 (self-report for subjects ≥ 8 years), PROMIS PII (self-report for subjects ≥ 6 years and parent proxy for subjects ≥ 6 - ≤ 17 years), and PROMIS (self-report for subjects ≥ 8 years and parent proxy for subjects ≥ 5 - ≤ 17 years).
[4] Karnofsky Scale for subjects > 16 years; Lansky Scale for subjects ≤ 16 years.
[5] Serum or urine pregnancy test for all FOCBP at Baseline, within 7 days prior to each Cycle, at EOT, Safety Follow-Up, & LTFU visit 1.
[6] Laboratory tests will include CBC with differential, creatinine, ALT, AST, total bilirubin, alkaline phosphatase, calcium, magnesium, phosphate, albumin, CPK. Labs will be performed at Baseline, bi-weekly (±1 day) during Cycle 1, Day 1 (±3 days) of Cycles 2-12, at EOT, and Safety Follow-Up.
[7] For subjects with Grade 4 neutropenia (neutrophil count decreased or febrile neutropenia), CBC with differential should be checked at least every other day until recovery to Grade 3 or until DLT criteria have been met based on investigator's clinical judgement. Dose modifications, delays, and discontinuation of cobimetinib should be managed according to Section 7.1.
[8] AVM Disease Evaluation, to be performed at Baseline, Cycle 7, and EOT, will include organ specific imaging (MRI/MRA or CT/CTA) as clinically indicated for the subject's disease. Baseline imaging of the subject's normal organ to be taken for comparison when amenable to imaging (i.e. If affected vessel is on right arm, left arm imaging to be done). Photographs of the AVM will be taken at Baseline, Day 1 (±7 days) of Cycle 1 & 7 and EOT. During LTFU, disease evaluation to be performed every 6 months (±14 days) from treatment discontinuation or at time of suspected relapse or progression. MRI/MRA or CT/CTA may be performed under anesthesia for if required for successful imaging.
[9] The AVM tissue along with the corresponding pathology report will be obtained from a prior biopsy or a biopsy performed at Baseline.
[10] For biomarkers testing, approximately 5-7 mL of blood will be collected at Baseline, Day 1 (±7 days) of Cycle 5 & 9, EOT, at time of progression or relapse, and LTFU Visit 4.
[11] ECHO are to be performed at Baseline (prior to Cycle 1), Day 1 (±7 days) of Cycles 2, 4, 6, 8, 10, & 12, EOT, and Safety Follow-Up. ECHO may be repeated more frequently if clinically indicated or if evidence of diminished LVEF or LVSF. After treatment delays for decreases in LVEF/LVSF, all subjects restarting treatment should have LVEF/LVSF measured at approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated until treatment discontinuation. If there are any significant findings and/or changes from Baseline, quantitative LVEF/LVSF will be performed at EOT if the most recent assessment is older than 12 weeks.
[12] Skin examinations are to be performed at Baseline prior to Cycle 1; Day 1 (±7 days) of Cycle 2, 4, 6, 8, 10, & 12, EOT, Safety Follow-Up, and LTFU; or more frequently as clinically indicated. These can be performed by the treating physician (dermatologist not required).
[13] Complete ophthalmologic exams are to be performed and interpreted by a qualified ophthalmologist at Baseline prior to Cycle 1, day 15 of cycle 1 (+/- 1 day), prior to start of cycle 2, 4, 6, 9, EOT, Safety Follow-Up, and LTFU; or more frequently as clinically indicated. Exams include visual acuity testing, as well as other ophthalmologic evaluations per discretion of ophthalmologist to ensure evaluation of retina and visual function which may include intraocular pressure measurement by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. Subjects < 3 years of age may require examination under anesthesia for successful evaluation.
[14] All concomitant medications started within 14 days prior to the Baseline visit and through the Safety Follow-Up must be recorded. Only concomitant anticancer medications will be collected during LTFU.
[15] Disease progression and survival status will be collected during LTFU every 3 months (at 3, 6, 9, and 12 months) after the last dose for up to 12 months or subject has died, withdrawn consent, or becomes lost to follow-up (whichever occurs first).
[16] Date/time of missed doses should be recorded in the diary, including vomited doses with approximate time after ingestion.

10. RISKS

For detailed information on toxicology, clinical and non-clinical studies, known precautions, warnings, and adverse reactions, refer to the current COBI IB. The following have been associated with cobimetinib either as monotherapy or in combination therapy.

