Title:	**VATCH (Vascular Anomaly Analysis for Therapy Choice)** Sub-protocol 1 – A Phase II Study of trametinib treatment in subjects with Ras/MAPK pathway driven vascular anomalies
Short Title	Trametinib in Ras/MAPK pathway Vascular Anomalies
Drug or Device Name(s):	Trametinib tablet, Trametinib powder for oral solution
FDA IND	IND Exempt (as determined by the FDA)
Regulatory Sponsor:	
eIRB Number	Pending
Protocol Date:	30 May 2025
Amendment 1 Date:	Amendment 3 Date:
Amendment 2 Date:	Amendment 4 Date:

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
AE(s)	Adverse Event(s)
AKT	Serine/threonine kinase AKT (protein kinase B)
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANG 1	Angiopoietins 1
ANG 2	Angiopoietins 2
AST	Aspartate aminotransferase
AVM	Arteriovenous Malformation
aPTT	Activated partial thromboplastin time
BID	Twice daily
BMI	Body Mass Index
BSA	Body surface area
BUN	Blood Urea Nitrogen
BRAT	Bananas, rice, apples, toast (diet)
BSA	Body surface area
C	Centigrade
CAG	Center for Applied Genomics
CaNVAS	Consortium of iNvestigators of Vascular Anomalies
CBA	Clinical Benefit Assessment
CBC	Complete blood count
cfDNA	Cell-free DNA
CHOP	Children's Hospital of Philadelphia
CI	Confidence Interval
CLA	Complex lymphatic anomalies
CLIA	Clinical Laboratory Improvement Amendments
CMP	Complete Metabolic Panel
CNS	Central nervous system
CO_2	Carbon dioxide
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report/Record form
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DICOM	Digital Imaging and Communications in Medicine
DDE	Direct Data Entry
ddPCR	Droplet digital polymerase chain reaction
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report/record form
EC	Endothelial Cell

ELISA	Enzyme-linked immunosorbent assay
EOT	End of Treatment
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	Fibroblast growth factor receptor
G1	Gap-1
GCP	Good Clinical Practice
GI	Gastrointestinal
GLA	Generalized lymphatic anomaly
GSD	Gorham Stout Disease
GT	Gastric Tube
HDL	High density lipoprotein
HDLEC	Human dermal lymphatic endothelial cells
Hgb	Hemoglobin
HIPAA	The Health Insurance Portability and Accountability Act of 1996
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTN	Hypertension
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IR	Intermediate Response
IRB	Institutional Review Board
IV	Intravenous
KLA	Kaposiform lymphangiomatosis
LAR	Legally Authorized Representatives
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LIC	Laboratory assessment of localized intravascular coagulation
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-activated protein kinase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
mg	Milligram(s)
ml	Milliliter(s)
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin serine/threonine protein kinase
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
NGT	Nasogastric tube
NTI	Narrow Therapeutic Index

OS	Overall Survival
OTC	Over the counter
PAS	Pharmacokinetic analysis set
PBPK	Physiologically based pharmacokinetic
PI	Principal Investigator
PI3K	Phosphatidylinositide 3-kinase(s)
PLT	Platelet
PFS	Progression-free survival
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcome Measurement Information System
PO	Orally administered
PT	Prothrombin time
QD	Once daily
QOD	Every other day
QTcF	QT interval corrected by Fridericia's formula
RAF	Serine/threonine-specific protein kinase Raf (Rapidly accelerated fibrosarcoma)
RAS/*RAS* Ras	(Rat sarcoma) proto-oncogene product/oncogene encoding RAS
RBC	Red blood cell(s)
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RPED	Retinal pigment epithelium detachment
RR	Response Rate
RVO	Retinal vein occlusion
SAE(s)	Serious adverse event(s)
SAS	Statistical adverse event(s)
SC	Subcutaneous
SD	Stable Disease
SOP	Standard operating procedure
SR	Substantial Response
TTP	Time to progression
ULN	Upper limit of normal
UMI	Unique molecular identifier
UNK	Unknown
VA	Vascular anomaly
VATCH	Vascular Anomaly Analysis for Therapy of Choice
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WD	Worsening Disease

ABSTRACT

Background

Children and adults with Ras/MAPK pathway driven vascular anomalies (VA) have an extremely heterogenous group of disorders including complicated lymphatic anomalies, Noonan Syndrome, and arterial venous malformations (AVMs). In the past, these lesions were treated with aggressive surgical and or interventional approaches. With recent phenotype genotype correlation, systemic therapy has been utilized to target the driver variants. Trametinib is an orally administered MEK inhibitor that has shown promising results in the directed therapy of VA.

Objectives

Primary objectives are:

1) To determine the proportion of subjects with objective beneficial response to trametinib at the end of cycle 6 (24 weeks) of therapy using an individualized response criterion based on radiologic assessment, Patient Reported Outcomes (PROs) Measures, and Clinical Benefit Assessment (CBA).
2) To assess the safety of oral trametinib in children and young adults with Ras/MAPK pathway driven VA.

Secondary and exploratory objectives include biomarker analysis, duration of response, and tolerability over time of trametinib in subjects with Ras/MAPK pathway driven VA.

Study Design

This study is a Phase II multi-center non-randomized clinical trial.

Setting/Subjects

The Vascular Anomaly Analysis for Therapy CHoice (VATCH) study is the platform for matching targeted therapy agent sub-protocols to children and young adults with VA driven by corresponding genetic drivers. This study will be performed in the outpatient center of the 25 institutions that are members of the Consortium for the INvestigation of Vascular Anomalies (CaNVAS). This is sub-protocol 1 and will enroll 39 evaluable eligible subjects with VA phenotypes and genotype alterations of the Ras/MAPK pathway. Subjects will be included that are deemed to need systemic medical treatment.

Study Interventions and Measures

The MEK inhibitor trametinib will be administered in this protocol for subjects with Ras/MAPK pathway alteration driven vascular anomalies (VA). The dose may be increased throughout the study depending on response at the discretion of the treating physician. PROs Measures and Clinical Benefit Assessment will be performed at screening and after every 6 cycles. Radiologic assessment will be performed at screening and after cycles 6 and 12 if deemed part of the individualized response criteria. If there are any signs of worsening prior to study evaluations, then the Principal Investigator (PI) should complete earlier assessment for evaluation of response. If there are any signs of worsening prior to study evaluations, then the Principal Investigator (PI) should complete earlier assessment for evaluation of response.

Study Outcomes

Assesment of individualized response criteria after 6 cycles for primary endpoint and then every 6 months.

Substantial response:

- Improvement in Radiologic assessment (if applicable) by 20% AND
- Improvement in Global Health PROs by 3T-score points AND
- Improvement in at least 1 CBA as reported by the clinician AND
- No clinically meaningful worsening in any measure

Intermediate response:
- Improvement in Radiologic assessment (if applicable) by 20% OR
- Improvement in Global Health PROs by 3 T-score points OR
- Improvement in at least 1 CBA as reported by the clinicians AND
- No clinically meaningful worsening in any measure

Stable disease:
- No clinically meaningful improvement or worsening from screening in
  - Radiologic assessment (if applicable), OR
  - Global Health PROs, OR
  - CBA as reported by the clinician

Worsening disease:
- Clinically meaningful worsening in
  - Radiologic assessment (if applicable) by 20%, OR
  - Global Health PROs by 3T-score points, OR
  - CBA as reported by the clinician
  - **Regardless** of any concomitant improvement in other measures.

PROTOCOL SYNOPSIS

Study Title	VATCH (Vascular Anomaly Analysis for Therapy Choice) – Sub-protocol 1 – Phase II Study of trametinib treatment in subjects with Ras/MAPK pathway driven vascular anomalies
Funder	CaNVAS, Novartis
Clinical Phase	PHASE II
Study Rationale	The purpose of this study is to assess the efficacy, and safety of trametinib in subjects with Ras/MAPK pathway driven vascular anomalies (VA). These diseases are rare and there is much heterogeneity of phenotype thus an innovative and individualized response criteria will be used based on: radiologic assessment, Patient Reported Outcome (PRO) Measurement, and Clinical Benefit Assessments (CBAs).
Study Objective(s)	**Primary** • To determine the proportion of subjects with an objective beneficial response to trametinib at the end of cycle 6 using an individualized response criterion based on radiologic assessment, Patient Reported Outcomes (PROs) and Clinical Benefit Assessment (CBA). • To determine the safety of oral trametinib in children and young adults with Ras/MAPK pathway driven vascular anomalies. **Secondary** • To assess the duration of response in subjects receiving trametinib at the end of cycles 12 and 24. • To assess the proportions of subjects with a response at the scheduled protocol visits for disease evaluation at the end of cycles 12 and 24. • To assess the changes in symptoms and complications/comorbidities associated with Ras/MAPK pathway driven variants in VA. • Determine the most common and most serious adverse events as defined by Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) in this VA population **Exploratory** • To correlate serum biomarkers before and during pharmacologic MEK suppression in subjects with Ras/MAPK pathway driven vascular anomalies. • To correlate cfDNA before and during pharmacologic suppression in subjects with Ras/MAPK pathway driven vascular anomalies.

	• To describe the distribution of genetic variants and their associated responses to trametinib treatment in subjects with vascular and complex lymphatic anomalies.
Study Drug	Trametinib tablet and powder for oral solution formulations
Study Design	This is a Phase II multi-center non-randomized study to assess the safety and efficacy of trametinib with Ras/MAPK pathway driven vascular anomalies.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 0. Signed informed consent and assent (when applicable) from the subject, parent/guardian/Legally Authorized Representative (LAR) must be obtained prior to any study related screening procedures. 1. Males or females age ≥ 2 months to ≤ 30 years at the time of informed consent. 2. Documented laboratory validated pathogenic **or likely pathogenic** germline or somatic Ras/MAPK-pathway variant. Variants of Unknown Significance (VUS) not predicted to be pathogenic will not be allowed. 3. Subjects must have a symptomatic vascular anomaly in need of medical therapy. 4. Measurable Disease: Subjects must have a disease-related lesion or lesions which can be measured objectively via: . Radiographic/imaging study OR a. Quantitative CBA measurement: If there is no quantifiable lesion by imaging, the quantitative CBA must be determined prior to enrollment and confirmed/approved by study PI and local PI. 5. Performance Level: Subjects must have a Lansky or Karnofsky performance status score of ≥ 50 (ECOG categories 0,1 or 2) within 14 days before study treatment start. Lansky scale to be used for subjects ≤ 16 years of age. Karnofsky to be used for subjects > 16 years of age. Subjects in a wheelchair, unable to walk due to condition but who are up in a wheelchair will be considered ambulatory. 6. Organ Function: Have acceptable organ function as defined as: . Renal function: i. Serum creatinine concentration ≤1.5 × institutional upper limit of normal (ULN) based on the age and sex, or creatinine clearance (CrCl) >50 mL/min (0.84 mL/s) (as measured preferably by a nuclear glomerular filtration rate scan, timed urine collection for CrCl, or calculated by the Schwartz formula [for subjects <18 years] or Cockcroft-Gault

[for subjects ≥18 years] and normalized to a BSA of 1.73 m2).

a. Hepatic function:
   i. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age except for subjects with confirmed Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
   ii. Alanine aminotransferase (ALT) or SPGT ≤ 3 x ULN
   iii. Aspartate aminotransferase (AST) or SGOT ≤ 5 ULN
   iv. Serum albumin may be lowered in this subject population and will not be used to evaluate adequate liver function
b. Adequate cardiac function as indicated by
   i. Left Ventricular Shortening fraction of ≥ 27% by echocardiogram **or** ejection fraction of ≥ 50% by MUGA
   ii. No documented history of congestive heart failure (New York Heart Association functional classification III-IV)
   iii. No history of long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
c. Adequate Bone Marrow Function
   i. Hemoglobin ≥ 8 g/dL (may receive RBC transfusions)
   ii. Absolute Neutrophil Count (ANC) ≥ 750 x 10^9/L
   iii. Platelets ≥ 1000 x 10^9/L (independent of transfusions) exception is made for Kaposiform lymphangiomatosis subjects who have a baseline coagulopathy and thrombocytopenia.

7. Persons who can get pregnant [3] 11 years of age or persons with early onset menarche must have a negative serum or urine pregnancy test within 7 days prior to the initiation of the study medication.
8. Males and females of reproductive potential must agree to the use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), IM progesterone depot, intrauterine contraceptive device, or an oral contraceptive, for the duration of time when they are receiving study drug and for 3 months following last dose.

9. Subjects must be able to swallow tablets or liquid or use a nasogastric or gastric tube for liquid study medication administration.
10. Subjects who require physiologic or stress doses of steroids due to endocrine deficiencies are eligible.
11. Subjects who have previously received MEK inhibitors are eligible if otherwise meeting all eligibility criteria and concomitant medication requirements.

Exclusion Criteria

12. Subjects seeking treatment for hypertrophic cardiomyopathy without a vascular anomaly
13. Concomitant/Prior Medications
    . No immunomodulating agents will be used concomitantly including mTOR inhibitors. Steroid premedication for imaging scans is allowed. Replacement therapy (eg., thyroxine, insulin, or physiologic or stress corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
    a. Prior treatment with a MEK inhibitor or a modulator of the Ras/MAPK pathway medication as single agents or in combination are eligible for this study provided there were no known hypersensitivity or allergic reactions attributed to any of the components of compounds of similar composition to trametinib, no utilization within 30 days prior to enrollment, and subjects have fully recovered from toxic effects of prior therapy (as determined by treating physician).
    b. mTOR inhibitors must not be given within 14 days of study drug initiation. Investigational drugs: Subjects currently receiving another investigational agent are not eligible.
    c. Investigational drugs: Subjects currently receiving another investigational agent are not eligible.
    d. Any investigational drug use within 30 days prior to enrollment. For agents that have known adverse events occurring beyond 30 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
    e. Cancer chemotherapy, radiotherapy, or immunomodulatory agents must not be given within 30 days of study drug initiation.

f. Cardiac medications: Subjects currently receiving treatment for left ventricular systolic dysfunction are not eligible.
g. Supportive care use of anticoagulants and compression garments is allowed. Subjects must have been using these interventions in an unchanged manner for 30 days before study.

14. Infection: Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment). Subjects with possible fungal infections must have had at least 2 weeks of appropriate anti-fungal antibiotics and be asymptomatic.
15. Subjects with history of hepatic sinusoidal obstructive syndrome (veno-occlusive disease of the liver) in the prior 3 months.
16. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with absorption of drug excluding PLE.
17. Subjects with history of or current risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) or uncontrolled glaucoma or ocular hypertension.
18. Allergic reactions: Subjects with a history of allergic reaction attributed to compounds of similar chemical or biological composition to trametinib are not eligible.
19. History of prior and or ongoing malignancy (within 5 years before informed consent except radically treated carcinoma in situ or radically treated basal-cell carcinoma of skin or thyroid gland, well-differentiated microcarcinoma or Stage 1 Wilms' tumor of a histology other than anaplastic), or ongoing investigations or treatment for malignancy at time of informed consent.
20. Subjects unable to comply with safety monitoring requirements.
21. Subject may not be pregnant or breast feeding.
22. Parents/guardian/LAR or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.
23. Debulking or other major surgery performed within 30 days, at time of informed consent;
24. Clinically meaningful bleeding related to VA: Grade 2 within 14 days or Grade 3 and more within 28 days before study treatment start as per CTCAE v. 5.0. Sclerotherapy/embolization for vascular complications performed within 14 days before informed consent.

	25. Subjects not able to understand and to comply with study instructions and requirements (in patients, legally authorized representatives, or guardians as applicable) at time of informed consent.
Number of Subjects	Enrollment is planned for 39 evaluable eligible subjects in total with participation of 25 sites across the United States.
Study Duration	Each subject's participation will last 24 cycles (96 weeks) with an extension period up to 36 total cycles (3 total years including the first 24 cycles of therapy) if the subject has been found to have a beneficial response.
Study Phases **Screening** **Study Treatment** **Follow-Up**	Intervention study 1. Screening: Screening for eligibility and obtaining consent 2. Intervention: Study intervention/experimental treatment. **3.** Extension period: Continued therapy for subjects with response and acceptable toxicity.
Efficacy Evaluations	1. Radiologic assessment (if applicable): - For subjects with radiologically evaluable disease only. Subjects without radiologically evaluable disease may have a CBA substituted for radiologic evaluation. -MRI evaluation will be at screening, and at the end of cycle 6, 12, and 24 (if applicable) on treatment. If there are signs of worsening, earlier assessment should be done. 2. Patient reported outcome (PRO) measurements: - Screening to end of study- Every 6 cycles 3. Clinical Benefit Assessment (CBA): - Screening to the end of study- every 6 cycles
Safety Evaluations	Safety assessments will be conducted through the study (according to the assessment schedule) • Monitoring of adverse events (AEs) and serious adverse events (SAEs) • Physical examination • Body weight and vital signs • Height and body mass index (BMI) • Karnofsky/Lansky performance status • Laboratory assessment including hematology, biochemistry, urinalysis, and coagulation. • Serum or urine pregnancy test for subjects of child-bearing potential • Echocardiography

	• Ophthalmologic exams
Statistical and Analytic Plan	For all the analyses, subjects who received any dose of trametinib will be included in the analyses. For the primary efficacy endpoint of objective response at the end of cycle 6, we will test a null hypothesis of response of 40% against an alternative hypothesis of response rate of 65%. We will follow the Simon's optimal two-stage design: an interim analysis will be conducted after 16 subjects have been observed for response, and if 6 or fewer intermediate, substantial, or stable responses are observed, the trial will be stopped for futility; otherwise, the trial will continue to enroll a total of 39 subjects and at the end of the trial if 20 or more responses are observed, the treatment will be declared promising. This design provides >=90% power when the true response rate is 65% and yields a one-sided type I error of <=0.05 when the true response rate is 40%. For evaluating toxicity, a sample size of 39 provides 86% probability to observe at least one toxicity event when the underlying true toxicity rate is 5%, so that we have good confidence to observe a rare toxicity type. In addition, this sample size provides a reasonable precision on the estimate of the toxicity rate. For example, with 7 observed toxicity events out of 39 subjects, the estimated toxicity rate is 18%, with the 95% exact confidence interval (CI) as 8% - 34%.
Data and Safety Monitoring Plan	This study will be monitored in accordance with a Data Safety Monitoring Plan for Phase II Studies. In brief, the role of the Data and Safety Monitoring Board (DSMB) is to protect the interests of subjects and the scientific integrity for clinical trials. The DSMB will monitor this trial at a frequency determined by the DSMB Chair, but at least twice annually. Approximately 2 weeks before each meeting of the DSMB, the study chair will be responsible for working with the study statistician to prepare study reports for review by the DSMB. The DSMB will provide recommendations to change the study or to continue the study unchanged. Monitoring and auditing procedures will be followed to ensure that the study is conducted, documented, and reported in accordance with the IRB approved protocol, the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements of federal regulations. Verification of eligibility and appropriate documentation of informed consent will be performed for **all** subjects enrolled into the study. Monitoring of timeliness of AE and SAE reporting will be done as events are reported. CRFs for **each** subject enrolled will be monitored for completeness and quality by comparing data in the CRFs to data in the source documents.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schema:

Day 1:

Begin Cycle

Day 28:

End of Cycle

A cycle of therapy is 28 days.