Very common (≥ 10%)

Anemia, serous retinopathy (may include chorioretinopathy, blurred vision, halos, or other visual disturbances), diarrhea, nausea, vomiting, pyrexia, chills, increased AST, increased ALT, increased GGT, increased CPK, photosensitivity (includes photosensitivity reaction, sunburn, solar dermatitis, and actinic elastosis), maculopapular rash, dermatitis acneiform rash, rash, hyperkeratosis, hypertension, hemorrhage (may include melena, rectal hemorrhage, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, gingival bleeding, metrorrhagia, uterine hemorrhage, hemorrhagic ovarian cyst, menorrhagia, menometrorrhagia, vaginal hemorrhage, hemoptysis, pulmonary, cerebral, subarachnoid hemorrhage, subgaleal hematoma, hematuria, epistaxis, contusion, traumatic hematoma, ecchymosis, purpura, nail bed bleeding, ocular, eye, conjunctival, and retinal hemorrhage)

Common (> 10% to ≥ 1%)

Retinal detachment, visual impairment, decreased left ventricular ejection fraction, dehydration, hyponatremia, hyperglycemia, hypophosphatemia, basal cell carcinoma, cutaneous squamous cell carcinoma, keratoacanthoma, and pneumonitis

Uncommon (> 1% to ≥ 0.1%)

Rhabdomyolysis

11. INDIVIDUAL COBIMETINIB DISCONTINUATION AND SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time for any reason. Subjects should be informed of circumstances under which their participation may be terminated or the cobimetinib may be discontinued without their consent. The PI may withdraw subjects from the study in the event of intercurrent illness, AEs, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure or any reason the PI feels that it is in the best interest of the subject to discontinue the cobimetinib or be withdrawn from the study. Any reason for cobimetinib discontinuation or withdrawal from the study must be documented and explained to the subject.

If the reason cobimetinib is discontinued and/or a subject is withdrawn from the study is an AE, the specific event will be recorded on the case report form (CRF). The subject should be followed until the AE has resolved.

If a subject decides to withdraw or become lost to follow-up, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. The PI/study staff will make all reasonable efforts to contact the subject or a responsible relative by telephone followed by registered mail to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study.

11.1 Criteria for Individual Cobimetinib Discontinuation

Cobimetinib may be discontinued for any of the following reasons:

- Progressive disease at any point
- Completion of 12 cycles of cobimetinib
- Unacceptable toxicity (AEs requiring discontinuation of cobimetinib)
- Pregnancy
- Subject election to discontinue cobimetinib (for any reason)
- Physician's judgment
- Study is terminated by Sponsor (ORRA) or drug manufacturer (Genentech)

Subjects who have discontinued cobimetinib are to be followed for a total of one year (12 months) from the last dose of cobimetinib or until they meet the criteria for subject withdrawal from study (see below). Follow-up data will be required unless subject withdraws consent.

11.2 Criteria for Subject Withdrawal

- Death
- Lack of subject compliance with study procedures, as determined by the discretion of the investigator, that will impact subject safety or study integrity
- Lost to follow-up
- Withdrawal of consent for any further data collection
- Completion of LTFU

12. STATISTICAL CONSIDERATIONS

12.1 Primary analysis and sample size justification

The primary endpoint is the objective response, defined as observing a partial or a complete response, after 12 cycles of cobimetinib treatment. All subjects will be counted in the primary analysis. Subjects who dropout or are withdrawn due to toxicity/safety at any point, including before the first assessment, are considered evaluable. Subjects who voluntarily withdraw, unrelated to an AE, will be considered "non-evaluable," but still counted towards accrual. Additional subjects will be added such that 14 evaluable subjects will be reached. Assuming a dropout rate of 20%, we will enroll 17 subjects to have at least 14 evaluable subjects. A single-stage exact test of proportions is proposed to test the following hypotheses:

H_0: $\pi \leq 0.02$ versus
H_1: $\pi \geq 0.20$

Because there is no current standard of care pharmacological treatment for AVM, a very small objective response of 2% was chosen for the null rate. With N = 14 subjects, a one-sample, single stage exact test of proportions will have 80.2% power to detect differences in hypothesized rates of this magnitude or larger. The observed α-level of this test is approximately 3.1%. Given this sample size, the null hypothesis will be rejected if 2 or more responses are observed.

12.2 Analysis of secondary and exploratory endpoints

Demographic and medical characteristics of the sample will be summarized using means, standard deviations, medians, and ranges for continuous variables, and counts and percentages for categorical variables. No statistical testing will be performed on secondary endpoints; instead, analyses will be descriptive in nature. Kaplan-Meier methods will be used to estimate time-to-event distributions for DOR, TTR, TTP, and PFS. Median time-to-event and 95% confidence intervals will be reported from these distributions. The association between treatment response and pERK, as well as other downstream biomarkers of MEK,

will be assessed using logistic regression analysis. Each biomarker will be evaluated separately and resulting odds ratios and 95% confidence intervals will be presented.

13. RESPONSE CRITERIA

13.1 Volumetric Assessment

For the purpose of determining the level of response (complete, partial, etc.), measurements from the follow-up scans are compared to the target AVM size in the pretreatment MRI/MRA or CT/CTA scan using volumetric data analysis. DOR, TTR, TTP, and PFS will be determined by blinded review of the volumetric MRI/MRA or CT/CTA performed by local study radiologists (sub-investigators). All MRI/MRA scans will first be clinically evaluated by a local study radiologist per standard of care. After the unblinded clinical reading of the MRI/MRA or CT/CTA scans, the scans will be de-identified and placed in the queue for blinded review by local study radiologists with expertise in volumetric assessments. The study radiologists performing the volumetric assessments will not be involved in the clinical reading of the MRI/MRA or CT/CTA scans. A single primary radiologist will perform the volumetric measurements. Two other radiologists will independently verify the volumetric measurements for accuracy. The study radiologists performing the volumetric assessments will be blinded to the identity of the subject and prior response on study.

Table 5: Level of Response Based on Volumetric Data Analysis	
Complete Response (CR)	Complete resolution of the target AVM
Partial Response (PR)	≥ 20% reduction in the volume of the target AVM
Stable Disease (SD)	< 20% increase or < 20% decrease in the volume of the target AVM
Progressive Disease (PD)	≥ 20% increase in the volume of the target AVM

13.2 Biomarkers

Blood and tissues samples will be tested for biomarkers indicative of downstream targets of MEK (e.g., ERK phosphorylation) to evaluate their association with the observed clinical responses (e.g., AVM volume reduction) to cobimetinib and its metabolite(s). Approximately 5-7 mL of blood will be required at each collection time. Blood samples will be transported to UAMS Proteomic Core on dry ice. AVM tissue, up to 6 slides (2 H&E and 4 unstained) per subject, will be obtained at Baseline along with the corresponding pathology report from the ACH Anatomical Pathology.

13.3 Photography of AVM

Photography will be performed if target AVM and/or its effects are visible and amenable to photography. The change in AVM-disfigurement from Baseline will be determined by unblinded review performed by physicians (sub-investigators) who are familiar with the condition. The physicians performing the disfigurement assessment will not be blinded. Photographs will be taken and uploaded into Epic per SoC; however, any photographs in the research record will be coded. Measures will be taken to protect subjects' confidentiality and prevent identification of the subjects from the photographs. Identifying features will be covered to the extent possible. For example, if the AVM is on the face, the subject's eyes will be blocked out in the photograph. Photography will be performed in accordance with the study assessment outline. All photographs at each time point should be taken from the same distance, using similar lighting and camera settings, if possible. Baseline photographs should be present at the time of follow-up photography to allow for the most accurate positioning and setting replication. Photographs will be retained for the duration of the study and then destroyed per Federal regulations and institutional policies.

14. DATA COLLECTION

Study data will be collected and managed using Research Electronic Data Capture (REDCap) hosted by Arkansas Children's and administered by the Arkansas Children's Research Institute (ACRI). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Even though REDCap is capable of 21 CFR 11 compliance, it is not currently validated as such for this study; therefore, the REDCap database will not be used to collect source data or as CRFs unless specifically validated for this study.

In order to maintain subject confidentiality and security of study data, only key study personnel will be granted access to this study's REDCap project. Access control to REDCap is brokered through Arkansas Children's domain and UAMS domain logins.

15. DATA HANDLING AND RECORDKEEPING

The PI will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a file and the data files will be kept in a separate file on the password-protected computer in the PI's locked office. The only individuals who will have access to the code and information that identifies the subject in this study will be limited to investigators and study staff on this study. All data will be de-identified after analysis is complete by destroying the code key. De-identified data will be maintained as per UAMS and ACRI policy (currently all data will be kept until the last subject is 21 years of age plus 2 years) and destroyed per institutional guidelines.

16. CLINICAL SITE MONITORING

Clinical site monitoring will be conducted by the UAMS Office of Research Regulatory Affairs (ORRA) to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable from source documents, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and applicable regulatory requirements.

Monitoring specialists from ORRA will conduct periodic on-site, comprehensive monitoring as determined by a protocol specific monitoring plan, which will be provided by to the PI the ORRA Monitoring Unit.