Subjects will receive study therapy daily for 28-day cycles.
Radiologic assessment will occur at screening and the end of cycles 6, 12, and 24 (if applicable). Radiologic assessment at other time points will be at the discretion of the treatment team. PROs Measurements and CBA will begin at screening and will occur at the end of every 6 cycles throughout the duration of the study and extension period. If there are any signs of worsening prior to study evaluations, then the Principal Investigator (PI) should complete earlier assessment for evaluation of response.

Therapy will be discontinued if there is evidence of worsening disease or drug related dose-modifying toxicity that requires removal from therapy. Treatment may otherwise continue to the end of the study intervention phase and subsequent extension period provided the subject meets the criteria for starting subsequent cycles and does not meet criteria for removal.

1 BACKGROUND AND RATIONALE

1.1 Introduction

Vascular anomalies (VA) encompass a broad range of phenotypes from vascular tumors to vascular malformations. VA are a heterogeneous group of disorders that arise from disrupted vascular morphogenesis of veins, arteries, lymphatics, and capillaries, alone or in combination.[1–3] Complex lymphatic anomalies (CLA) are a subgroup of vascular malformations with highly variable presentations. CLAs can present as multi-focal lymphatic malformations, soft tissue swellings, chylous and pericardial effusions, ascites, lymphangiectasia of the intestines with subsequent protein and intestinal blood loss, poor growth, lymphedema, and osteolytic bony lesions. Subjects with VA and CLAs suffer from significant morbidity, disfigurement, and mortality with limited available systemic treatment options. Supportive measures include interventional procedures to control or diver lymphatic flow, low fat diets, and diuretics. Sirolimus, a mTOR inhibitor, has been successful in some subjects with severe CLAs, but has limitations.[4,5] Recently, many VAs and CLAs have been identified to be due to pathogenic variants in the Ras/MAPK pathway.[6,7] Other RASopathies, including Noonan syndrome, cardiofaciocutaneous syndrome, and Costello syndrome, may also exhibit lymphatic abnormalities.[8,9] Recently, MEK inhibition has been demonstrated to show promise in management of complex lymphatic anomalies as well as fast-flow vascular anomalies.[10–16]

Vascular Anomaly analysis for Therapy CHoice (VATCH) is a collaborative nationwide clinical trial run through the Consortium for the iNvestigation of Vascular Anomalies (CaNVAS) as a multi-agent/multi-arm clinical trial designed to provide a therapy which is targeted to the specific genetic drivers of a subject's specific CLA or VA.

1.2 Pathway

The Ras-Raf-MEK-ERK pathway also known as the or the mitogen-activated protein kinase MAPK pathway is one proliferative/growth signaling pathway where alterations can drive the development of VA and CLA.[6,7,17,18] Anomalies or conditions associated with alterations in the Ras-Raf-MEK-ERK pathway include but are not limited to Kaposiform Lymphangiomatosis (KLA), Generalized lymphatic anomaly (GLA), Noonan's syndrome, Gorham Stout Disease, Arteriovenous malformations (AVM), cardiofaciocutaneous syndrome, and Costello syndrome.[8,9,16,18,19] Targeted blockade of the Ras/MAPK pathway can be achieved with a class of medications known as MEK inhibitors.

The Ras-Raf-MEK-ERK pathway also known as the MAPK or MAPK/ERK or Ras pathway is a cell signaling cascade of proteins that communicates a signal from the cell surface to the nucleus of the cell where it often contributes to cell growth and proliferation.[20,21] This signal originates at the cell surface with binding of a mitogen to a cell surface receptor and ultimately triggering Ras protein binding of GTP. This activated Ras then activates the protein kinase activity of a Raf kinase which in turn activates a MEK kinase (MEK1/MEK2 most commonly) which in turn activates a mitogen-activated protein kinase (MAPK) formerly known as extracellular signal-regulated kinases (ERKs) as shown in **Figure 2.3**.[20–22] This activation contributes to cell cycle progression, growth, and proliferation. This pathway has multiple other mechanisms of regulation/activation/modulation as well as cross interactions with alternative cell signaling cycles.[23] Pre-clinical and clinical studies have demonstrated the efficacy of targeting MEK1 and MEK2 as ways to pharmacologically regulate this Ras/MAPK pathway activation in a variety of conditions and pathway activations ranging from activating mutations in Raf kinases in melanoma to loss of negative regulators in neurofibromatosis.[24–28] Ongoing studies in malignancies have demonstrated clinical activity and safety of MEK inhibitors both alone and in combination with other molecularly targeted agents.[27–33]

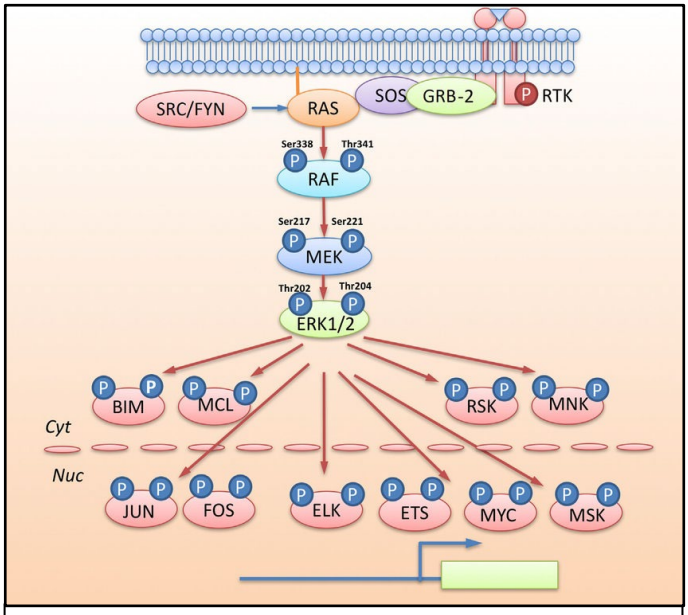


Figure 2.3: MAPK signaling pathway as displayed in Liu et al., 2018.[19]

1.2.1 Non-Clinical Studies

Non-clinical studies pertinent to this trial include evaluation of pre-clinical studies in the zebra-fish model of lymphatic development, and mouse model of Gorham Stout Disease (GSD), animal toxicology, and preclinical pharmacology.

<u>Animal Models of Lymphatic Anomalies</u>
Human dermal lymphatic endothelial cells (HDLECs) transduced with a gain of function *ARAF* variant in a zebra fish model of lymphatic disease resulting in increased ERK1/2 activity, enhanced lymphangiogenic capacity, and changes to actin skeleton and VE-cadherin junctions in HDLECs. Cell changes were rescued when cultured in increasing concentrations of trametinib. Similarly, in mutated *ARAF* transgenic zebrafish the thoracic duct is severely dilated and partially reversed by cobimetinib, another MEK-inhibitor.[10]
In a mouse model of GSD, a vascular anomaly syndrome characterized by abnormal lymphatics and progressive osteolysis of bone, mice expressing a *KRAS* variant develop

ectopic lymphatics of bone, chylothoracies, retrograde lymphatic flow, and fewer lymphatic valves. Trametinib-treated *iLEC^{Kras} ;mT/mG* mice have significantly more lymphatic valves than vehicle treated mice suggesting prevention of lymphatic valve regression.[34]

Animal Toxicology

In juvenile rat toxicity studies, there were dose-dependent effects on growth (body weight and long bone length), bone (physeal thickening), serum phosphorus (increased), eye (corneal mineralization/dystrophy), skin, liver, heart (increased heart weight) and the female reproductive system (delay in a physical landmark of sexual maturity and mammary gland development, lower corpora lutea and ovarian weights). All of the female reproductive effects were reversible. With the exception of the heart and eye findings, similar effects have been observed in adult animals given trametinib. In bone, physeal thickening was reversible following a recovery period. Bone changes may be associated with inhibition of MEK-dependent fibroblast growth factor (FGF) signaling, as similar effects have been observed in rats given a small molecule inhibitor of FGF receptor (FGFR) tyrosine kinase as well as in FGFR3-deficient mice.[35,36] Unlike in adults, where bone growth has completed and the physeal plates have closed, children (2 to 11 years of age) and adolescents (12 to <18 years of age) may represent sensitive populations to chronic MEK inhibitor treatment, manifested as decreased growth velocity.

Gonadal maturation and development is a potentially sensitive process in children who have yet to reach sexual maturity. In female rats given trametinib at subclinical exposures, ovarian function perturbations were observed, including increases in cystic follicles and decreases in cystic corpora lutea. Pharmacologic inhibition of MEK activity in ovarian granulosa cell cultures blocked ovulatory gene expression, follistatin signaling and granulosa cell survival, indicating a potential role of MEK in folliculogenesis.[37–39] In juvenile rats, similar ovarian findings occurred, as well as delays in onset of physical hallmarks of sexual maturity and mammary gland development. Therefore, onset of female reproductive maturation is a theoretical concern in pediatric populations receiving trametinib.

1.2.2 Clinical Studies in Adults

A phase I/II trial of single agent trametinib in adults with RAS mutated, multiply relapsed or refractory - myeloid malignancies (n=57) demonstrated a 21% response rate compared with a 3% response rate in subjects with RAS wild-type or unknown leukemia (n=30). Hepatic toxicities (9%), gastrointestinal disorders (7%) and rash (5%) were the most frequent Grade 3/4 AEs. AEs possibly related to inhibition of MEK signaling were blurred vision (total, 13%; Grade 3, 1%) and decreased cardiac ejection fraction (total, 9%; Grade 3, 6%).[40]

The Maximum Tolerated Dose (MTD) of trametinib in adults is 3 mg once daily, and the RP2D of trametinib is 2 mg once daily. Five monotherapy studies administered trametinib 2 mg daily to 499 adult subjects. The most common adverse events were rash, diarrhea, fatigue, peripheral edema, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. In these studies, up to 32% of subjects reported serious AEs (SAEs), and up to 13% permanently discontinued study treatment due to AEs. Rash, diarrhea, visual disorders, hepatic disorders,

cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (observed with other MEK inhibitors) or potentially life-threatening.

Cardiac-related adverse events are known to occur in adults treated with trametinib. In a Phase II trial, subjects (n=97) underwent serial assessment of LVEF, three subjects (3%) developed asymptomatic and reversible Grade 3 LVEF reduction.[24] In a phase III trial comparing trametinib versus dacarbazine plus paclitaxel, 14 of the 211 subjects who received at least one dose of trametinib developed cardiac-related adverse events (7%), 11 developed decreased LVEF, and three had LV dysfunction.[41] Cardiomyopathy resolved in 10 of the 14, but four subjects had serious cardiac-related events that were considered to be drug-related and led to permanent discontinuation of the study drug. Across clinical trials of trametinib at the recommended adult dose (2 mg daily), approximately 11% of subjects have developed evidence of decrease in LVEF below the institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline; 5% have developed decrease in LVEF below the institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline.[42]

Ocular effects and visual impairments, including central serous retinopathy (CSR), retinal pigment epithelium detachment, and retinal vein occlusion (RVO), are reported with trametinib as well as other MEK inhibitors in clinical development. At the 2 mg daily dose, 14% to 18% of the subjects in three clinical trials experienced visual disorders. The majority of these were Grades 1 or 2 in severity (71% to 93%); 7% to 29% of subjects experienced Grade 3 and none experienced Grade 4 visual disorders. With the exception of Grade 3 RVO and Grade 2 CSR, all cases were reversible with or without drug interruption. CSR is a visual impairment due to fluid accumulation under the retina, which causes blurry vision. As of September 18th, 2014, 17 (1.2%) cases of CSR have been reported amongst subjects treated with trametinib, either as monotherapy or in combination with other anti-cancer agents. Two cases (0.3%) of RVO have been observed with trametinib, of which one case was considered drug-related. (Investigator Brochure)

1.2.3 Clinical Studies in Children with Cancer

A 3-part phase I/II, open-label, multicenter study of trametinib in pediatric patients 1 month or older with recurrent or refractory tumors (NCT02124772) is underway. Results from part A, the dose escalation portion of the study, which included 40 subjects has been presented in abstract form.[43] Dose limiting toxicity (rash and mucositis) occurred in 5/15 subjects (33.3%) receiving 0.04 mg/kg/dose, whereas a dose of 0.025 mg/kg resulted in dose limiting toxicity in 3/19 (16%) subjects.

No significant safety concerns specific to pediatric subjects were noted in a preliminary analysis beyond what is already known from prior adult studies including in subjects between 1 month and 6 years of age. In particular, the only serious adverse event in the 12 patients under 6 years of age treated at 0.032 mg/kg/day was mitral valve regurgitation in one patient who had received trametinib for 6 months which resolved after holding treatment and the patient has since resumed trametinib at 0.025 mg/kg/day without further toxicity.

1.3 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, and 312. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 RATIONALE

2.1 Investigational drug: Trametinib (Mekenist®)

Trametinib is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. Trametinib interferes with cellular signal-transduction and inhibits cell proliferation by inducing apoptosis in tumor cell lines in vitro and human tumor xenografts in mice. Trametinib has demonstrated anti-proliferative activity against a broad range of tumor cell lines and xenograft models, and the activity of trametinib was most pronounced in human tumor models harboring BRAF-activating variants. Trametinib inhibits ERK phosphorylation leading to Gap-1 (G1) cell cycle arrest and tumor xenograft growth inhibition in vivo following oral dosing.

Subjects will receive oral trametinib daily in continuous 28-day cycles at 0.025 mg/kg/day with a maximum dose of 2 mg. A single dose reduction will be permitted in individual subjects who experience toxicity while still having evidence of clinical benefit and is assessed per the investigator.

This trial will enroll subjects with symptomatic vascular anomalies with causative variants of the Ras/MAPK pathway and evaluate objective response using individualized subject response criteria. Subjects will also be evaluated for toxicity using CTCAE v5.0. Stopping rules for toxicity and response are included in the statistical section.

Trametinib is a MEK inhibitor with safety data in children and adults with promising pre-clinical and clinical data supporting efficacy in subjects with VA and CLA.[10–12,14,17,29,34,44,45] In summary, this Phase II, non-randomized, interventional, open-label, sub-protocol of the VATCH trial provides trametinib to subjects with Ras/MAPK pathway driven vascular anomalies. This protocol represents the first collaborative multicenter trial for the targeted treatment of children and young adults with vascular anomalies driven by Ras/MAPK pathway activation.

2.1.1 Rationale for Dose/Age

A Phase I/II study (NCT02124772) of trametinib in pediatric patients with relapsed/refractory solid tumors revealed a 16% (3/19) DLT rate at 0.025 mg/kg/day and a 33% (5/15) DLT rate at 0.04 mg/kg/day. Frequent treatment related adverse effects (TRAEs) included paronychia, diarrhea, and rash. Treatment related serious adverse events (TRSAEs) of hyponatremia and pyrexia each occurred in 2 patients. The recommended dose (RD) was determined to be 0.025 mg/kg for patients >6 years. More than 50% of the patients under the age of 6 years receiving a dose of 0.025 mg/kg were noted to have steady state trough levels below the target level established in adults with melanoma treated at the approved trametinib dose that is associated with malignancy efficacy (trough of ~11 ng/mL). Dose was subsequently escalated to 0.032 mg/kg/day and 0.04 mg/kg/day for patients less than 6 years including multiple patients under 2 years of age with no dose modifying toxicities. Based on tolerance and pharmacokinetics a dose of 0.032 mg/kg was selected as recommended dose for the population less than 6 years of age with a refractory solid malignancy.

[43] However, the use of 0.032 mg/kg/day dosing has not yet been evaluated in the VA and CLA population leading to the recommendation to have initial dosing at 0.025 mg/kg/day.

Treatment physicians may elect to start patients at a lower dose of 0.0125mg/kg/day for critically ill patients, infants < 10kg at enrollment, or based on clinical discretion.