17. PROTOCOL DEVIATIONS AND VIOLATIONS

17.1 Protocol Deviation

A deviation is any unintentional change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be tracked and compiled on the Protocol Deviation Log. Deviations that potentially cause concern for the subject's health, safety, or rights will be reported to the Sponsor as soon as possible for reporting guidance.

17.2 Protocol Violation

A violation is a change to, or non-compliance with, the IRB-approved procedures without prior Sponsor and IRB approval (excluding changes made to eliminate apparent immediate

hazard to subjects). A violation may affect health, safety, or rights of a subject. Any violation will be reported immediately to the Sponsor for guidance on reporting.

If the protocol deviation/protocol violation does not represent a significant alteration in the approved protocol and/or affect the safety or welfare of the subject, it will be reported to the UAMS IRB at the time of Continuing Review. If the protocol deviation/violation represents a significant alteration in the approved protocol and/or if it affects the safety or welfare of the subject, it must be reported to the Sponsor and UAMS IRB immediately.

18. ADVERSE EVENTS

Following study entry, safety will be measured by assessment of AEs (serious and non-serious) through the duration of the study, which is approximately 2 years. Subjects may report AEs at any point during the study (clinic visits, on diaries, by phone or email, etc.). All AEs will be recorded on the appropriate CRF at every visit by the study staff. All supportive information related to the AEs will be filed with the source documents. The completed CRF summarizing the AEs should be reviewed and signed off by the PI and/or delegated designee. Toxicities and AEs will be collected, evaluated, and assessed based on NCI CTCAE v5.0 or as specified in the grading system specified in the protocol (**Table 11**). Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

18.1 Definitions

Adverse Event (AE)

An AE is any untoward, unintended, unfavorable, or undesirable medical occurrence, symptom, sign (including an abnormal laboratory finding), illness/disease, or experience that develops or worsens in severity during the course of the study, regardless of relatedness to the investigational drug product (cobimetinib). Intercurrent illnesses or injuries should be regarded as AEs. Each AE is a unique representation of a specific event used for medical documentation and scientific analysis. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Extracranial AVM that were not present prior to the AE reporting period,
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations),
- AEs that occur prior to cobimetinib initiation associated with medication washout, no treatment run-in, or other protocol-mandated intervention,
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period,
- Abnormal results of diagnostic procedures that require further diagnostic tests, additional treatment, study withdrawal, or that the investigator deems to be clinically significant,
- Abnormal laboratory values that require cobimetinib dose modification, treatment or any other therapeutic intervention, study withdrawal, or that the investigator deems to be clinically significant.

Serious Adverse Event (SAE)

SAEs are a subset of AEs. An event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be subjects), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. An SAE is any untoward medical occurrence that at any dose results in any of the following:

- Death (i.e., the AE actually causes or leads to death),

- Life-threatening experience - Disease/condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the endpoint of the clinical trial analysis is survival (i.e., the AE, in the investigator's opinion, places a subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- Inpatient hospitalization or prolongation of existing hospitalization; any AE that results in hospitalization or prolonged hospitalization,
- Persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions),
- Congenital anomaly/birth defect in subject's offspring (i.e., a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to cobimetinib),
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

The term AE encompasses all adverse events (serious and non-serious). AEs are either serious (SAE) or non-serious (non-SAE). To avoid confusion, as the terms "serious" and "severe" are not synonymous, the following clarification is given: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. [ICH-E2A(II)(B)]

AEs of Special Interest (AESIs)

AESIs, potential safety problem identified during safety monitoring, are a subset of "Events to Monitor" of scientific and medical concern specific to the product, for which ongoing safety monitoring and rapid reporting by the PI to the Sponsor and Genentech is required. An AESI might require further investigation in order to characterize and understand it. Depending on the nature of the AESI, rapid communication by the Sponsor to FDA may also be warranted.

AESIs include the following (all Grades unless otherwise specified):

- Cases of potential drug-induced liver injury that include an elevated ALT and/or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT and/or AST > 3 x ULN in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT and/or AST > 3 x ULN in combination with clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  - No other reason can be found to explain the combination of increased ALT and/or AST such as: liver metastasis; viral hepatitis A, B, or C; alcoholic and autoimmune hepatitis; other liver diseases; or exposure to other drugs known to cause liver injury
- Data related to a suspected transmission of an infectious agent by the study treatment (STIAMP), 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 subject exposed to a drug product. This term applies only when a contamination of study treatment is suspected.

- Cobimetinib-specific AESIs include:
  - Any grade serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, serous retinopathy, or central serous chorioretinopathy
  - Significant liver toxicity: AST and/or ALT > 10 x ULN potential
  - Symptomatic heart failure and/or ≥ Grade 2 LVEF reduction
  - ≥ Grade 3 Rhabdomyolysis
  - ≥ Grade 3 CPK elevation
  - ≥ Grade 3 diarrhea
  - ≥ Grade 3 rash

Pre-existing Conditions

A pre-existing medical condition is any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent at the start of the study.

Attritbution (Relatedness)

An AE is related if more likely than not it was caused by the research activity or if there is evidence to suggest a causal relationship to the study. The relatedness of an AE is determined using the following criteria:

- **Yes:** There is a plausible temporal relationship between the onset of the AE and administration of cobimetinib, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to cobimetinib; and/or the AE abates or resolves upon discontinuation of cobimetinib or dose reduction and, if applicable, reappears upon re-challenge.
  - Definite - The AE is clearly related to cobimetinib. The AE onset occurs in a plausible time relationship to cobimetinib administration and other contributing factors (e.g. concurrent disease or concomitant medications/treatments) can be ruled out.
  - Probable - The AE is likely related to cobimetinib. The AE onset occurs in a plausible time relationship to cobimetinib administration and the influence of other contributing factors (e.g. concurrent disease or concomitant medications/treatments) is unlikely.
  - Possible - The AE may be related to cobimetinib. The AE onset occurs in a plausible time relationship to cobimetinib administration; though, other factors (e.g. concurrent disease or concomitant medications/treatments) may have contributed to it.
  - Unlikely - The AE is doubtfully related to cobimetinib. The AE onset does not occur in a plausible time relationship to cobimetinib administration, and other contributing factors (e.g. concurrent disease or concomitant medications/treatments) are likely.
- **No:** Evidence exists that the AE has an etiology other than cobimetinib (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to cobimetinib administration (e.g., cancer diagnosed 2 days after first dose).
  - Not related - The AE is clearly NOT related to cobimetinib. There is not a causal relationship between the AE and the cobimetinib administration.

Expectedness

Expected AEs are those AEs that are listed or characterized in the current FDA-approved Package Insert, the COBI IB or this COBI-AVM protocol.

Unexpected AEs are those not listed in the package insert or current IB or not identified. This includes AEs for which the specificity, nature, intensity, severity, incidence, or frequency is not consistent with the description in the package insert, IB, or this COBI-AVM protocol previously reviewed and approved by the IRB. For example, under this definition, hepatic necrosis would be unexpected if the package insert or IB only referred to elevated hepatic enzymes or hepatitis.

Study Period

Following consent, baselines/pre-existing conditions will be recorded and assessed until initiation of cobimetinib. All AEs will then be recorded and assessed from initiation of cobimetinib through the Safety Follow-Up visit. Thereafter, all AESIs and SAEs, regardless of attribution, and only non-serious AEs that are definitely/probably/possibly related to the cobimetinib will be recorded and assessed during the LTFU.

18.2 Monitoring, Recording and Reporting of AEs

All subjects will be monitored for AEs (serious and non-serious) during the study. AE data collection and reporting, which are required as part of every study, are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols.

All AEs occurring during the study period whether volunteered by the subject; discovered by study personnel during questioning; or detected through physical examination, observation of clinical symptoms, laboratory, pathological, radiological, or surgical findings, or other appropriate means must be recorded and reported appropriately. AEs are to be reported in a routine fashion and at scheduled times during the study. Certain AEs must be reported in an expedited fashion to allow for timely monitoring of subject safety and care.

Pre-existing Conditions

Pre-existing medical conditions should be reported as part of the subject's medical and surgical history. All relevant historical medical conditions that are known/diagnosed prior to administration of cobimetinib are to be recorded in the medical record. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Diagnosis versus Signs and Symptoms

If known at the time of reporting that a laboratory abnormality, sign, or symptom is one component of a diagnosis or syndrome, the diagnosis or syndrome should be reported as the AE (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, it is acceptable to report the information currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Laboratory Values

If the laboratory abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE. Dates used in AE reporting for laboratory test abnormalities should be the date the sample was collected (not the date the sample was processed or the date the results were reported). AEs reported from offsite laboratories are graded using

normal values of the processing laboratory. Source documents from offsite laboratories, such as copies of laboratory test results, are filed in the subject medical record and/or research chart, as applicable.