2.2 Rationale for Individualized Evaluations

Enrolled patients must have a documented laboratory validated pathogenic or likely pathogenic germline or somatic vascular anomaly driven by Ras/MAPK-pathway alteration. The phenotype and clinical characteristics of disease manifestation will be heterogenous between subjects. The optimal measure of disease response in subjects with complex vascular anomalies has not been established. Current practice includes changes in physical exam, radiographic (i.e., MRI) evaluations, laboratory assessments and/or quality of life measures. These methods individually are challenging to assess because of heterogeneity in growth patterns, diversity of associated clinical and laboratory abnormalities and a fluctuating clinical course dependent upon factors other than treatment, such as intercurrent infections, puberty, and trauma. Further, lesion size, determined radiographically and clinical changes or quality of life (QOL) measures is not clearly correlated. For these reasons the efficacy of trametinib treatment will be based on an Individualized Response Criteria protocol with three distinct components: Radiologic evaluation, PROMIS Patient reported outcome (PRO) measurements, and Clinical Benefit Assessments (CBA). CBA can be substituted for radiologic evaluation in subjects without radiologically evaluable disease. These three components will be performed at discrete time points to quantitatively determine the individualized response to trametinib therapy for subjects with vascular anomalies driven by Ras/MAPK alterations. Similar response criteria has been used in other studies.[46]Primary response outcome based solely on imaging criteria has not proven effective.

2.3 Rationale for Exploratory Aims

To correlate serum biomarkers with single cell findings before and during pharmacologic MEK suppression

The angiopoietin-TIE2/TEK signaling pathway is critical for blood and lymphatic development and maintenance.[47–50] Angiopoietins 1 (Ang1) and 2 (Ang2) are endothelial-specific growth factors. Ang-1 activates the TIE2 receptor, leading to vessel remodeling, stabilization, and quiescence. Mutations involving TIE2 have been associated with venous and arteriovenous malformations. Ang-2 can promote vascular leakage, inflammation, and metastasis in blood endothelial cells (ECs), and in lymphatic ECs may activate lymphangiogenesis.[51,52] Elevated levels of Ang-2 and low Ang-1 levels have been found in KLA as well as other CLAs.[49] Measurement of Ang-2 is now a clinical test for diagnosis and monitoring of treatment response. However, the cell populations expressing Ang-1 and Ang-2 in different VA are not well defined. Cell populations expressing Ang-2 will be identified using scRNA-seq analysis, and levels of Ang-2, and other biomarkers will be correlated with transcriptomic findings. Ang-2 will be measured using our clinically validated ELISA in serum samples from enrolled subjects with VA before treatment, and at the end of cycles 6 and 12 into treatment. Ang-2 biomarker levels will be correlated with diagnosis, genotype, disease progression and severity, blood cell counts and treatment response. Additional biomarkers, including VEGFR3 (soluble VEGFR3), Tenascin C, VEGF-A, -C, -D, CXCl12, will also be identified by scRNA-seq analysis and correlated with clinical features.

To evaluate cell free DNA (cfDNA) for acquired variants as disease causing biomarker in plasma samples from vascular anomalies subjects and follow variant load in plasma every six cycles as response to therapy

The center for applied genomics (CAG) at CHOP, has optimized methods for isolation and purification of cell-free DNA (cfDNA) from low concentrations of cell-free DNA, addressing instability and the small fragment sizes. This highly valuable material is of critical importance for variant detection in subjects with vascular malformations, using NGS technologies for data generation and ddPCR or NGSure for variant validation. CAG uses the Streck Cell-Free DNA BCT, collecting samples from different bodily fluids, including blood, chylous fluid and lymph fluid. CAG has successfully uncovered disease causing variants in over 30 patients using cfDNA (impossible to make diagnosis any other way), leading to better informed decisions regarding treatment plans, therapeutic effectiveness. We use our UMI panel with 49 of the most relevant disease causing (lymphatic/vascular malformation) genes. We have successfully identified and validated variants across the PIK3CA/mTOR and Ras/MAPK pathway genes using cfDNA in the allele frequency range of 0.05% and higher, using our customized UMI panel with sequence fold coverage of 30,000-60,000x. We propose to analyze all subjects entering this study using our customized UMI gene panel in the CLIA-certified laboratory at the CAG, including deep coverage of 49 candidate lymphatic/vascular malformation genes. For those who are positive (estimate over 40% of subjects today with growing success rate as the technology matures), we will then obtain new sample for cfDNA isolation at week 24 and 48 to follow

variant load in response to therapy with Trametinib and other drugs as informed by the variants identified. We anticipate the variant load will go down and possibly resolve completely as we continue long-term treatment of these subjects.

3 OBJECTIVES AND ENDPOINTS

3.1 Specific Hypothesis

Trametinib is effective and safe for subjects with Ras/MAPK pathway driven VA.

3.2 Primary Objectives

- To determine the proportion of subjects with an objective beneficial response to trametinib at the end of cycle 6 using an individualized response criterion based on Radiologic Assessment, Patient Reported Outcomes (PROs) and Clinical Benefit Assessment (CBA).
- To determine the safety of oral trametinib in children and young adults with Ras/MAPK pathway driven VA at the end of 6 cycles.

3.3 Secondary Objectives

- To assess the duration of response in subjects receiving trametinib at the end of cycles 12 and 24.
- To assess the proportions of subjects with a response at the scheduled protocol visits for disease evaluation at the end of cycles 12 and 24.
- To assess the changes in symptoms and complications/comorbidities associated with Ras/MAPK pathway driven variants in VA.
- Determine the most common and most serious adverse events as defined by Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) in this vascular anomalies population

3.4 Exploratory Objectives

- To correlate serum biomarkers before and during pharmacologic MEK suppression in subjects with Ras/MAPK driven VA
- To correlate cfDNA before and during pharmacologic suppression in subjects with Ras/MAPK driven VA
- To describe the distribution of genetic anomalies and their associated responses to trametinib treatment in subjects with vascular and complex lymphatic anomalies.

4 INVESTIGATIONAL PLAN

4.1 General Schema of Study Design

This study is a single-arm, open-label investigational Phase II study of trametinib administered orally or by naso- or gastric-tube on a continuous 28-day cycle, for up to 24 cycles in subjects ages 2 months to 30 years with genetically confirmed Ras/MAPK pathway

associated vascular or complex lymphatic anomalies. Subjects in the absence of toxicity and with clinical benefit may continue into the extension period for 36 cycles total.

4.2 Registration, Enrollment, and Screening

Potential subjects will be identified by VA provider-referral or self-referral and screened using protocol inclusion and exclusion criteria.

The investigational nature and objectives of the study, the procedures and treatments involved, benefits and potential adverse effects, and potential alternative therapies will be carefully explained to the subject or to the subject's parents or guardian/LAR. A signed informed consent and assent will be obtained according to institutional guidelines.

Documentation of the informed consent for screening will be maintained in the subject's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for screening values even if the studies were done before informed consent was obtained.

All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 14 days at the start of therapy. Laboratory tests need not be repeated if therapy starts within 14 days of obtaining labs to assess eligibility.

Subjects will be given a study specific identified assigned by CASTOR when they are registered in CASTOR, the study's data management system.

4.2.1 Optional Biologic Studies

Correlative molecular biology studies will be conducted as part of the current trial. All subjects should be approached for consent to all of these biology studies. Subjects may participate in the treatment portion of this trial without consenting to the biology studies.

Biomarker samples (frozen serum or plasma samples) will be analyzed in Dr. Tim LeCras's lab at Cincinnati Children's Hospital Medical Center. Biomarker analysis can include measurement of levels of VEGF-A, C, D, Endothelin-1 and Angiopoietin-1, 2. Frozen serum samples are preferred but in some instances frozen plasma samples can be used. Serum and plasma samples should be frozen at -70-80C and transported frozen on dry ice.

Cell-free DNA will be analyzed in Dr. Hakon Hakonarson's lab at Children's Hospital of Philadelphia (Appendix VII).

These biomarkers will be collected at screening, at the end of Cycle 6, and at the end of Cycle 12.

Samples that are not immediatlety analyzwed will be stored in Dr. Hakon Hakonarson's lab at Children's Hospital of Philadelphia. Leftover and or unused samples will be deidentified and used in future research.

4.3 Study Treatment Phase (start of the study intervention)

Trametinib is administered orally once daily under fasting conditions (on an empty stomach) at least 1 hour before and 2 hours after a meal. If a subject misses a dose, subject should not double the next regularly scheduled dose. However, subject can take the missed dose immediately if the next scheduled dose is at least 12 hours later. Subject should take the next dose at its usual time.

4.3.1 Dosing

Eligible subjects will be treated with trametinib administered at 0.025 mg/kg/dose (or 0.0125mg/kg/dose for critically ill subjects, infants < 10kg at enrollment, or based on clinical discretion) daily given orally by tablet or by oral solution via a nasogastric tube (NGT) or gastric tube (GT) at dose level 1 for each disease strata. Dosing will be daily on a continuous 28-day cycle, for up to 24 total cycles. Dosing will be based on weight in kilograms (kg) obtained within 7 days of starting each cycle or pre-determined dosing weight in those subjects whom fluid status fluctuates. The total daily trametinib dose should not exceed the adult dose (2mg) in any subject.

Refer to Section 10 for dose modifications for toxicity.

Trametinib formulations include:

Powder for oral solution: The liquid concentration is 0.05 mg/mL. Doses of trametinib oral solution will be rounded to nearest 0.1mL (0.005 mg) for doses $\leq$ 0.11 mg (in oral syringes $\leq$ 3 mL), 0.2 mL (0.01mg) for doses > 0.11 mg (in oral syringes of 5-10 mL volume). Trametinib pediatric oral solution formulation will be administered with a graduated syringe.

Tablet formulation: Doses of tablet formulation should be rounded to the nearest 0.5mg. It is recommended that subjects drink 4 to 6 mL of water/kg body weight following dosing.

A dosing nomogram (see Appendix II) based on weight and dose level will be used to prescribe trametinib to minimize inter-subject dosing variability. If vomiting occurs after taking the oral solution formulation, the dose should not be repeated, and next dose given at its scheduled time.

4.4 Follow-up Phase

Subjects who have stopped trametinib therapy due to completion of therapy or toxicities will be followed for 30 days after treatment cessation or resolution of toxicities, whichever is longer.

4.5 Extension Phase

Subjects showing clinical benefit may continue into the extension period for up to 12 additional cycles (36 total cycles, including the treatment phase). This will be at the discretion of the treating physician and subject's family.

4.6 End of Treatment

Treatment will be discontinued if one of the below conditions are met:

- after completing up to 24 cycles of therapy (for subjects who do not participate in the extension phase); or
- after completing up to 36 cycles of therapy (for subjects who participate in the extension phase); or
- by subject (or legal guardian/LAR) decision; or
- by physician's decision if the subject has progressive disease, severe side effects or does not comply with the study requirements; or
- by decision of CaNVAS based on Safety Monitoring Board

4.7 Study Duration, Enrollment and Number of Sites

4.7.1 Duration of Study Participation

The study duration per subject may be up to 30 days of the Screening Phase, up to 24 complete cycles of Study Treatment Phase, and up to 30 days follow-up once medication has been discontinued. Subjects deriving benefit from study drug may be eligible for the 12 cycles of the Extension Phase following the initial 24 cycles of treatment.

Active recruitments will take 2 years and there will be follow up after discontinuation of study treatment for a period of 30 days.

4.7.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be a multi-site trial through the CaNVAS Consortium which currently comprises 25 sites throughout the United States.

Recruitment will stop when 39 evaluable subjects are enrolled. It is expected that approximately 45 subjects will be enrolled to produce 39 evaluable subjects.

4.8 Study Population

Study entry is open to subjects regardless of gender or ethnic background. While there will be every effort to seek out and include females and minority subjects, the subject population is expected to be no different than that of subject backgrounds at the CaNVAS consortium membership sites.

5 SUBJECT ELIGIBILITY

The study plans to enroll approximately 39 evaluable subjects in total. The study will enroll both adult and pediatric participants ≥ 2 months old

5.1 Inclusion Criteria

The eligibility criteria listed below are interpreted literally and cannot be waived. Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent and assent (when applicable) from the subject, parent/guardian/LAR must be obtained prior to any study related screening procedures.
2. Males or females age ≥ 2 months to ≤ 30 years at the time of informed consent.
3. Documented laboratory validated pathogenic **or likely pathogenic** germline or somatic Ras/MAPK-pathway variant. Variants of Unknown Significance (VUS) not predicted to be pathogenic will not be allowed.
4. Subjects must have a symptomatic vascular anomaly in need of medical therapy.
5. Measurable Disease: Subjects must have at least one disease-related lesion which can be measured objectively via:
    a. Radiographic/imaging study OR
    b. Quantitative CBA measurement (Appendix X) If there is no quantifiable lesion by imaging, the quantitative CBA must be determined prior to enrollment and confirmed/approved by study PI and local PI.
6. Performance Level: Subjects must have a Lansky or Karnofsky performance status score of ≥ 50 (ECOG categories 0,1 or 2) within 14 days before study treatment start. Lansky scale to be used for subjects ≤ 16 years of age. Karnofsky to be used for subjects > 16 years of age. Subjects in a wheelchair, unable to walk due to condition but who are up in a wheelchair will be considered ambulatory.
7. Organ Function: Have acceptable organ function as defined as:
    a. Renal function:
        i. Serum creatinine concentration ≤1.5 × institutional upper limit of normal (ULN) based on the age and sex, or creatinine clearance (CrCl) >50 mL/min (0.84 mL/s) (as measured preferably by a nuclear glomerular filtration rate scan, timed urine collection for CrCl, or calculated by the Schwartz formula [for subjects <18 years] or Cockcroft-Gault [for subjects ≥18 years] and normalized to a BSA of 1.73 m2).
    b. Hepatic function:
        i. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age except for subjects with confirmed Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
        ii. Alanine aminotransferase (ALT) or SPGT ≤ 3 x ULN
        iii. Aspartate aminotransferase (AST) or SGOT ≤ 5 ULN

iv. Serum albumin may be lowered in this subject population and will not be used to evaluate adequate liver function

c. Adequate cardiac function as indicated by
   i. Left Ventricular Shortening fraction of $\geq$ 27% by echocardiogram **or** ejection fraction of $\geq$ 50% by MUGA
   ii. No documented history of congestive heart failure (New York Heart Association functional classification III-IV)
   iii. No history of long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome

d. Adequate Bone Marrow Function
   i. Hemoglobin $\geq$ 8 g/dL (may receive RBC transfusions)
   ii. Absolute Neutrophil Count (ANC) $\geq$ 750 x 10^9/L
   iii. Platelets $\geq$ 75 x 10^9/L (independent of transfusions) exception is made for Kaposiform lymphangiomatosis subjects who have a baseline coagulopathy and thrombocytopenia.

8. Persons who can get pregnant 11 years of age or persons with early onset menarche must have a negative serum or urine pregnancy test within 7 days prior to the initiation of the study medication.
9. Males and females of reproductive potential must agree to the use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), IM progesterone depot, intrauterine contraceptive device, or an oral contraceptive, for the duration of time when they are receiving study drug and for 3 months following last dose.
10. Subjects must be able to swallow tablets or liquid or use a nasogastric or gastric tube for liquid study medication administration.
11. Subjects who require physiologic or stress doses of steroids due to endocrine deficiencies are eligible.
12. Subjects who have previously received MEK inhibitors are eligible if otherwise meeting all eligibility criteria and concomitant medication requirements.

5.2 Exclusion Criteria

A potential subject must meet all of the inclusion criteria above. A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Patients seeking treatment for hypertrophic cardiomyopathy without a vascular anomaly
2. Concomitant/Prior Medications
   a. No immunomodulating agents will be used concomitantly including mTOR inhibitors. Steroid premedication for imaging scans is allowed. Replacement therapy (eg., thyroxine, insulin, or physiologic or stress corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
   b. Prior treatment with a MEK inhibitor or a modulator of the Ras/MAPK pathway medication as single agents or in combination are eligible for this study provided there were no known hypersensitivity or allergic reactions

attributed to any of the components of compounds of similar composition to trametinib, no utilization within 30 days prior to enrollment, and patients have fully recovered from toxic effects of prior therapy (as determined by treating physician).

c. mTOR inhibitors must not be given within 14 days of study drug initiation. Investigational drugs: Patients currently receiving another investigational agent are not eligible.
d. Investigational drugs: Patients currently receiving another investigational agent are not eligible.
e. Any investigational drug use within 30 days prior to enrollment. For agents that have known adverse events occurring beyond 30 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
f. Cancer chemotherapy, radiotherapy, or immunomodulatory agents must not be given within 30 days of study drug initiation.
g. Cardiac medications: Patients currently receiving treatment for left ventricular systolic dysfunction are not eligible.
h. Supportive care use of anticoagulants and compression garments is allowed. Patients must have been using these interventions in an unchanged manner for 30 days before study.

3. Infection: Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment). Patients with possible fungal infections must have had at least 2 weeks of appropriate anti-fungal antibiotics and be asymptomatic.
4. Patients with history of hepatic sinusoidal obstructive syndrome (veno-occlusive disease of the liver) in the prior 3 months.
5. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with absorption of drug excluding PLE.
6. Patients with history of or current risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) or uncontrolled glaucoma or ocular hypertension.
7. Allergic reactions: Patients with a history of allergic reaction attributed to compounds of similar chemical or biological composition to trametinib are not eligible.
8. History of prior and or ongoing malignancy (within 5 years before informed consent except radically treated carcinoma in situ or radically treated basal-cell carcinoma of skin or thyroid gland, well-differentiated microcarcinoma or Stage 1 Wilms' tumor of a histology other than anaplastic), or ongoing investigations or treatment for malignancy at time of informed consent.
9. Patients unable to comply with safety monitoring requirements.
10. Patient may not be pregnant or breast feeding.
11. Parents/guardian/LAR or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.
12. Debulking or other major surgery performed within 30 days, at time of informed consent;

13. Clinically meaningful bleeding related to VA: Grade 2 within 14 days or Grade 3 and more within 28 days before study treatment start as per CTCAE v. 5.0.
14. Sclerotherapy/embolization for vascular complications performed within 14 days before informed consent.
15. Subjects not able to understand and to comply with study instructions and requirements (in patients, legally authorized representatives, or guardians as applicable) at time of informed consent.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

6 STUDY PROCEDURES

Subjects will be evaluated for study eligibility at a screening visit up to 30 days prior to enrollment on study. All laboratory tests done to confirm eligibility must be performed within 14 days unless otherwise noted prior to enrollment. Radiologic disease evaluations must be done within 30 days of enrollment. Subjects will be seen by medical providers for prior history, physical exam, and required assessments as noted below to monitor for toxicities and assess disease status. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. All on-study visit procedures are allowed a window of ± 7 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation but should be noted in the source documents.

6.1 Screening Assessments

Eligibility/screening studies and procedures to be performed at the screening visit (up to 30 days prior to enrollment with the exception of those noted # below).

- Informed Consent: A written, signed informed consent form (ICF)/a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.
- Documentation of validated laboratory result demonstrating a germline or somatic Ras/MAPK-pathway alteration.
- Medical history, physical examination (PE) including skin examination (Screening photograph(s) of cutaneous lesions, lymphedema, or other), medications, and medical records review including history of prior treatments and any residual toxicity relating to prior treatment.
- Height and Weight
- Vital Signs: temperature, pulse, blood pressure, respiratory rate, oxygen saturation by pulse oximeter
- Performance Status: Karnofsky/Lansky Performance Score.
- Laboratory Studies: as outlined in Table 6-1: Protocol-required Safety Laboratory Assessments

Table 6-1: Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Comprehensive Metabolic Panel	• Sodium • Potassium • Chloride • Carbon Dioxide • Urea Nitrogen • Creatine • Fasting Glucose • Calcium • Total Bilirubin • Total Protein • Albumin • Alkaline Phosphatase • Alanine Aminotransferase • Aspartate Aminotransferase
CBC with Differential	• Absolute Neutrophils • Absolute Lymphocytes • Absolute Monocytes • Absolute Eosinophils • Absolute Basophils • Absolute Immature Granulocyte • Nucleated RBC Automated • Platelet count • MPV • Neutrophils % • Lymphocytes % • Monocytes % • Eosinophils % • Basophils % • Immature Granulocyte % • Absolute Neutrophils • Absolute Lymphocytes • Absolute Monocytes • Absolute Eosinophils • Absolute Basophils • Absolute Immature Granulocyte • Nucleated RBC Automated
Coagulation	• Fibrinogen • D Dimer • PT/INR • PTT Profile
Additional Lab Studies	• CK • Lipase • Phosphorous • Magnesium
Pregnancy testing[1]	• Serum or urine pregnancy testing (within 7 days of starting study medication)
WBC= white blood cell; RBC= red blood cell; HGB= hemoglobin; HCT= hematocrit; MCV= mean	

corpuscular volume; MCH= mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; RDW= red cell distribution; MPV= mean platelet volume; PT/INR = prothrombin time/international normalized ratio; PTT= partial thromboplastin time; CK=creatine kinase

[1] Standard pregnancy testing for all people who can get pregnant of childbearing age

    - Optional Biologic Studies
        - Biomarker
        - cfDNA
- Cardiac Assessment:
    - Echocardiogram
        - An age-appropriate transthoracic echocardiogram is recommended with interpretation by a pediatric or adult cardiologist. Documentation of left ventricular shortening fraction and left ventricular ejection fraction is required. Multigated acquisition scan (MUGA) may be substituted for echocardiogram at the discretion of the investigator with a documentation of the left ventricular ejection fraction. It will be completed at screening, at the end of cycles 1, 2, and 3, and after every 3 cycles until the end of the study.
    - ECG
        - An age-appropriate ECG is recommended with interpretation by a pediatric or adult cardiologist. Documentation of the corrected QTC interval is required. To be performed as part of screening, at the end of cycles 1, 2, and 3, and after every 3 cycles until the end of the study (not triplicate). To be repeated at investigator discretion only if clinically indiciated.
- Ophthalmologic exam (Within 12 weeks of enrollment on trial): an age-appropriate ophthalmologic examination that avoids any sedation should be performed by an ophthalmologist at screening. This includes a Snellen examination (if age appropriate as determined by the ophthalmologist). The examination must include a funduscopic evaluation to rule out retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED), can be dilated or non-dilated at discretion of ophthalmologist and can be accomplished using imaging with a non-mydriatic fundus camera.
- Individualized Response Criteria
    - Radiologic assessment (within 4 weeks of enrollment)
        - Radiologic assessment/imaging modality of choice based on underlying vascular anomaly (MRI, MRL, US, X-rays, CT scan)
    - Patient Reported Outcome (PRO) Measurement
        - PROMIS measures are not applicable or validated for subjects younger than 1 year of age. If infants younger than 1 year of age are enrolled in this study, they will not have PROs, and their response criteria will be determined by radiologic response and CBA.

Construct	**Adult Subject**	**Parent Proxy**	**Parent Proxy 5-**	**Pediatric Subject 8-17**

	18+ y/o	**1-5 y/o**	**17 y/o**	**y/o**
Primary Outcome for Individualized Response				
Global Health – Physical Health Subscale	PROMIS Scale v1.2 - Global Health	PROMIS Early Childhood Parent-Report Scale v1.0 - Global Health 8a	PROMIS Parent Proxy Scale v1.0 - Global Health 7+2	PROMIS Pediatric Scale v1.0 - Global Health 7+2
Secondary Outcome for Individualized Response				
Pain Interference	PROMIS Short Form v1.1 - Pain Interference 4a	N/A	PROMIS Parent Proxy SF GenPop v3.0 - Pain Interference 8a	PROMIS Pediatric SF GenPop v3.0 - Pain Interference 8a
Exploratory Outcomes				
Fatigue	PROMIS Short Form v1.0 - Fatigue 4a	N/A	PROMIS Parent Proxy SF GenPop v3.0 - Fatigue 10a	PROMIS Pediatric SF GenPop v3.0 - Fatigue 10a
Anxiety	PROMIS Short Form v1.0 - Anxiety 4a	PROMIS Early Childhood Parent-Report Short Form v1.0 - Anxiety 4a	PROMIS Parent Proxy SF GenPop v3.0 - Anxiety 8a	PROMIS Pediatric SF GenPop v3.0 - Anxiety 8a
Depression	PROMIS Short Form v1.0 - Depression 4a	PROMIS Early Childhood Parent-Report Short Form v1.0 - Depressive Symptoms 4a	PROMIS Parent Proxy SF GenPop v3.0 - Depressive Symptoms 6a	PROMIS Pediatric SF GenPop v3.0 - Depressive Symptoms 8a

- Clinical Benefit Assessments (CBA)

At the screening visit, the site PI and treatment team with parental/patient input will determine the CBA or CBAs to be followed for that subject and will document during that study visit. If the site PI has any questions, they will be discussed with the Chair and Co-chair of the protocol.

Some suggestions for CBA: See Appendix X.

Examples of testing or assessments that can be followed to complete this grading scale include:

- Pulmonary function testing
- Lymphedema staging
- Laboratory parameters
- Bleeding assessment
- PLE grading
- Effusion assessment
- Infection rates
- Seizure grading
- Photography
- Videos
- Patient narratives

6.2 Study Treatment Phase

Subjects must meet all eligibility criteria by Day 1 to continue into the study treatment phase. The study treatment phase begins with Cycle 1, day 1 and continues through 28-day cycles. Please refer to Table 8-1 Schedule of Assessments for required assessments.

6.2.1 Treatment Compliance and Adherence

Subjects will document medication adherence in a medication diary, Appendix III or Appendix IV. The diary will be provided to the Investigator or designee at each visit, and the subject will then receive a new diary. Remaining medication volume or tablets will be reviewed at each study visit to assess adherence. At the dispensing visit, subjects will be asked to bring all remaining study drug supplies to their onsite visit to assess adherence to treatment.

6.3 Extension Phase of the Study

Subjects in the absence of toxicity and with clinical benefit may continue into the extension period for up to 12 additional cycles (36 total cycles, including the treatment phase). This will be at the discretion of the treating physician and subject/subject's family. A subject may receive extension therapy for a total duration of 36 cycles (including the first 24 cycles of study treatment).

6.4 Follow-up Phase

All subjects, including those who discontinue protocol therapy early, will be followed at least 30 days following cessation of study drug unless withdrawal of consent occurs.

There will be one scheduled visit 30 days following completion of the trial (after cycle 24 if not continuing on to the extension phase) or cessation of study drug. The following procedures will be performed at the follow-up visit:

- Medical history and Assessment for adverse events
- Concomitant medications
- PE with dermatologic examination (Photograph(s) of new or changing cutaneous lesions, lymphedema, or other)
- Height, weight, and vital signs: temperature, pulse, blood pressure, respiratory rate, oxygen saturation by pulse oximeter
- Performance Status: Karnofsky/Lansky Performance Score.
- Laboratory studies as outlined in section 6.1 Screening Assessments
- Pregnancy testing for all subjects of childbearing potential: serum or urine pregnancy testing
- Collect unused study drug and diary
- If not done within 3 months of the study termination the following needs be to performed:
    - Ophthalmologic exam as outlined in section 6.1 Screening Assessments
    - ECHO as outlined in 6.1 Screening Assessments

6.5 Unscheduled Visits

Unscheduled visits will occur for any symptoms or concerns for toxicity, drug tolerance, acute changes in physical well-being, or other concerns. Study subjects will call study team representative and be seen in the clinic or by their local medical provider, or emergency department with communication with study team.

6.6 Subject Completion/Withdrawal

Criteria for withdrawal of subjects and plans for provision of care after withdrawal.

Subjects may withdraw from the study at any time without prejudice to their care. They may also discontinue study participation at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, due investigator discretion, or family/subject preference. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

7 SUPPORTIVE CARE AND CONCOMITANT MEDICATION

7.1 Other Treatment(s)

All subjects will be allowed to receive concomitant medication and/or other non-medication treatment (e.g., rescue surgery) when clinically indicated to control comorbidities and/or complications of their VA. Rescue surgery is defined as a salvage intervention, and includes e.g. debulking surgery, orthopedic surgery, invasive vascular surgeries/procedures. As much as possible, surgery targeting VA-related lesion volume reduction should be avoided. Systemic therapy targeting Ras/MAPK pathway other than trametinib and/or any investigational/not approved medication for VA are not allowed during the conduct of the study.

During the course of the study, the subject must also not receive anti angiogenic agents for the purpose to treat VA.

The subject must discontinue from specific treatment with small molecules (such as mTOR inhibitors, AKT inhibitors) before any of study related assessments and at least 30 days before study treatment start per inclusion/exclusion criteria.

Subjects are not allowed to receive any other investigational drugs.

7.2 Concomitant Therapy

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study.

At each study visit subjects should be asked: "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?".

All medications (other than trametinib) including non-prescription medication(s), vitamins and herbal product(s), taken during the study will be recorded in the CRF. Any significant non-drug therapies should also be noted in the subject's CRF.

Subjects should receive all necessary supportive care during the study.

Examples of permissible concomitant therapies:

- Transfusions of blood and blood components
- Pain relief medication
- Anti-infective medications (see prohibited and cautioned medications in Section 7.2.1 and 7.3). Investigators should discuss prescription of anti- fungal, anti-viral agents with Novartis.
- Treatment for concomitant medical conditions, adverse events (see prohibited and cautioned medications in Section 7.2.1 and 7.3)
- Supplemental nutrition (enteral, parenteral)
- Routine vaccinations including live vaccines as needed based on subject age
- Supportive care use of anticoagulants and compression garments is allowed. Subjects must have been using these interventions in an unchanged manner for 30 days before study enrollment
- Replacement therapy (e.g., thyroxine, insulin, or physiologic or stress doses of corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) are permitted. Steroid premedication for imaging scans is allowed.

7.2.1 Permitted concomitant therapy requiring caution and/or action

As trametinib is metabolized predominantly via deacetylation mediated by hydrolytic enzymes(e.g. carboxylesterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions. Trametinib repeat-dose exposure was not affected by co administration with a CYP3A4 inducer. Based on in vitro and in vivo data, trametinib is

unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters.

Please refer to the latest version of trametinib IB for additional information pertaining to trametinib[63].

7.3 Prohibited medication

No other cancer chemotherapy, radiotherapy, or immunomodulatory agents including mTOR inhibitors will be permitted while on treatment with study drug. Agents must not be given within 30 days of study drug initiation.

7.4 Rescue Medication Administration

Supportive care measures including but not limited to antimicrobials, topical steroids, antiemetics, blood products, fluids, electrolytes, albumin infusions, immunoglobulin infusions will be permitted while on study as rescue medications for adverse events or other causes (acute hypotension, acute or chronic anemia, acute or chronic hypoalbuminemia, acute infection, etc.). Decision for supportive care will per administered per the provider's discretion at the time subject presents with symptoms or signs requiring escalation of care (emergency department, urgent care, inpatient setting, primary provider).

8 STUDY EVALUATIONS AND MEASUREMENT

8.1 Schedule of Assessments

The schedule of assessments Table 8-1 lists all the assessments to be performed as part of the study, an "X" in the table indicates the visit(s) when they are to be performed.

All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the end of treatment visit will be performed. At this visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

During the course of the study, test procedures should occur on schedule whenever possible as per allowable visit. For Cycles 1-3, the window is +/- 3 days; for all other cycles, the window is +/- 7 days.

If the COVID-19 or other pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls or virtual contacts (e.g. teleconsultation), can replace on-site study visits, for the duration of the pandemic until it is safe for the subject to visit the site again.

Table 8-1 Schedule of Assessments

Footnotes:

Day[1]: Cycles 1-3: +/- 3 days; Cycles 6-24: +/- 7 days
Laboratory studies[2]: as outlined in section 6.1 Screening Assessments
Urine or serum pregnancy[3]: as outlined in section 6.1 Screening Assessments
ECG[4]: repeat during the study if abnormal at screening or as clinically indicated per treating team (not triplicate)
X[4]: repeat during the study if abnormal at screening or by decision of the treating team (not triplicate)
Ophthalmologic exam[5]: As outlined in section 6.1 Screening Assessments
Radiologic assessment[6]: At screening and at the end of every cycle 6 cycles on treatment are mandatory. Following radiologic assessments as per decision of local treating team
X[7]: Within 4 weeks (28 days) of screening
Optional Biologic Studies[8]: As outlined in section 6.1 Screening Assessments
X[9]: All labs, physical exams, and vital signs, must be done within 14 days of starting Trametinib
X[10]: If applicable, dependent on treating team

8.1.1 Medical Record Review

The following will be abstracted from the medical chart (paper or electronic):

- Demographic characteristics (age, gender, race, ethnicity)
- Location/locations of vascular anomaly
- Histologic Diagnosis
- Diagnostic vascular anomaly data
- Vascular Anomaly Past Medical History including:
    - Surgical procedures
    - Interventional Radiology procedures
    - Prior vascular anomaly directed medical therapy (medication, dates, response)
- General Past Medical History:
    - Diagnoses and relevant dates
    - Surgeries and relevant dates
    - Medications
- Current laboratory testing (within 14 days of screening)
- Current radiologic assessment

8.1.2 Physical Examination

General physical examination will include assessments of the following systems: General, Head/Ears/Eyes/Nose/Throat (HEENT), Respiratory, Circulatory, Abdominal, Neurologic, Musculoskeletal, Dermatologic, Lymphatic, Psychiatric, and Dental exam.

8.1.3 Vital Signs

Vital signs to be collected per institutional age-appropriate standards: Height, Weight, Temperature, Pulse, Respiratory Rate, Blood pressure, and Pulse Oximetry.

8.1.4 Laboratory Evaluations

- Blood sampling will be performed per institutional standards.
- Laboratory studies as outlined in section 6.1 Screening Assessments.

8.1.5 Pregnancy Testing

Pregnancy testing as outlined in section 6.1 Screening Assessments.

8.1.6 Other Evaluations, Measures

- Echocardiogram: As outlined in 6.1 Screening Assessments.
- Electrocardiogram (ECG): As outlined in 6.1 Screening Assessments.
- Ophthalmologic examination: As outlined in 6.1 Screening Assessments.

8.2 Efficacy Evaluations

The optimal measure of disease response in subjects with complex vascular anomalies has not been established. Current practice includes changes in physical exam, radiographic (MRI) evaluations, laboratory assessments and/or quality of life measures. These lesions are difficult to assess with any one method because of heterogeneity in growth patterns, diversity of associated clinical and laboratory abnormalities and a fluctuating clinical course dependent upon factors other than treatment, such as intercurrent infections, puberty, and trauma. It is currently unclear if there is a good correlation between lesion size, determined radiographically and clinical changes or quality of life measures. For these reasons we have elected to assess disease response using three distinct criteria generating a single composite assessment or Individualized Response Criteria:

Radiologic Response	PROMIS	Assessment of Clinical Benefit (examples)
-MRI (recommended) -MRL (see notation below) -CT Scan -US -Xray -Dexascan	See below (8.2.2)	**Parameters for grading the Clinical Benefit Assessment (Appendix X)** Examples of testing or assessments that can be followed to complete this grading scale include: ○ Pulmonary function testing ○ Lymphedema staging ○ Laboratory parameters ○ Bleeding assessment ○ PLE grading ○ Effusion assessment ○ Infection rates ○ Seizure grading ○ Photography ○ Videos ○ Patient narratives

8.2.1 Radiographic Response

8.2.1.1 MRI/MRL:

MRI or MRL imaging will be recommended as primary imaging modality for all subjects enrolled in VATCH sub-protocols. For subjects with disease manifestation better characterized by alternative quantitative imaging modality (i.e. X-ray or ultrasound) this may be substituted and used as alternative imaging. MRI or MRL is the preferred method of imaging. MRI/MRL imaging will be done at screening and at the end of cycles 6, 12, and 24 on treatment. Additional assessments can be performed in accordance with the local institutional practice. For each imaging assessment timepoint initial radiographic response will be reviewed by each site's radiologist.

When possible and appropriate, volumetric imaging will be used in combination with standard vascular MRI protocols to assess vascular anomaly response. MRI will be performed using a 1.5 Tesla system (HDX 15.0 series MRI, GE and Espree B-15 series MRI, Siemens). Coronal and axial fast spin-echo T2-weighted sequences will be performed with and without fat suppression. Up to 3 lesions should be identified as target lesions and recorded and measured at screening. Target lesions should be selected on the basis of their size and their suitability for accurate repeated measurements (either by imaging techniques or clinically). The same method of assessment and the same technique should be used to characterize each target lesion at screening and during follow up (APPENDIX VI).

8.2.1.2 Other Radiographic Assessment

Other imaging modalities including, but not limited to Computed tomography (CT) Scan, Ultrasound (US) or X-ray may be utilized for radiographic assessment criteria either in supplement to or in replacement of MR imaging as noted above. Target lesions should be selected on the basis of their size and their suitability for accurate repeated measurements (either by imaging techniques or clinically). The modality and imaging methods will be determined for enrollment screening and the same method of assessment, and the same technique, should be used to characterize each target lesion at screening and during each imaging follow up. Examples of imaging would be X-Ray for bone disease, ultrasound for pleural effusions, dexascan for lymphatic anomalies with bone lesions, and US (contrast or non-contrast for superficial lesions to assess size and other characteristics such as flow.

8.2.2 Assessment of Patient Reported Outcome Measures (PROMs)

Quality of life is an essential component of high-quality clinical care.[53] The Patient Reported Outcomes Measurement Information System (PROMIS) is a validated parent/patient-reported scoring system that was developed with the National Institutes of Health (NIH) that can compare values across a variety of medical conditions.[33,34] PROMIS is validated in individuals aged 8 years and older.[56–58] A caregiver proxy report for the PROMIS measure is also available for use in children; for individuals younger than 8 years old, assessments must be completed by a caregiver proxy. PROMIS is considered to be the gold standard for HRQOL measurement in clinical trials. The recall timeframe for each question includes the past week.

Each question has five response categories. A raw score can be calculated for each PROMIS subscale. Raw scores are then translated into a T-score metric with mean of 50 (standard deviation of 10). A higher PROMIS T-score represents more of the concept being measured. Additional details for scoring and measure interpretation are available at https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis. Higher scores represent better functioning. A difference or change in score of three points on the PROMIS Pediatric scale is considered a minimally important difference (MID).

In consultation with subjects, patient advocates, clinicians, and psychometricians, we will use global health measures as the **primary outcome** and pain interference as the **secondary outcome**. For exploratory outcomes, we will administer PROMIS measures for fatigue, anxiety, and depression. This survey battery will be administered every 6 cycles, starting at enrollment and continuing during participation in the study.

For subjects **18+ years old at enrollment**, please refer to "Adult subject 18+ y/o" column in Table 8-3. In total, this battery of measures will include **26 items**. We will also include 2 open-ended questions for exploratory analysis: 1) What positive or negative changes have you noticed since you started taking the medication? 2) What else would you like us to know? For adults with cognitive impairment, guardian/LAR may provide proxy answers for the surveys at the discretion of the study chair and co-chair on a case-by-case basis.

For subjects **8-17 years old at enrollment**, please refer to "Pediatric Subject 8-17 y/o" column in Table 8-3. In total, this battery of surveys will include **43 items**. We will also include 2 open-ended questions for exploratory analysis: 1) What good or bad changes have you noticed since you started taking the medication? 2) What else do you want us to know? For subjects aged 8-17 years old at enrollment, we will simultaneously administer subject-report and proxy-report surveys. (see next paragraph for proxy measures)

For subjects **5-17 years old at enrollment**, please refer to "Parent Proxy 5-17 y/o" column in Table 8-3In total, this battery of surveys will include **41 items**. We will also include 2 open-ended questions for exploratory analysis: 1) What positive or negative changes have you noticed since your child started taking the medication? 2) What else would you like us to know?

For subjects **1-5 years old at enrollment**, please refer to "Parent Proxy 1-4y/o " column in Table 8-3. In total, this battery of surveys will include **16 items.**

If subjects change age category after enrollment, they will continue using the same measures from their time of enrollment, rather than switching measures.

Table 8-3

Construct	Adult Subject 18+ y/o	Parent Proxy 1-5 y/o	Parent Proxy 5-17 y/o	Pediatric Subject 8-17 y/o

Primary Outcome for Individualized Response				
Global Health – Physical Health Subscale	PROMIS Scale v1.2 - Global Health	PROMIS Early Childhood Parent-Report Scale v1.0 - Global Health 8a	PROMIS Parent Proxy Scale v1.0 - Global Health 7+2	PROMIS Pediatric Scale v1.0 - Global Health 7+2
Secondary Outcome for Individualized Response				
Pain Interference	PROMIS Short Form v1.1 - Pain Interference 4a	N/A	PROMIS Parent Proxy SF GenPop v3.0 - Pain Interference 8a	PROMIS Pediatric SF GenPop v3.0 - Pain Interference 8a
Exploratory Outcomes				
Fatigue	PROMIS Short Form v1.0 - Fatigue 4a	N/A	PROMIS Parent Proxy SF GenPop v3.0 - Fatigue 10a	PROMIS Pediatric SF GenPop v3.0 - Fatigue 10a
Anxiety	PROMIS Short Form v1.0 - Anxiety 4a	PROMIS Early Childhood Parent-Report Short Form v1.0 - Anxiety 4a	PROMIS Parent Proxy SF GenPop v3.0 - Anxiety 8a	PROMIS Pediatric SF GenPop v3.0 - Anxiety 8a
Depression	PROMIS Short Form v1.0 - Depression 4a	PROMIS Early Childhood Parent-Report Short Form v1.0 - Depressive Symptoms 4a	PROMIS Parent Proxy SF GenPop v3.0 - Depressive Symptoms 6a	PROMIS Pediatric SF GenPop v3.0 - Depressive Symptoms 8a

*For adults with cognitive impairment, guardian/LAR may provide proxy answers for the surveys at the discretion of the study chair and co-chair on a case-by-case basis.

8.2.3 Assessment of Clinical Benefit

A set of clinical benefit assessments will supplement the radiographic and the PROMIS measures. The clinical benefit assessment tools will be determined at initial screening evaluation for the subject. The same clinical benefit assessment tools will be completed at enrollment and then every 6 cycles for the duration of the study. The investigator will determine the clinical benefit assessment and have this reviewed by the study PI if no radiologic assessment is noted.See Appendix X.

8.2.3.1 Photography/Videos

Assessment with photography and video evaluation can be performed if clinically relevant. If selected as a clinical benefit assessment at initial screening evaluation for the subject this will be documented and obtained as part of enrollment screening. Photography will be obtained at each assessment. Images will be obtained per institutional standard for inclusion into the medical record. Photography under the same conditions and positioning to allow for accurate quantification and qualification on lesional changes is recommended.

8.2.3.2 Patient Narratives

To capture patient narratives, we will administer 5 open-ended questions along with the patient-reported outcome measures at the 6-month time point. Participant responses will be reported in the electronic data capturing system. The questions are listed below.

The study team would like to learn how this medication has affected you. We are interested in any changes caused by the medication. Below, the questions will be about how the medication has affected your vascular anomaly and your overall health. You can skip questions that do not apply to you, or you can respond "none".

1. **How has your vascular anomaly gotten better since starting on medication? It is okay to write "none" if nothing has gotten better.**
    a. **How has the rest of your health gotten better since starting on medication in this study? It is okay to write "none" if nothing has gotten better.**
2. **How has your vascular anomaly gotten worse since starting on medication? It is okay to write "none" if nothing has gotten worse.**
    a. **How has the rest of your health gotten worse since starting on medication in this study? It is okay to write "none" if nothing has gotten better.**
3. **What else would you like us to know about your experience taking this medication**

8.3 Assessment of Overall Response

8.3.1 Definitions

Evaluable for Toxicity: All subjects will be evaluable for toxicity from the time of their first study drug treatment.

Evaluable for Objective Response: Only those subjects have received at least one therapy cycle and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable for response.)

Target Lesions: All measurable lesions up to a maximum of three lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at screening radiographic assessment

or clinical photograph. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective lesion response.

Nontarget Lesions: All other lesions (or disease sites), including any measurable lesions over and above the three target lesions should be identified as nontarget lesions and should also be recorded at screening. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver lesions"). Bone lesions may be measurable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

8.3.2 Response Criteria for Overall Response

The primary endpoint of this VATCH sub-protocol is to determine whether the MEK inhibitor trametinib administered once a day on a continuous dosing schedule to subjects with Ras/MAPK pathway driven Vascular Anomalies provides an objective response at the end of cycle 6. Assessment of response is an individualized response criterion based on radiologic assessment, Patient Reported Outcome Measurements (composite score) and Clinical Benefit Assessment. Disease Response is determined by the local institution/investigator and is defined below.

Clinically meaningful response:

A clinically meaningful response includes a substantial response, Intermediate response or stable disease at the timing of protocol assessment.

Assessment of individualized response criteria after 6 cycles for primary endpoint and then every 6 months.

Substantial response:

- Improvement in Radiologic assessment (if applicable) by 20% AND
- Improvement in Global Health PROs by 3T-score points* AND
- Improvement in at least 1 CBA as reported by the clinician AND
- No clinically meaningful worsening in any measure

Intermediate response:

- Improvement in Radiologic assessment (if applicable) by 20% OR
- Improvement in Global Health PROs by 3 T-score points* OR
- Improvement in at least 1 CBA as reported by the clinicians AND
- No clinically meaningful worsening in any measure

Stable disease:

- No clinically meaningful improvement or worsening from screening in
  - Radiologic assessment (if applicable), OR
  - Global Health PROs*, OR
  - CBA as reported by the clinician

Worsening disease:

- Clinically meaningful worsening in
  - Radiologic assessment (if applicable) by 20%, OR
  - Global Health PROs by 3T-score points*, OR
  - CBA as reported by the clinician
  - **Regardless** of any concomitant improvement in other measures.

*Prior review articles have indicated that a change of 2 to 6 T-score points is the minimum important change (MIC) for PROMIS measures. PROMIS leadership recommends 3 T-score points as the MIC[61,62].

8.3.3 Duration of Response

Duration of Overall Response: The overall response (substantial or intermediate) duration is measured from the time of primary endpoint measurement (6 cycles) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the worsening disease criteria are met, or patient on evaluation has a substantial or intermediate response.

9 STATISTICAL CONSIDERATIONS

This is a Phase II non-randomized study to evaluate trametinib in children and young adults with Ras/MAPK Driven Vascular Anomalies. The primary efficacy endpoint is objective response at the end of cycle 6 and the primary safety endpoint is toxicity of trametinib. Secondary endpoints duration of response, response at scheduled protocol visits during the extension period, and assessment of changes in symptoms and complications over time. Biomarker analysis is exploratory in this protocol.

9.1 Sample Size and Power

For the primary efficacy analysis of objective response at the end of cycle 6, we will test a null hypothesis of response of 40% against an alternative hypothesis of response rate of 65%. We will follow the Simon's optimal two-stage design: an interim analysis will be conducted after 16 subjects have been observed for response, and if 6 or fewer response is observed, the trial will be stopped for futility; otherwise the trial will continue to enroll a total of 39 evaluable subjects and at the end of the trial if 20 or more responses are observed, the treatment will be declared promising. This design provides >=90% power when the true response rate is 65% and yields a one-sided type I error of <=0.05 when the true response rate is 40%.

For evaluating of toxicity, a sample size of 39 provides 86% probability to observe at least one toxicity event when the underlying true toxicity rate is 5%, so that we have good confidence to observe a rare toxicity type. In addition, this sample size provides a reasonable precision on the estimate of the toxicity rate. For example, with 7 observed toxicity events

out of 39 subjects, the estimated toxicity rate is 18%, with the 95% exact confidence interval (CI) as 8% - 34%.

9.2 Safety monitoring

We will monitor the incidence of severe toxicity that occurs during the first 2 courses and is associated with the treatment (Grade 4 non-hematologic toxicity with specific exclusion of Grade 4 fever/pyrexia which response to Grade <2 within 72 hours with supportive care, Grade 3-4 Left ventricular ejection fraction decrease, Grade 3-4 Retinal detachment or retinal vein occlusion, Grade 2 pneumonitis, Grade 4 rash, Grade 4 hypertension, or Grade >2 allergic reaction). An early stopping rule will be invoked to pause the study if there is evidence that the observed severe toxicity rate is higher than the acceptable rate of 10%. Specifically, if the lower bound of the two-sided 95% exact CI exceeds 10% then the stopping rule will be triggered. We will monitor severe toxicity continuously, after five subjects are enrolled. Toxicity will be reviewed and if the number of subjects with a severe toxicity is equal or greater than the number indicated in the table below, accrual will be paused. Based on simulations, the stopping rule implies that the probability of early stopping will be 5% if the underlying true toxicity rate is 10%, the probability of early stopping will be 55% if the underlying true toxicity rate is 20%, and the probability of early stopping will be 91% if the underlying true toxicity rate is 30%.

Number of subjects	Trial will be paused if the number of subjects with severe toxicity >=
5-6	3
7-11	4
12-17	5
18-23	6
24-29	7
30-36	8
37-39	9

9.3 Statistical Analyses Plan

For all the analyses, subjects who received any dose of trametinib will be included in the analyses. The primary efficacy endpoint is objective response (including both response and partial response) at the end of cycle 6 and the primary safety endpoint is toxicity of trametinib. We will use binomial distributions to estimate the response and the toxicity rates with their 95% exact CIs. For the second primary efficacy endpoint of responses at the end of cycles 12 and 24, the response rate will also be calculated with 95% CI. For the secondary endpoint of duration of response, time from initial response to disease progression will be examined, and subjects will be censored at the last adequate disease assessment if no progression occurred by that time. We will use the log-rank tests and/or Cox proportional hazard regression to analyze the endpoint. Should the data suggest the violation of the

proportional hazard assumption, we will consider an alternative method such as accelerated failure time model analysis.

Secondary data analyses will be performed for the secondary outcomes of longitudinal measurements of radiologic assessment, PROMIS Patient Reported Outcome measurements, and Clinical Benefit Assessments, taken at screening, and at the end of cycles 6, 12, 18, and 24. The longitudinal data will be analyzed separately at each follow-up time point and together longitudinally. The paired t-test will be used to look at changes in these measures from pre-treatment levels to the post-treatment level (follow-up at cycle 3) to evaluate the treatment's short-term effects. Mixed effects models will be used for longitudinal analysis to evaluate changes in these measures over time. Should the data suggest the distributions of the measurements deviate from normal distributions, we will consider nonparametric alternatives such Wilcoxon signed rank test or transformation. Relationships between PROMIS measures and other variables such as pain will be investigated using correlation analysis. Lastly, exploratory analyses will be performed for biomarker measures such as cell-free DNA. Descriptive statistics will be generated to summarize data.

10 DOSE MODIFICATION AND MANAGEMENT OF ADVERSE EVENTS

10.1 Dose Modifications

10.1.1 Dose Escalation

Patients with critical illness may be initiated at starting dose of 0.0125 mg/kg with approval of study chair or co-chair. If in the opinion of the site investigator this dose is tolerated may then increase to the standard 0.025 mg/kg dosing. This should take place no later than after 3 cycles of treatment.

0.032 mg/kg dosing: Prior Oncologic dosing in patients less than 6 years of age has demonstrated tolerability in those populations at 0.032 mg/kg dosing. Escalation to 0.032 mg/kg dosing prior to completion of 6 cycles of treatment only after approval of study chair or co-chair.

10.1.2 Dose Interruptions

Dose interruption because of safety and/or other medically relevant reason may last up to 60 days, afterward the subject may restart study therapy. If a patient is off therapy for up to 60 days, the study chair needs to be notified.

10.2 Dose Reduction

10.2.1 Definition of Dose-Modification Toxicity

Dose-modification toxiticy will be defined as any of the following events that are possibly, probably or definitely attributable to trametinib.

Dose modifying hematological and non-hematological toxicities are defined differently.

10.2.1.1 Non-Hematological Dose-Modifying Toxicity

- See Section 10.2.6 for management guidelines for toxicities of special interest. Note that dose modification or discontinuation of trametinib for toxicity is considered a dose modifying toxicity.
- Any Grade 4 non-hematological toxicity with specific exclusion of:
  - Grade 4 fever/pyrexia that resolves to Grade < 2 within 72 hours with supportive care (anti-pyretics)
- Dose-modifying hypertension will be considered as the following:
  - Grade 4 hypertension,
  - A blood pressure > 25 mm Hg above the 95th percentile for age, height, and gender, confirmed by repeated measurement

  Note: if elevated, take 3 serial blood pressure readings from the same extremity with the patient in the same position, separated by at least 5 minutes. Avoid using the lower extremity if possible. Use the mean average of the 3 measurements.
- Any Grade 3 non-hematological toxicity with the specific exception of:
  - Grade 3 nausea and vomiting of less < 3 days duration

- Grade 3 fever or infection < 7 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation within 7 days
- Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered a dose-modifying toxicity
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption
- Grade 2 left ventricular ejection fraction disease
- Grade 2 cardiac valvular toxicity (mitral/aortic/tricuspid)
- Grade 2 pneumonitis
- Treatment interruption longer than 14 days due to delayed recovery from toxicity will be cause for dose modification

10.2.2 Hematological Dose-Modifying Toxicity

Hematologic will be defined as failure to recover a peripheral ANC > 500/µL and platelets > 20,000/µL by 42 days after the first treatment day, not due to malignant infiltration.

Note: Grade 4 febrile neutropenia will not be considered a dose-modification toxicity.

10.2.3 Dose Modifications for Non-Hematologic Toxicity

If a subject experiences a dose-modifying non-hematologic toxicity as defined in Section 10.2.1, the treatment will be held.

If the toxicity does not resolve to meet inclusion/exclusion parameters or baseline within 14 days of drug discontinuation the subject must be removed from protocol therapy unless specifically documented in toxicities of special interest Section 10.2.6.

If the toxicity resolves to meet inclusion/exclusion parameters or baseline within 14 days of drug discontinuation the subject may resume treatment with a reduction to the next lower dose according to Appendix II. See Appendix II for dosing modification in subjects receiving oral solution or the specified dose reduction in subjects receiving tablets.

- Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose, unless otherwise specified in the toxicities of special interest Section 10.2.6.
- If the same dose-modifying toxicity recurs in a subject who has resumed treatment, the subject must be removed from protocol therapy.

10.2.4 Dose Modifications for Hematologic Toxicity

The study chair must be notified for any dosage modification or use of myeloid growth factors.

- If a subject experiences a dose modifying hematologic toxicity as defined in Section 10.2.2, the treatment will be held until improvement to Grade 3 or less.
- Subjects will be allowed 1 episode of Grade 4 hematologic toxicity without dose reduction.
- If there is > 1 hold for Grade 4 hematologic toxicity, dose will be reduced per guidance in Appendix II. Counts should be checked twice weekly during this time.
- Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.
- If dose-modifying toxicity recurs in a subject who has resumed treatment at the reduced dose, the subject must be removed from protocol therapy.

10.2.5 Dose Modifications for Hepatic Toxicity

If a subject experiences Grade ≥ 3 ALT or AST or total bilirubin elevation, treatment will be held. If toxicity resolves to meet eligibility criteria within 7 days, the drug may be resumed at the same dose. Grade ≥ 3 ALT or AST or bilirubin that persists ≥ 7 days will be considered dose-modifying and require dose modification per Section 10.1.3.

Grade	0	1	2	3	4
SGOT (Serum glutamic oxaloacetic transaminase) (AST)	WNL	>ULN to 3x ULN	>3 to 5x ULN	>5 to 20x ULN	>20x ULN
SGPT (Serum glutamic pyruvic transaminase) (ALT)	WNL	>ULN to 3x ULN	>3 to 5x ULN	>5 to 20 x ULN	>20x ULN
Bilirubin	WNL	>ULN to 1.5x ULN	>1.5 to 3x ULN	>3 to 10x ULN	>10x ULN

Safety Follow-Up Procedures for subjects with ALT or AST ≥3 times ULN or bilirubin ≥1.5 times ULN:

- Monitor subjects weekly until liver chemistries resolve, stabilize, or return to within baseline values.

Safety Follow-Up Procedures for subjects meeting DLT criterion as above (ALT or AST ≥5 times ULN and bilirubin ≥3 times ULN) greater than 7 days:

- This event is considered an DLT.
- Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Subjects should have close follow-up for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, ALP, and bilirubin) resolve, stabilize or return to within baseline values.

- In addition, every attempt should be made to carry out the liver event follow-up assessments described below:
    - Viral hepatitis serology, including:
        - Hepatitis A IgM antibody
        - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM
        - Hepatitis C RNA
        - Cytomegalovirus IgM antibody
        - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, then obtain heterophile antibody or monospot testing)
    - Serum creatine kinase (CK) and lactate dehydrogenase (LDH).
    - Fractionate bilirubin, if total bilirubin ≥2 X upper limit of normal (ULN).
    - Obtain a complete blood count (CBC) with differential to assess eosinophilia.
    - Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE CRF.
    - Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication CRF.
    - In the appropriate clinical setting optional assessments as below should be considered:
        - Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
        - Liver imaging (ultrasound, MRI or CT) to evaluate liver disease.
        - Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week.

10.2.6 Guidelines and Dose Modifications for Trametinib Events of Special Interest

Dose modification and adverse event (AE) guidelines are outlined in the sections below for AEs that are deemed events of special interest including:

- Rash
- Creatinine Kinase (CK) or Creatinine Phosphokinase (CPK) elevations
- Ejection Fraction Changes
- Pneumonitis
- Diarrhea
- Visual Disturbances
- Hypertension
- Paronychia

10.2.6.1 Treatment Dose Modifications and Guidelines for Rash

Dermatologic complications are the most frequent adverse events in subjects receiving trametinib and so both proactive/prophylactic (Section 10.1.6.2) and reactive (Section 10.1.6.3) approaches will be taken. Rashes associated with trametinib have included many different types and can begin as early as cycle 1 or 2. Descriptions include: erythematous rash, maculopapular rash, pruritic rash, acneiform dermatitis, exfoliative rash. Grade 3 rashes are often associated with pruritus and can have scaling. Based on the experience on the current adult Phase I/II study the following recommendations should be followed. For Grade 3 rash trametinib should be held until resolution to Grade 1 or better and then treatment can be resumed at a reduced dose as outlined in the dose reduction table (Appendix II). For eczematous rashes, moisturizers or low-dose topical corticosteroids may be used if based on the rash appearance they would be considered appropriate treatment. For pustular rash, topical clindamycin gel or lotion may be applied twice daily. For more severe cases, oral tetracyclines may be useful in older children. Ketoconazole shampoo may be used for scalp rash. If oral corticosteroids are required for severe rash, trametinib should be held until improvement to < Grade 1 at a reduced dose as outlined in the dose reduction table (Appendix II).

10.2.6.2 Prophylactic Treatment to Prevent Dermatologic Toxicity (Rash)

1) All subjects should avoid unnecessary sunlight and use sunscreen whenever there is possible exposure. Broad-spectrum sunscreen with skin protection factor (SPF)≥ 30 should be applied at least twice daily if subject will be exposed to sun.
2) Recommend a thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. For prepubescent subjects may consider bleach baths.
    a. Add ¼ to ½ cup of regular strength bleach to a full bathtub (or approximately 1 teaspoon per gallon) and soak for 5-10 minutes
    b. Recommended frequency is three times per week
    c. Follow immediately by alcohol-free hypoallergenic skin moisturizer as above
3) Non-alcohol containing mouth rinse (e.g. Biotene, Peridex, or biosimilars) for subjects experiencing mouth sores.
4) Mild strength topical steroid (e.g., hydrocortisone 1% cream) and topical antibiotics (e.g., clindamycin lotion 1.0%) applied at least twice daily starting on Day 1 of study treatment, to baseline affected body areas such as face, chest and upper back with escalation to higher strength and/or oral steroid as detailed in reactive dermatologic toxicity guidelines, Section 10.1.6.3.
5) Agents with the potential to dry skin, such as benzoyl peroxide, salicylic acid, acne skin washes, scrubs, exfoliants, anti-aging creams, alcohol (cleansers, wipes) or other agents that can dry skin such as topical retinoids should be avoided unless directed by dermatologist.
6) Ketoconazole shampoo may be used for scalp rash.

10.2.6.3 Reactive Treatment of Dermatologic Toxicity (Rash)

This is meant to be in supplement to prophylactic measures undertaken per Section 10.1.6.2.

Rash Management (Reactive/Symptomatic) Recommendations Table

Subject Group	Prepubescent Subjects		Postpubescent Subjects
Mild Rash	Dermatitis • Add Hydrocortisone 2.5% cream/ointment BID to affected face and skinfolds, consider escalation to Triamcinolone 0.1% ointment on trunk and extremities	Acneiform Rash • Add Clindamycin lotion 1% BID if not already in use. • Hydrocortisone 2.5% cream/ointment BID can also be added	Acneiform Rash • Add Clindamycin lotion 1% BID if not already in use. • Hydrocortisone 2.5% cream/ointment BID can also be added, consider escalation to triamcinolone 0.1% ointment • Add systemic antibiotic with a tetracycline (e.g. doxycycline or minocycline) for 3 months
Moderate to Severe Rash	Dermatitis • Add Hydrocortisone 2.5% cream/ointment BID to affected face and skinfolds, consider escalation to Triamcinolone 0.1% ointment on trunk and extremities	Acneiform Rash • In addition to above systemic antibiotics with: Cephalexin 20mg/kg/day divided BID (with max dose of 500 mg) for up to 6 weeks OR Amoxicillin 25 mg/kg/day divided BID (with max dose of 875 mg) for up to 6 weeks	
Dermatology referral	Dermatitis which is uncontrolled with recommended supportive care or requiring escalation recommend referral to Dermatology. Additional management may include stronger potency topical steroids, additional antibiotics, or oral retinoids.		

Skin toxicity in the form of rash, fissuring, desquamation, or paronychia is a frequent adverse event (AE) in subjects treated with trametinib. We will use the following management, including dose modification.

CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	Initiate prophylactic and reactive/symptomatic treatment measures Reassess after 2 weeks	Continue treatment If rash does not recover to baseline within 2 weeks despite best supportive care, dose reduction to the next lower dose as per Appendix II.
Grade 2	Initiate prophylactic and reactive/symptomatic treatment measures Reassess after 2 weeks.	Dose reduction: dose reduce to the next lower dose as per Appendix II. Reassess after 2 weeks: • If rash recovers to ≤ grade 1 or

		baseline within 2 weeks, increase dose to previous dose level • If no recovery to ≤ grade 1 or baseline within 2 weeks, interrupt treatment until recovery to grade ≤ 1 or baseline, restart with dose reduction to the next lower dose according to Appendix II.
Grade ≥3	Escalate reactive/supportive treatment measures to include use of moderate strength topical steroids (Consider a brief period of oral high dose steroid such as methylprednisolone) Consult dermatologist	• Interrupt treatment until rash recovers to grade ≤1 or baseline • Restart treatment, dose reduction to the next lower dose according to Appendix II. If no recovery to grade ≤ 2 within 4 weeks, discontinue treatment
Other	If recurrent subjectively intolerable toxicity with at least a week interruption on 2 occasions that is not controlled by optimal supportive medications.	• Interrupt treatment until rash recovers to grade ≤1 or baseline • Restart treatment, dose reduction to the next lower dose according to Appendix II. • If toxicity remains intolerable discontinue treatment.

10.2.6.4 Treatment Dose Modifications and Guidelines for CK or CPK Elevations

Creatine phosphokinase (CPK) also known as creatine kinase (CK) elevations have been observed in subjects receiving trametinib. To reduce the risk of CPK/CK elevations, subjects will be evaluated with serial lab tests as per Section 8.1. Dose modification and supportive care guidelines for CPK/CK elevations are described in the tables and text below.

Grade	0	1	2	3	4
Creatine phosphokinase (CPK)/Creatine Kinase (CK)	WNL	>ULN to 2.5x ULN	>2.5 to 5x ULN	>5 to 10x ULN	>10x ULN

For Grade 1 or 2 and Grade 3 asymptomatic CPK elevations:

- Maintain dose; continue monitoring as per protocol, or more frequently if clinically indicated.

For Grade 3 symptomatic or Grade 4 CPK elevations:

- This event is considered an DLT.
- Hold treatment until resolution to ≤ Grade 1 and dose reduce as per Section 10.2.3

10.2.6.4.1 Recommendations for Elevated CK or CPK

Recommendations for work up of elevated CK or CPK ***Please consider other interventions per institution and patients' condition***
Repeat level
Blood work: • Comprehensive Metabolic Panel (CMP) • Calcium • Uric Acid
Urine for Myoglobin
EKG
Rule out other causes: • Trauma • Alcohol ingestion • Other medications • Cardiac issues • Central Nervous Systems (CNS Issues)

Treatment (symptomatic or CK level greater than 5,000U/L
• Aggressive hydration and diuresis • Admission

10.2.6.5 Treatment Dose Modifications and Guidelines for Reduced Left Ventricular Ejection Fraction Changes

Decreases of the left ventricular ejection fraction (LVEF) have been observed in subjects receiving trametinib. Therefore, ECHO/MUGAs must be performed at screening, at the end of cycle 1, at the end of cycle 3 and then after every 3 cycles thereafter during treatment cycle (e.g. following Cycles 6, 9, and 12). Refer to Table 6-1 Schedule of Assessments for exact schedule. Any additional or ECHO/MUGAs obtained thereafter should be done only if clinically indicated. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at screening and at follow-up visit(s).

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinical Manifestations	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic [c]	Absolute decrease of >10% in LVEF compared to baseline **and** ejection fraction below the institution's LLN.	Interrupt treatment and repeat ECHO/MUGA within 2 weeks. [a] • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): ▪ Consult with the study chair and request approval for restart. ▪ Restart treatment with trametinib at reduced dose.[b] ▪ Repeat ECHO/MUGA 2, 4, 8, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF does not recover within 4 weeks: ▪ Consult with cardiologist. ▪ Permanently discontinue trametinib. ▪ Report as SAE ▪ Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.
Symptomatic [c,d]	Ejection fraction decreased: • Grade 3: resting LVEF 39-20% or ≥20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%. Left Ventricular Systolic Dysfunction: • Grade 3: Symptomatic due to drop in ejection fraction responsive to intervention.	• Permanently discontinue trametinib. • Report as SAE. • Consult with cardiologist. • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.

	• Grade 4: Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated.	

[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
[b] Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from the study chair is required.
[c] Symptoms associated with a decreased ejection fraction may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
[d] Symptoms associated with a decreased ejection fraction can be graded as per CTCAE v5.0 criteria for Left Ventricular Systolic Dysfunction and/or Ejection fraction decreased.

10.2.6.6 Treatment Dose Modifications and Guidelines for Pneumonitis

Pneumonitis has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms and evaluated with routine physical examination and pulse oximetry measurements done as part of routine vitals. Additional imaging to include CXR, CT scan or PFTs if there is clinical concern for pneumonitis. Dose modification and supportive care guidelines for pneumonitis are described in the tables below.

Dose Modification for Pneumonitis

Pneumonitis (NCI CTCAE v5.0)	**Recommended Management Guidelines**	**Dose Modification Requirement**
Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression – re-image at least every 3 weeks. ▪ Monitor for symptoms every 2-3 days – Clinical evaluation and laboratory work-up for infection. ▪ Monitoring of oxygenation via pulse oximetry recommended. ▪ Consultation of pulmonologist recommended.	Continue treatment at the same dose level.

Grade 2	CT scan (high-resolution with lung windows) ▪ Monitor for symptoms daily, consider hospitalization ▪ Clinical evaluation and laboratory work up for infection ▪ Consult pulmonology ▪ Pulmonary function tests- if normal at screening, repeat every 8 weeks ▪ Bronchoscopy with biopsy and/or BAL recommended ▪ Symptomatic therapy including corticosteroids if clinically indicated (systemic corticosteroids at dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated).	1st occurrence: ▪ Interrupt treatment until recovery to ≤ Grade 1 or baseline. Once recovered, dose reduce as per Section 10.2.3 [a] ▪ If no recovery to ≤ Grade 1 within 4 weeks, permanently discontinue treatment. ▪ If worsens treat as Grade 3 or 4.
Grade 3	CT scan (high-resolution with lung windows) ▪ Clinical evaluation and laboratory work-up for infection ▪ Consult pulmonologist ▪ PFTs- if < normal, repeat every 8 weeks until normal ▪ Bronchoscopy with biopsy and/or BAL if possible ▪ Treat with intravenous steroids as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours or equivalent). ▪ If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication.	Interrupt treatment until recovery to Grade ≤ 1 or baseline. ▪ Once recovered, dose reduce as per Section 10.2.3[a] If no recovery to Grade ≤ 1 or baseline within 4 weeks, permanently discontinue treatment.
Grade 4	Same as Grade 3.	Same as Grade 3
[a] Escalation of trametinib to previous dose level can be considered if no recurrence of pneumonitis for 4 weeks after restarting of trametinib. Approval from the study chair is required.		

10.2.6.7 Treatment Dose Modifications and Guidelines for Diarrhea

Etiology and attribution:
Consider evaluation for an alternative etiology of diarrhea as clinically indicated. These include medications (e.g., stool softeners, laxatives, antacids, etc.), infection by C. difficile,

partial bowel obstruction, malabsorption/lactose intolerance, fecal impaction, or diets high in fiber or lactose.

For Grade ≤ 2 diarrhea:
Dietary modifications may include stop all lactose-containing products and eat small meals. A banana, rice, apples, toast (BRAT) diet can be helpful. Encourage oral hydration according to institutional weight oral hydration guidelines as clinically appropriate.

For all subjects consider administration of loperamide with dosing per institutional guidelines or as suggested below. Continuation of loperamide is suggested until the subject is diarrhea-free for at least 12 hours.

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

- If diarrhea resolves to Grade ≤ 1 or baseline within 72 hours of anti-diarrheal measures or supportive care measures, continue study treatment without interruption or dose reduction.
- If Grade 2 diarrhea persists after 72 hours total treatment with loperamide or supportive measures in children < 2 years, hold study treatment and consider start of second-line agents (octreotide) as clinically indicated.
- If diarrhea resolves to Grade ≤ 1 or baseline >72 hours but within 7 days then may resume study treatment with a dose reduction as per Section 10.2.3.
- If Grade 2 diarrhea does not resolve to Grade ≤ 1 or baseline in ≤ 7 days without study treatment, discontinue protocol therapy.

For Grade 3 diarrhea:

- If loperamide has not been initiated, initiate loperamide immediately using institutional or protocol guidelines for dosing as above. For dehydration, use intravenous fluids as appropriate; if severe dehydration, consider administration of octreotide.
- Hold study treatment until symptoms resolve to ≤ Grade 1 or baseline.
    - If diarrhea resolves to Grade ≤ 1 or baseline within 72 hours of anti-diarrheal measures or supportive care measures, may resume study treatment without dose reduction as per Section 10.2.3. If diarrhea Grade ≥ 3 recurs subject is not eligible for resumption of treatment without dose reduction.
    - If diarrhea resolves to Grade ≤ 1 or baseline >72 hours but within 7 days, then may resume study treatment with a dose reduction as per Section 10.2.3.
    - If diarrhea does not resolve to Grade ≤ 1 or baseline in ≤ 7 days without study treatment, discontinue protocol therapy.

For Grade 4 diarrhea:

- If loperamide has not been initiated, initiate loperamide immediately using institutional or protocol guidelines for dosing as above. For dehydration, use intravenous fluids as appropriate; if severe dehydration, consider administration of octreotide.
- Hold study treatment until symptoms resolve to ≤ Grade 1 or baseline.
    - If diarrhea resolves to Grade ≤ 1 or baseline ≤ 7 days without study treatment, then may resume study treatment with a dose reduction as per Section 10.2.3.
    - If diarrhea does not resolve to Grade ≤ 1 or baseline in ≤ 7 days without study treatment, discontinue protocol therapy.

10.2.6.8 Treatment Dose Modifications and Guidelines for Visual Disturbances

Trametinib is known to be associated with visual adverse events. An age-appropriate comprehensive ophthalmologic examination should be performed by an ophthalmologist (without sedation) at screening, including a dilated funduscopic evaluation to rule out retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED). During the study, ophthalmologic exams will be repeated by an ophthalmologist per Study Assessments Section 8.1. These exams will be directed by the subject's complaints but will still include best corrected visual acuity, evaluation of the anterior segment, and direct or indirect ophthalmoscopy. A dilated eye exam is encouraged, but not required at each follow-up visit. Optical coherence tomography (OCT) will not be performed during these exams unless the child has a symptom or exam finding that the physician believes warrants this type of imaging. As is the standard of care for any subject on a MEK inhibitor the development any visual complaint will necessitate immediate evaluation and Ophthalmology should be consulted.

Management and Trametinib Dose Modifications for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade (NCI v5.0)	**Recommended Management Guidelines**	**Dose Modification Requirement**
Grade 1: Asymptomatic; clinical or diagnostic observations only. Note: if visual changes are clearly unrelated to study treatment (i.e.allergic conjunctivitis), monitor closely but ophthalmologic exam not required	Initiate local therapy and consult ophthalmologist within 7 days of onset	If dilated fundoscopic examination cannot be performed within 7 days of onset, hold treatment until RPED and RVO can be excluded by ophthalmologist. If RPED and RVO excluded, continue (or restart) treatment at same dose. ▪ If RPED suspected/diagnosed: see RPED dose modification table below (following this table); report as SAE ▪ If RVO diagnosed: permanently discontinue treatment and report as SAE.
Grade 2 and Grade 3: Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL	Consult ophthalmologist immediately	For RPED and RVO: ▪ Hold treatment. ▪ If RPED and RVO excluded: restart treatment at same dose level. ▪ If RPED diagnosed: see RPED dose modification table below (following this table); report as SAE. ▪ If RVO diagnosed: permanently discontinue treatment and report as SAE. For uveitis: ▪ Hold treatment.
Grade 4: Sight threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	Consult ophthalmologist immediately	Interrupt treatment. ▪ If RPED and RVO excluded: consider restarting treatment at the same or reduced dose level, after discussion with study chair. ▪ If RVO or RPED diagnosed: permanently discontinue treatment and report as SAE.

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

Retinal Detachment (NCI CTCAE v5.0)	Recommended Management Guidelines	Dose Modification Requirement
Grade 1–2: (Asymptomatic; clinical or diagnostic observations only)	Retinal evaluation monthly.	▪ Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
Grade 3–4: (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	Retinal evaluation monthly.	▪ Hold treatment. ▪ If improved to ≤ Grade 1, restart treatment at reduced dose (to the next lower dose according to Appendix II). ▪ If no recovery within 4 weeks permanently discontinue trametinib treatment

10.2.6.9 Treatment Dose Modifications and Guidelines for Hypertension

Increases in blood pressure (BP) have been observed in subjects receiving trametinib. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender (Appendix V).

If subject is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section 10.1.6.11.

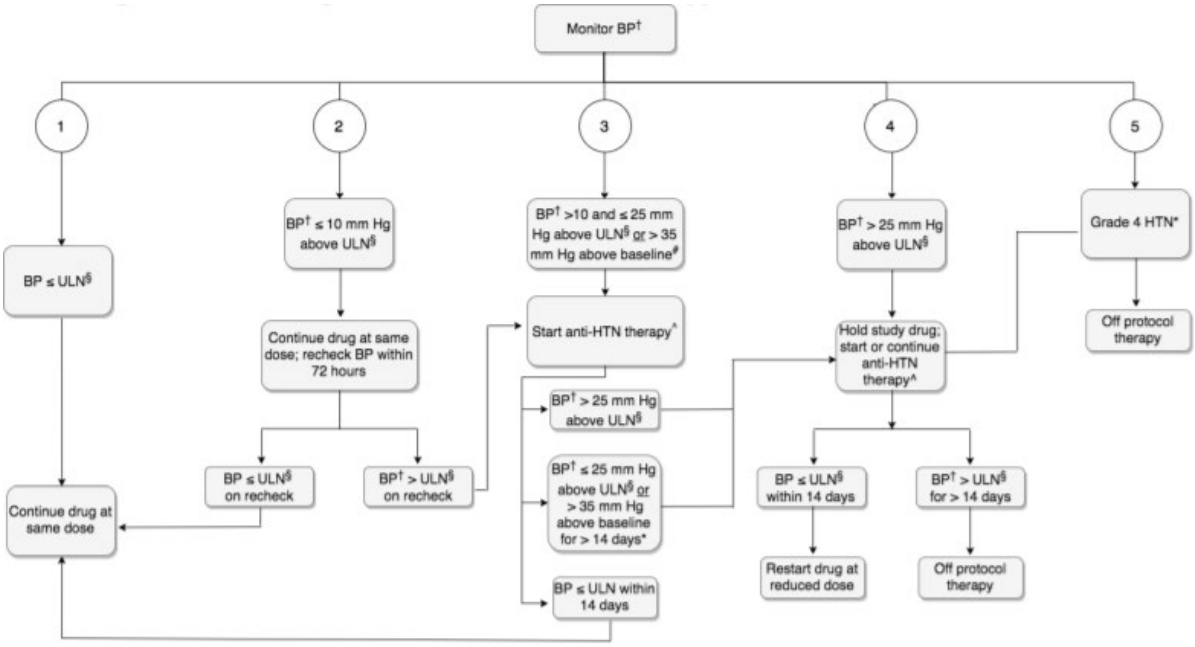
10.2.6.10 Screening Blood Pressure

- Screening blood pressure (BP) is defined as the blood pressure obtained at the examination used for study enrollment. BP should be obtained as follows: Obtain blood pressures from the same extremity with the subject in the same position at rest with an appropriately sized cuff. Avoid using the lower extremity if possible.

10.2.6.11 Management of Hypertension

- The upper limit of normal (ULN) is defined as a BP equal to the 95th percentile for age, height, and gender. (Appendix V)
- The NCI CTCAE v5.0 will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Subjects with an elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage trametinib related hypertension.

- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.



Elevations in BP are based on systolic or diastolic pressures.
†Elevated blood pressure measurements should be repeated on the same day to confirm the elevation. Subjects with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.
§ULN is a BP equal to the 95th percentile for age, height, and gender-appropriate normal values (Appendix V).
*If BP > 25 mm Hg above ULN for age (verified) or Grade 4 hypertension at any time, hold drug. Study drug should also be held for BP ≥ 25 mm Hg above the ULN for 14 days or ≥ 35 mm Hg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.
^ Antihypertensive therapy should be prescribed as clinically indicated, including use of multiple anti-hypertensive agents.
#Screening BP as defined in Section 10.1.6.10

Arm 1 of algorithm:

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

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue trametinib at the same dose and recheck the BP within 72 hours.
    - If the BP is ≤ ULN on recheck, continue trametinib at the same dose.

- If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

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

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN hold trametinib, monitor BP, and administer/adjust antihypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, trametinib may be restarted at a reduced dose.
  - If the BP is > ULN for >14 days, the subject must be removed from protocol therapy

Arm 5 of algorithm:

- If the subject develops Grade 4 hypertension, discontinue trametinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The subject is Off Protocol Therapy.

10.2.6.12 Treatment Dose Modifications and Guidelines for Paronychia

Management of Paronychia:

Systemic antibiotics can be used for initial treatment of paronychia. For recurrent paronychia, or paronychia involving other additional digits flurandrenolide (e.g. Cordran) tape or a topical steroid cream such as triamcinolone can be used in the morning and mupirocin and ketoconazole topical ointments in the evening. If no improvement is seen, a dermatology or surgery consultation is recommended. For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated. Rarely, surgical removal of the nail may be necessary as clinically indicated.

10.3 Follow-up for toxicities

All subjects must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment (trametinib).

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or a clinically significant laboratory value must be followed until resolution or stabilization of the event, whichever comes first. Further guidelines and recommendations for the management of specific study treatment induced toxicities are provided below.

10.4 Criteria for Removal from Protocol Therapy and Off Study Criteria

10.4.1 Criteria for Removal from Protocol Therapy

a) Intolerable toxicity (leading to treatment interruption >4 weeks)

b) Worsening disease at any time at the discretion of the investigator

c) Refusal or withdraw of consent for further protocol therapy by parent/guardian/LAR or subject

d) Physician determines it is in subject's best interest

e) Completion of planned therapy

f) Non-compliance with protocol requirements (e.g., unexcused missing more than one scheduled study visit or missing > 15% of doses of study drug)

Subjects who are off protocol therapy are to be followed (as indicated) until they meet the criteria for Off Study (see below). For subjects who withdrawal due to AE, the medical condition will be tracked for at least a month after discontinuing the study drug or until resolution of the AE.

Follow-up data will be required until one of the following off study criteria is met.

10.4.2 Off Study Criteria

a) Death

b) Lost to follow-up

c) Withdrawal of consent for any further follow up data submission

d) Completion of protocol defined follow-up period.

10.5 Adverse Reporting Requirements

10.5.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

10.5.2 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

10.6 Routine Reporting Procedures for All AEs

Grade 2 dose modifying and above AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment. Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including Serious Adverse Events (SAEs)) will be reported to the IRB of record in accordance with the IRB of record's SOPs and required timelines. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report per the IRB of record's SOPs.

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include: "How are you feeling?" or, "How does your child seem to feel?" "Have you had any (other) medical problems since your last visit/contact?" or, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

Grade 2 dose modifying and above AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

The severity of toxicities will be graded in accordance with the Common Terminology Criteria for AE (CTCAE) version 5.0. If an adverse event is not covered by one of the

available CTCAE Adverse Event descriptions, and the Investigator deems it medically or clinically significant to document, the applicable "Other" category can be used.
Observed or volunteered AEs Grade 2 attributed to study drug and all Grade 3 and higher AEs, regardless of suspected causal relationship to study drug, will be recorded as AEs in the CRFs.

10.7 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

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

Laboratory results from non-pediatric institutions or laboratories often have significantly different lab reference ranges, not specific for age. In the event of a greater than ±10% difference in the reference range for a specific lab result, either CHOP or other nationally recognized pediatric standards may be used to determine the grade of the laboratory value.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from screening, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided. In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay. However, any clinically significant safety assessments that are associated

with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

10.9 Relationship of SAE to study drug or other intervention

An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily "*caused by a therapeutic intervention*". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational agent/intervention	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Rechallenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical

condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.10 Treatment Dose Modifications and Guidelines for Adverse Event Reporting specific to study drug

Dose modifying hematological and non-hematological toxicities are defined differently. Dose modification or discontinuation of trametinib for toxicity is considered a dose modifying toxicity. Guidelines for management and dose modifications are also provided for the toxicities of special interest.

Trametinib Dose Modification Schedule for Adverse Events

Grade (CTC-AE)*	**Schedule** **Grade (CTC-AE)* Dose Modifications**
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and Reduce by one dose level when resuming therapy.

***** The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

10.11 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of record of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written

reports will be filed with the IRB of record and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 business days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

10.11.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

10.12 Investigator Reporting of a Serious Adverse Event to Coordinating Center

Any serious adverse event that is life threatening or causes death (as defined in Section 10.7 above) whether anticipated or not, must be reported to the coordinating center (CHOP) within one business day of the investigator becoming aware of the event (expedited reporting). Events that are not life-threatening and do not result in death, must be reported within 7 business days of discovery. If only limited information is initially available, follow-up reports are required until resolution. The original SAE Form must be kept on file at the study site.

Reporting will be conducted in full accordance with all applicable Institutional Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH).

10.13 Medical Emergencies

For any medical emergencies, the Investigator or her physician designee will be responsible for investigating the emergency and resolving issues surrounding the emergency. Study

teams and medical personnel associated with the subject will proceed accordingly to provide best care.

10.14 Reporting of Study Treatment Errors Including Misuse/Abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not they are associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

11 STUDY ADMINISTRATION

11.1 IRB Approval

The Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB) will serve as the reviewing IRB for this multi-center study. All participating sites have agreed to adhere to the single IRB (sIRB) Policy (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html) and to rely on CHOP as the sIRB.

The CHOP IRB will serve as a Privacy Board to fulfill the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR 164.512(i)) for use or disclosure of protected health information for research purposes. The CHOP IRB has extensive experience with providing IRB oversight for external institutions and complies with the registration requirements for both the Office for Human Research Protections (OHRP) and the U.S. Food and Drug Administration (FDA) (IRB00000316 and IRB00000317). Prior to initiating the study, all participating sites will sign an authorization/reliance agreement that will clarify the roles and responsibilities of the sIRB and participating sites.

When the CHOP IRB serves as the reviewing IRB for other sites, it will need information from each relying institution about local context, consent form requirements (i.e. injury compensation language), applicable state/local laws and any local conflict of interest determinations. The CHOP IRB will provide approval notices and approved informed consent documents customized with the site Principal Investigator name, contact information and any other site-specific wording (i.e. injury compensation, HIPAA) for each relying institution.

As the sIRB, the CHOP IRB will communicate with the overall Principal Investigator through eIRB, which CHOP investigators also use for all other IRB submissions at CHOP. Communication with relying sites and their Principal Investigators will occur through the same system. This avoids the need to have the overall Principal Investigator collect the information from all of the relying sites and submit them to the CHOP IRB. eIRB provides the ability for Principal Investigators from each relying institution, after a simple registration process, to log in and provide site-specific documents and information (i.e. annual reports, site-specific recruitment materials) to the CHOP IRB. The CHOP IRB, in turn, will post site-specific packages (i.e. approval letters, stamped consent forms) for the use of the relying site Principal Investigators.

11.2 Data Collection and Management

The CASTOR system will be used as a central resource for data processing and management. Data transfer agreements will be in place with each site and the coordinating center to allow for data collection. CASTOR is a web application and back-end database model designed to support data capture for research studies. CaNVAS has a license with CASTOR that is housed on a password protected server and therefore afforded the same protections as other sensitive clinical systems. CASTOR was developed specifically around HIPAA-security guidelines with features such as data encryption. It provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and

export procedures, automated export procedures for seamless data downloads to common statistical packages, including SAS and procedures for importing data from external sources. Standard operating procedures will be used to guide all data management activities, such as the naming and identification of variables, data cleaning and handling of missing data. Participating site data will be entered directly into the CASTOR database. Data entry screens will be designed to incorporate range checks and concurrent checks to minimize errors.

11.2.1 Protection Against Risks

All sites will obtain institutional review board approval for this study. Subject's risks of participating in research will be kept to a minimum with measures to protect confidentiality and planned interim analysis for safety monitoring.

Best of care will be provided to subjects in the event of toxicities associated with treatment. Subjects and, as applicable, parents/guardian/LAR, will be provided appropriate contact number(s) for treating physicians at the clinical site in accordance with institutional IRB guidelines.

11.2.2 Drug Accountability

Adequate records of study drug receipt and disposition will be maintained by each study site the investigational drug pharmacy. Records of receipts, investigational drug orders, dispensing records, and disposition forms will be examined during the course of the study. The purpose of these records is to ensure regulatory authorities that the investigational new drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol. Supplies returned by subjects will be destroyed once returned quantities are documented. Unused supplies that expire during the study as well as those that are unused or partially used at study completion will be destroyed according to site specific SOPs.

11.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a of any Protected Health Information (PHI).

Electronic documentation will be username and password encrypted.

11.4 Regulatory and Ethical Considerations

11.4.1 Data and Safety Monitoring Plan

- Principal Investigator

The PI will have responsibility for monitoring the overall safety during the study and they or a designated appropriately clinically trained member of the study team will personally be at all of the study visits. In addition, the study coordinator will be involved in all studies and will also monitor for safety. All adverse events will be reported to the IRB in a timely fashion in compliance with all applicable regulations.

- Data Safety Monitoring Board (DSMB): The DSMB will be made up of representatives who are independent of the study sponsor and investigators.

The investigators place the highest priority on ensuring the safety of subjects participating in clinical trials. Every interventional trial conducted through CaNVAS includes a plan for safety and data monitoring.

This study will be reviewed by the CHOP Data and Safety Monitoring Board (CHOP DSMB). A summary of the CHOP DSMB activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMB within 5 calendar days of study staff's knowledge.)
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for subjects

A copy of the CHOP Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The board will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMB letters will be submitted to the IRB of record as required.

11.4.2 Audits

Auditing is essential to ensure that research conducted is of the highest quality and meets regulatory agency standards.

In accordance with ICH GCP and the audit plan, Regulatory authorities, the IRB, and/or sponsor may request access to all source documents, data capture records, and other study documentation for audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities including;

review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of case report forms (CRF) data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

All data will be collected in an electronic CRF system. All entries must be completed in English. Concomitant medications and AEs will be coded. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

11.5 Risk Assessment

Vascular anomalies caused by Rasopathy pathways are serious conditions with no approved pharmacological treatment targeting the underlying causes of the disease. Current therapy includes lymphatic interventions, surgical procedures, and vascular occlusive procedures which mainly address symptoms and complications of the disease. There is a high unmet medical need for an effective systemic treatment that will treat the underlying cause of the disease. These patients are high risk secondary to significant morbidity of their disease and have no other medical options.

The main risks to this study are from trametinib administration. In the pediatric population, no serious suspected adverse reaction was considered expected for reporting purposes in trametinib monotherapy.

For dual therapy, the most common adverse events experienced in the trials to date as listed in the Trametinib Investigator's Brochure Edition 16 are diarrhea, nausea/vomiting, pneumonitis, rash, eye and cardiac disorders.

11.6 Potential Benefits of Trial Participation

Trametinib is considered to be a promising treatment option for pediatric and adult subjects with confirmed vascular anomalies caused by Rasopathy. Treatment with trametinib related to variants in Vascular anomalies caused by Rasopathies may provide clinical benefit compared to available treatment options. The participants enrolled in this study are planned to receive trametinb as active treatment for their disease. Based on published clinical data[13-15], treatment with trametinib is expected to be tolerated with a manageable safety profile

11.6.1 Risk-Benefit Assessment

The low frequency and generally mild severity of AEs with trametinib treatment suggest good tolerability and an acceptable and manageable safety profile in pediatric and adult subjects. This represents an acceptable risk benefit assessment where the benefits of treatment outweigh the risks. These patients are high risk secondary to significant morbidity of their disease and have no other medical options.

11.7 Recruitment Strategy

Subjects will be recruited primarily through the CaNVAS member institutions with consideration given to outside provider referrals. Subjects with complex lymphatic anomalies and diminished quality of life due to condition with suspected or known Ras-pathway variants will be referred by their primary vascular anomalist, geneticist, or provider to the CaNVAS member institution. Recruitment will also include listing through clinicaltrials.gov for subjects cared for outside of the member network and at CaNVAS member sites as documented in the protocol.

There is no concern for ability to recruit this subject population given current and ongoing trends in requests for treatment of subjects with trametinib.

11.8 Informed Consent/Assent and HIPAA Authorization

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the subject (and parent/guardian/LAR if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject or parent/guardian/LAR and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, institutional IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the subject and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, hospital staff was present for consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Subjects that require re-consenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be re-consented for continuing reviews. The protocol will follow the institutional IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the signed consent is sent to the Medical Records Office to be scanned into the legal medical record. A copy will also be given to the subject.

11.8.1 Waiver of Consent

Waiver of consent is not requested.

> **45 CFR 46.116(d)** An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
>
> (1) the research involves no more than minimal risk to the subjects;
>
> (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
>
> (3) the research could not practicably be carried out without the waiver or alteration; and
>
> (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

11.9 Payment to Subjects/Families

Reimbursement is not provided as part of this protocol.

12 REPORTING OF PROTOCOL VIOLATIONS/DEVIATIONS AND UNANTICIPATED PROBLEMS

Any protocol violations, deviations, or unanticipated problems should be documented and reported according to the coordinating center's Manual of Operations. See the Manual for more detailed instructions.

In addition, each participating site should report protocol deviations/violations or unanticipated problems according to their site's policies, procedures and applicable regulations.

13 COORDINATING CENTER RESPONSIBILITIES:

13.1 SAE/SAE Reporting

All SAEs, regardless of attribution or expectedness, must be reported using a FDA MedWatch 3500a Form. For participating sites, this form must be submitted to the coordinating center within 24 hours of learning of the event. Participating sites are required to notify their local IRBs according to institutional reporting policies.

MedWatch 3500a Reporting Guidelines: In addition to completing appropriate subject demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

• Treatment regimen (dosing frequency, combination therapy)

• Protocol description (and number, if assigned)

• Description of event, severity, treatment, and outcome, if known

• Supportive laboratory results and diagnostics

• Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow up information to a safety report should be submitted as soon as the relevant information is available. Additional information may be added to a previously submitted report by any of the following methods:

• Adding to the original MedWatch 3500a report and submitting it as follow-up

• Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form

• Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B., initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event 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.)

13.2 SAE reporting in the Follow Up Period

In the event that during the 1-year follow up period the Investigator identifies what is believed to be a new (unexpected) long-term risk or short-term risk (in the event the subject continued therapy on study drug) attributable to the study drug, this SAE must be reported to the Sponsor and to the site's IRB consistent with any Unanticipated Problem reporting policy, as this would be a new risk directly related to any subject that might be participating in the research.

13.3 Sponsor Responsibilities to be performed by the Coordinating Center:

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis Patient Safety (clinicalsafetyop.phuseh@novartis.com) immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information.

Any SAEs experienced after the 30-day period should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis Patient Safety (clinicalsafetyop.phuseh@novartis.com) within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

13.3.1 Unexpected Fatal or Life-Threatening Suspected Adverse Reaction Reports

Notify the FDA as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information. Either the sponsor or the investigator can make the determination of life-threatening. (Food and Drug Administration: Fax: (800) FDA – 0178)

13.3.2 Unexpected, Serious Suspected Adverse Reactions

Any suspected adverse reaction that is both serious and unexpected, per 21 CFR 312.32(c)(1)(i), **only if there is evidence to suggest a causal relationship between the drug and the adverse event**, must be reported to the FDA as soon as possible but no later than 15 calendar days after the sponsor determines the information qualifies for reporting. (Food and Drug Administration: Fax: (800) FDA – 0178) The following must be reported:

a. Single Occurrence – event is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome). See SOP Form 32-1.3-001 Adverse Event Reporting for the Sponsor: Single Occurrence.

b. Multiple Occurrences – event occurs one or more times and is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

c. Aggregate Analysis of Specific Events Observed in the Clinical Trial – analysis of events, e.g., known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy, that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

13.3.3 Serious Adverse Event Reporting Procedures to the CHOP IRB

The Sponsor will report any unexpected life-threatening event or death (Grade 4 or 5) adverse event to the CHOP IRB and within 24 hours after the Sponsor is made aware of the event.

Unexpected Grade 3 adverse events at least possibly attributable to the research will be reported to the CHOP IRB only at the time of the annual progress report.

14 PUBLICATION

Authorship of publications from data generated in study will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
    - Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work AND
    - Drafting the article or revising it critically for important intellectual content; AND
    - Final approval of the version to be published; AND
    - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group will identify the individuals who accept direct responsibility for the manuscript. This individual will fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to CaNVAS for review and approval. The study contract between the institution, principal investigator, Co-investigator and CaNVAS or its delegate will outline the requirements for publication review.

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APPENDICES

APPENDIX I: PERFORMANCE SCORES

Karnofsky Performance Scale For Patients 16 Years and Older	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs of symptoms of disease.
80	Normal activity with effort; some signs of symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead

Lansky Performance Scale For Patients Less Than 16 Years of Age	
Lansky Score	**Play Score**
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activity
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participate in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping, play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

APPENDIX II: DOSING NOMOGRAM

Trametinib dosing will be weight based. The drug is supplied in tablet form or in oral solution form. Dosing nomogram for tablet formulation below. **The maximum dose is 2 mg per day.**

Note: If switching from trametinib solution to trametinib tablets or vice versa in subjects requiring dose reduction, match up the subject's starting dose to ensure the proper dose reduction is being made.

Subject Weight ≥ 35 kg Formulation: Trametinib Tablets 0.5 mg and 2 mg						
Dose Level	Dose Level 1: 0.025 mg/mg/dose once daily Maximum Dose 2 mg Daily			Dose Level -1: 0.020 mg/mg/dose once daily Maximum Dose 1.5 mg Daily		
Weight[#] (kg)	Dose	Number of 0.5 mg Tablets	Number of 2 mg Tablets	Dose	Number of 0.5 mg Tablets	Number of 2 mg Tablets
35 – 50	1 mg	2	0	Oral Solution only 0.75 mg (15 mL)		
50.1 – 70	1.5 mg	3	0	1 mg	2	0
≥ 70.1	2 mg	0	1	1.5 mg	3	0

[#] Weight measured within 7 days of the start of a cycle or pre-determined dosing weight in those subjects whom fluid status fluctuates.

Formulation: Trametinib Oral Solution (0.05 mg/mL)				
Dose Level	Dose Level 1: 0.025 mg/mg/dose once daily Maximum Dose 2 mg Daily		Dose Level -1: 0.020 mg/mg/dose once daily Maximum Dose 1.5 mg Daily	
Weight[#] (kg)	Dose	Volume of Oral Solution	Dose	Volume of Oral Solution
9.0-9.9kg	0.12 (0.0125mg/kg)	2.3mL	0.18mg	3.6mL
10.0-10.9kg	0.2mg	4mL	0.2mg	4mL
11-11.9	0.25mg	5mL	0.22mg	4.4mL
12-13.9	0.3mg	6mL	0.24mg	4.8mL
14-15.9	0.35mg	7mL	0.28mg	5.6mL
16-17.9	0.4mg	8mL	0.32mg	6.4mL
18-19.9	0.45mg	9mL	0.36mg	7.2mL
20-22.9	0.5mg	10mL	0.4mg	8mL
23-24.9	0.6mg	12mL	0.46mg	9.2mL
25-29.9	0.7mg	14mL	0.5mg	10mL
30-34.9	0.8mg	16mL	0.6mg	12mL
35 – 50	1 mg	20 mL	0.75 mg	15 mL
50.1 – 70	1.5 mg	30 mL	1 mg	20 mL
≥ 70.1	2 mg	40 mL	1.5 mg	30 mL

[#] Weight measured within 7 days of the start of a cycle or pre-determined dosing weight in those subjects whom fluid status fluctuates.

APPENDIX III: MEDICATION DIARY (TABLETS)

Complete each day with the date due, date received, observations, and any comments. Trametinib should be taken by mouth on an empty stomach once a day, at least 1 hour before or 2 hours after a meal. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs within 30 minutes of taking the tablet formulation, the dose of trametinib can be repeated once. Return the diary to your institution at the end of each cycle. Return all unused tablets at the end of each cycle. Store tablets in the refrigerator.

Sites will fill out the cycle, dates and number of prescribed tablets per Appendix II.

Trametinib in the Treatment of _____

Cycle _____

_____ _____

Patient Name DOB

Drug	Dosage	Route	Day
Trametinib			

Date Due	Date Received	Week	Day	Dose given	Comments
		1	1	❑	
			2	❑	
			3	❑	
			4	❑	
			5	❑	
			6	❑	
			7	❑	
		2	8	❑	
			9	❑	
			10	❑	
			11	❑	
			12	❑	
			13	❑	
			14	❑	
		3	15	❑	
			16	❑	
			17	❑	
			18	❑	
			19	❑	
			20	❑	
			21	❑	
		4	22	❑	
			23	❑	
			24	❑	
			25	❑	
			26	❑	
			27	❑	
			28	❑	
			29/1	❑	

Each Cycle = 28 days

Observations:

APPENDIX IV: MEDICATION DIARY (ORAL SOLUTION)

Complete each day with the date, time and volume in mL of trametinib oral solution taken. Make note of other drugs and supplements taken. Your doctor will tell you what foods you should avoid. Trametinib should be taken by mouth on an empty stomach once a day, at least 1 hour before or 2 hours after a meal. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs after taking oral solution formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. Return the completed diary to your institution at the end of each treatment cycle. Please return all unused solution at the end of each cycle. Store the solution at room temperature (25°C or 77°F).

Immediately prior to the removal of dose for administration swirl the bottle of solution gently 2-3 times, if any foam appears allow the bottle to sit for at least 1 minute for the foam to dissipate. Remove the required dose using a suitable graduated syringe:

a. Ensure that the syringe plunger is fully pushed into the barrel.

b. Insert the syringe tip into the Adapter, then invert the bottle and dispense at least 5 mL of solution into the syringe and then pump the entire solution back into the bottle to purge the syringe of any air bubbles. Repeat this step until the syringe is free from air bubbles.

c. Withdraw the required dosing volume. Then re-invert the bottle and remove the syringe from the Adapter and administer the dose to the subject as soon as possible.

Sites will fill out the cycle, dates and the volume of prescribed solution per day per Appendix II.

Trametinib in the Treatment of _____

Cycle _____

_____ _____

Patient Name DOB

Drug	Dosage	Route	Day
Trametinib			

Date Due	Date Received	Week	Day	Dose given	Comments
		1	1	❑	
			2	❑	
			3	❑	
			4	❑	
			5	❑	
			6	❑	
			7	❑	
		2	8	❑	
			9	❑	
			10	❑	
			11	❑	
			12	❑	
			13	❑	
			14	❑	
		3	15	❑	
			16	❑	
			17	❑	
			18	❑	
			19	❑	
			20	❑	
			21	❑	
		4	22	❑	
			23	❑	
			24	❑	
			25	❑	
			26	❑	
			27	❑	
			28	❑	
			29/1	❑	

Each Cycle = 28 days

Observations:

APPENDIX V: BLOOD PRESSURE

Blood Pressure Levels for Children by Age and Height Percentile

Blood pressure (BP) levels for Boys:

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Blood pressure (BP) levels for Girls:

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

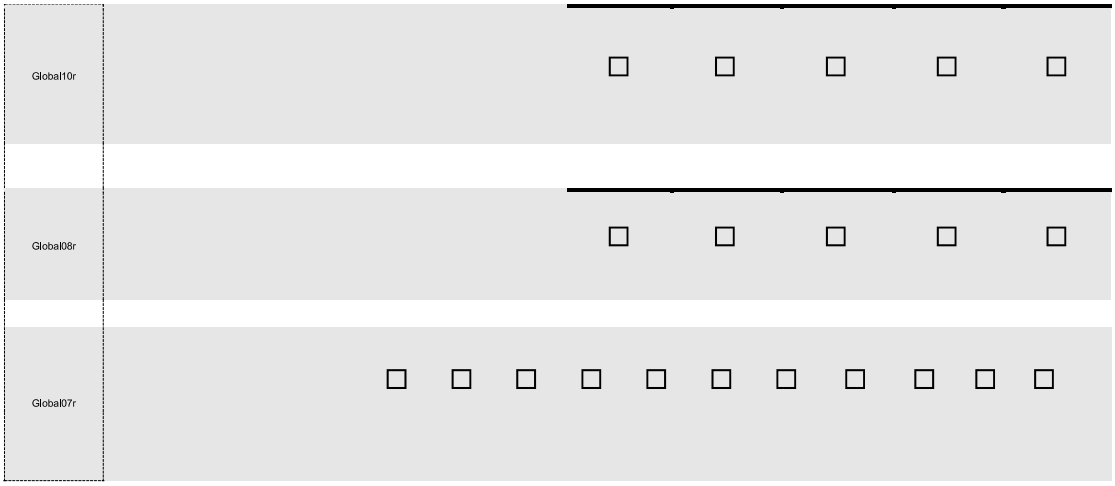
Instructions for using this BP Chart:
1. Measure the subject's blood pressure using an appropriate size cuff.
2. Select appropriate chart for female or male subject.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 10.1.6.9 for definition of dose modifying hypertension. See Section 10.1.6.11 for management and grading of hypertension.

Note: For subjects ≥ 18 yrs, ULN BP is 140/90 mmHg.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX VI: PROMIS MEASURES

Global01		☐	☐	☐	☐	☐
Global02		☐	☐	☐	☐	☐
Global03		☐	☐	☐	☐	☐
Global04		☐	☐	☐	☐	☐
Global05		☐	☐	☐	☐	☐
Global09r		☐	☐	☐	☐	☐
Global06		☐	☐	☐	☐	☐


Global10r
Global08r
Global07r

Early Childhood Parent Report Global Health 8a

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01_PXR1	In general, would you say your child's health is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02_PXR1	In general, would you say your child's quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03_PXR1	In general, how would you rate your child's physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04_PXR1a	In general, how would you rate your child's mental health?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04_PXR1b	How would you rate your child's mood?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
glo_ec3r1	How would you rate your child's social skills?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04_PXR1c	How would you rate your child's ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
glo_ec1	How well is your child meeting developmental milestones?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS® Parent Proxy Scale v1.0 – Global Health 7+2

Parent Proxy Global Health 7+2

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01_PXR1	In general, would you say your child's health is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02_PXR1	In general, would you say your child's quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03_PXR1	In general, how would you rate your child's physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04_PXR1	In general, how would you rate your child's mental health, including mood and ability to think?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
PedGlobal2_PXR1	How often does your child feel really sad?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Always	**Often**	**Sometimes**	**Rarely**	**Never**
PedGlobal5_PXR1	How often does your child have fun with friends?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PedGlobal6_PXR1	How often does your child feel that you listen to his or her ideas?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
Pf4fatigue3r	My child got tired easily.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2pain5r	My child had trouble sleeping when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS® Pediatric Scale v1.0 – Global Health 7+2

Pediatric Global Health 7+2

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01R1	In general, would you say your health is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02R1	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03R1	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04R1	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
PedGlobal2R1	How often do you feel really sad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Always	**Often**	**Sometimes**	**Rarely**	**Never**
PedGlobal5R1	How often do you have fun with friends?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PedGlobal6R1	How often do your parents listen to your ideas?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…					
		Never	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
2876R1r	I got tired easily	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3793R1r	I had trouble sleeping when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Interference – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Parent Proxy Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
Pf2pain5r	My child had trouble sleeping when he/she had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3pain7r	My child felt angry when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2pain2r	My child had trouble doing schoolwork when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3pain2r	It was hard for my child to pay attention when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2pain4r	It was hard for my child to run when he/she had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1pain4r	It was hard for my child to walk one block when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3pain4r	It was hard for my child to have fun when he/she had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf4pain6r	It was hard for my child to stay standing when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pediatric Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
1698bR1r	I felt angry when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2035R1r	I had trouble doing schoolwork when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3793R1r	I had trouble sleeping when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9004r	It was hard for me to pay attention when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2045R1r	It was hard for me to run when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2049R1r	It was hard for me to walk one block when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
1703R1r	It was hard to have fun when I had pain ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2180R1r	It was hard to stay standing when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

HI7		☐	☐