Hospitalizations for Medical or Surgical Procedures

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, document the event responsible for the procedure, not the procedure itself, as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations or prolonged hospitalization required to allow efficacy measurement for the study, for scheduled therapy of the target disease, or for diagnostic or elective surgical procedures for pre-existing conditions do not require reporting.

Pregnancy

If a female subject or female partner of a male subject becomes pregnant while receiving the cobimetinib or within 90 days after the last dose of cobimetinib, a report should be completed and expeditiously submitted to Genentech and the Sponsor. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious (unless due to personal circumstances), and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the cobimetinib should be reported as an SAE.

Follow-Up of AEs

All AEs, which completely resolve and then recur, should be recorded as a new AE, regardless of relatedness. In addition to new AEs, any increase in the severity or frequency of a pre-existing condition that occurs after the first administration of cobimetinib is considered an AE. An AE that persists from one cycle to another is only reported once unless the grade becomes more severe in a subsequent course. An AE that resolves and then recurs during a different cycle is reported each course cycle it recurs.

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the cobimetinib or study participation is not the cause. If an AE does not return to baseline, the resolution date is recorded as "ongoing". SAEs that are still ongoing at the end of the study period must be followed for up to 30 days to determine the final outcome. Any AE occurring more than 30 days after the last dose of cobimetinib that is possibly/probably/definitely attributable to cobimetinib must be reported according to the instructions in this protocol.

Post-Study AEs

All SAEs and AESIs definitely/probably/possibly related to the cobimetinib will be reported until 12 months after the final dose of cobimetinib (LTFU). Any SAE occurring after the study period, (defined as end of the LTFU or 12 months (365 days) after the last dose of cobimetinib) that is considered possibly/probably/definitely related to the cobimetinib or study participation will be reported immediately to the Sponsor.

The investigator will report all deaths, regardless of cause, and any SAE that is considered related to prior exposure to cobimetinib, including development of cancer or a congenital

anomaly in a subsequently conceived offspring of a female subject or female partner of a male subject to prior exposure to cobimetinib.

Eliciting AEs

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Assessment of AEs

Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to cobimetinib (see following guidance), and actions taken. To ensure consistency of AE causality assessments, investigators should apply the following general guideline.

The reporting of these events depends on the characteristics of the event:

1. Seriousness (grading of event)
2. Relatedness to study therapy
3. Expectedness

Steps to Determine if the Event Requires Expedited Reporting:

1. Identify the type of event using NCI CTCAE v5.0
2. Grade the event using NCI CTCAE v5.0
3. Determine whether the AE is related to the investigational drug.
4. Determine expectedness of event. Expected events are those previously identified resulting from administration of the agent. An AE is considered unexpected when the type or severity of the event is not listed in:
    - Current US FDA-approved Package Insert
    - Current COBI IB
    - Protocol

For AEs that are not specifically listed in the NCI CTCAE v5.0, **Table 11** below should be used for severity grading scale.

Table 11: Severity Grading Scale for AEs Not Specifically Listed in NCI CTCAE v5.0

Grade	Grade Description
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 ADLs [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care ADLs [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to AE [d]

a. Instrumental ADLs living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care ADLs include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by subjects who are not bedridden.
c. If an AE is assessed as a "significant medical event," it must be reported as a SAE.
d. Grade 4 and 5 events must be reported as SAEs.

18.3 Expedited Reporting of AEs

The Investigators are responsible for ensuring that all AEs/SAEs observed or reported during the study are collected and reported to the Sponsor, FDA, UAMS IRB, and Genentech in accordance with 21 CFR 312.32 (IND Safety Reports).

IRB Reporting

Any serious or immediately life-threatening AE, including those resulting in death, occurring while the subject is receiving cobimetinib or within 30 days of the subject's last dose of cobimetinib will be reported to the UAMS IRB. Only AEs meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) criteria will need to be reported to the UAMS IRB within the required 10-day allotment of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s) (including physical, psychological, economic, or social harm). Examples of a UPIRTSO include theft of a computer containing subject information, pregnancy of a subject during study participation, or incarceration of a subject (if not approved for research on prisoners). UPIRTSO may or may not result in actual harm.

All other AEs should be recorded and reported to the UAMS IRB at Continuing Review and to FDA on the Annual Progress Report.

Sponsor Reporting

The Sponsor will be promptly notified of all SAEs. SAEs that are possibly/probably/definitely related to the study intervention and unanticipated/unexpected will be reported to the Sponsor using the MedWatch Form FDA 3500A. The Sponsor will report SAEs meeting expedited reporting criteria to FDA in accordance with 21 CFR 312. All other SAEs will be reported to FDA in the Annual Progress Report.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death". Deaths that are related to the research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research subject would be considered anticipated and not related to the research and will be reported at Continuing Review and the Annual Progress Report.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21 CFR 312.

19. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with all applicable government regulations and institutional research policies and procedures. This protocol and any amendments will be submitted to and approved by the UAMS IRB prior to study initiation and implementation.

The formal consent of each subject, using the IRB-approved informed consent form (ICF), will be obtained before that subject is submitted to any study procedure. All subjects in this study and parents of minors will be provided a copy of the ICF describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. Parental consent/HIPAA and adolescent assent will be obtained for subjects < 18 years of age; consent/HIPAA will be obtained for subjects ≥ 18 years of age. The person obtaining

consent will carefully and thoroughly explain each element of the ICF, the investigational nature of the study, and outline requirements of the study, the benefits and risks/discomforts, and potential alternative therapies to the subject or the subject's parent(s) or guardian.

The consent process will take place in a quiet, private room. Subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This ICF must be signed by the subject/LAR, and the person obtaining consent. A copy of the signed ICF will be given to the subject/LAR, and the consent process will be documented in the research record. Assent will be obtained, and assenting minors will be consented if they reach the age of majority during the study. The PI will retain the original ICFs.

Subjects will be encouraged to allow blood samples to be used for future research related to vascular malformations. The de-identified blood samples and AVM disease history will be stored indefinitely. However, subjects may participate in this research study without agreeing to participate in future research.

20. DISSEMINATION OF DATA

Results of this study may be used for local and/or national presentations, posters, or publications. The presentations and publications will not contain any identifiable information that could be linked to a subject.

In accordance with federal requirements, the study will be registered in ClinicalTrials.gov.

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22. APPENDICES

22.1 Appendix A: CYP3A Fact Card

List of Moderate and Strong CYP3A Inducers and Inhibitors

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

Aprepitant, ciprofloxacin, clarithromycin, conivaptan, diltiazem, erythromycin, fosamprenavir, ketoconazole, imatinib, indinavir, nefazodone, posaconazole, ritonavir, telaprevir, voriconazole

CYP3A Moderate Inhibitors

Atazanavir, darunavir, dronedarone, verapamil, grapefruit juice

CYP3A Strong Inducers

Carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort

CYP3A Moderate Inducers

Bosentan, efavirenz, etravirine, modafinil

22.2 Appendix B: Performance Status Scales/Scores

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

22.3 Appendix C: Reporting Requirements to Genentech

1. Exchange of Single Case Reports

The PI will be responsible for collecting all protocol-defined AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study for cobimetinib.

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports), and Product Complaints with an AE should be sent to:

- Fax: 650-238-6067
- Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be sent to:

- Product Complaint Hotline Number: (800) 334-0290

The PI will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study. These single case reports will be exchanged between Genentech and the PI as outlined below so that regulatory obligations are met.

SAEs, AESIs, pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the subject has been exposed to cobimetinib, will be sent on MedWatch Form FDA 3500A to Genentech Drug Safety after attaching the safety cover sheet (Appendix D). The completed MedWatch Form FDA 3500A should be sent to the Genentech contact specified above.

Transmission of these reports (initial and follow-up) will be either electronic via email or fax and within the timelines specified below:

- Serious Adverse Drug Reactions (SADR) - SAE reports that are related to the product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- Other SAEs - SAE reports that are unrelated to the product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- AESIs - AESIs shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.

- Special Situation Reports
  - Pregnancy Reports
    While such reports are not SAEs or ADRs per se, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence to obtain the follow-up information.

- Pregnancies in Female Partners of Male Subjects
  Male subjects will be instructed in the ICF to inform the study physician immediately if their partner becomes pregnant during the study or within 90 days after the last dose of cobimetinib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- Other Special Situation Reports
  In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an AE and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the product usage during breastfeeding
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

  In addition, reasonable attempts should be made to obtain and submit the age or age group of the subject, in order to be able to identify potential safety signals specific to a particular population

- Product Complaints
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

2. Case Transmission Verification of Single Case Reports

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports.

The PI agrees to conduct the Case Transmission Verification to ensure that all single case reports have been adequately received by Genentech. The PI will email Genentech a Quarterly line-listing documenting single case reports sent by the PI to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the mutually agreed upon time period.

If discrepancies are identified, the PI and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party will handle the matter on a case-by-case basis until satisfactory resolution. The PI will receive reconciliation guidance documents in the 'Activation Package'.

Following Case Transmission Verification, the PI will forward single case reports that have not been sent to Genentech within five (5) calendar days of Genentech's request.

At the end of the study, the PI will be send a final cumulative Case Transmission Verification report to Genentech at ctvist_drugsafety@gene.com.

3. *Reporting Requirements for AE Originating from Patient Reported*

Although sites are not expected to review the PRO data, if investigator/study personnel become aware of a potential AE during site review of the PRO questionnaire data, he/she will determine whether the criteria for an AE have been met and, if so, these must be reported using the MedWatch Form FDA 3500A.

4. *MEDWATCH Form FDA 3500A Reporting Guidelines*

In addition to completing appropriate subject demographic (Section A) and suspect medication information (Section C & D), the report should include the information below in the Event Description (Section B.5) of the MedWatch Form FDA 3500A

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information:

- Additional information may be added to a previously submitted report by any of the following methods:
  - Add to the original MedWatch Form FDA 3500A report and submit it as follow-up
  - Add supplemental summary information and submit it as follow-up with the original MedWatch Form FDA 3500A

  Summarize new information and fax it with a cover letter including subject identifiers (i.e. DOB, initial, subject number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

  The MedWatch Form FDA 3500A (Mandatory Reporting) is available at www.fda.gov/media/69876/download.

5. *Reporting to the FDA, the IRB and Sub-Investigators*

The Sponsor (UAMS) will be responsible for the expedited reporting of safety reports originating from the study to FDA in compliance with federal (US) regulations.

The PI will be responsible for the expedited reporting of safety reports originating from the study to the UAMS IRB in accordance with local regulations. The PI will also be responsible for the distribution of safety information to its own sub-investigators, where relevant, in accordance with local regulations.

Additional Reporting Requirements for IND Holders: requirements for reporting to FDA in accordance with the guidance set forth in 21 CFR 600.80.

AEs meeting the following criteria need to be submitted to FDA as expedited IND Safety Reports according to the following guidance and timelines.

- ***7 Calendar Day Telephone or Fax Report***

  The Sponsor is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the Investigator to be possibly related to the use of cobimetinib. An unexpected AE is one that is not already described in the COBI IB. Such reports are to be telephoned or faxed to Genentech by the PI within 7 calendar days of first learning of the event.

- ***15 Calendar Day Written Report***

  The Sponsor is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of cobimetinib. An unexpected AE is one that is not already described in COBI IB.

  Written IND Safety reports should include an Analysis of Similar AEs in accordance with regulation 21 CFR 312.32. All safety reports previously filed by the Sponsor with the IND concerning similar AEs should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

  Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the AE. The FDA prefers these reports on a MedWatch Form FDA 3500, but alternative formats are acceptable (e.g., summary letter).

  All written IND Safety Reports submitted to FDA by the Sponsor must also be faxed to Genentech Drug Safety by the PI to (650) 225-4682 or (650) 225-4630.

  FDA fax number for IND Safety Reports:
  - Fax: 1 (800) FDA 0178

The PI will be responsible for the distribution of safety information to the UAMS IRB via the UAMS CLARA system: https://clara.uams.edu/clara-webapp/.

For questions related to safety reporting, contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com

6. *Aggregate Report IND Annual Reports*

All IND annual reports submitted to FDA by the Sponsor should be sent to Genentech by the PI. Copies of such reports should be emailed to Genentech Drug Safety CTV mailbox at ctvist_drugsafety@gene.com.

Genentech agrees to forward to the PI and the Sponsor an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that the PI or Sponsor may cross-reference the executive summary of the Genentech DSUR, as applicable.

7. *Final study Report*

Upon completion of the study, the PI will forward a copy of the Final Study Report to Genentech at ctvist_drugsafety@gene.com.

8. Study Close-Out

Any study report submitted to FDA by the Sponsor should be sent to Genentech by the PI. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study and to Genentech Drug Safety CTV oversight mailbox at ctvist_drugsafety@gene.com.

9. Queries

Queries related to the study will be answered by the PI. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between Genentech and the PI. Genentech shall have the final say and control over safety queries relating to the product. The PI agrees that it shall not answer such queries from regulatory authorities and other sources relating to the product independently but shall redirect such queries to Genentech.

Genentech and the PI will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. Genentech and the PI will clearly indicate on the request the reason for urgency and the date by which a response is required.

10. Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that UAMS, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If UAMS issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and/or triggers any changes to the Study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist UAMS with signal and risk management activities related to the Product within the Study.

Genentech will provide UAMS with any new relevant information that may modify or supplement known data regarding cobimetinib (e.g., relevant Dear Investigator Letter).

22.4 Appendix D: Safety Reporting Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET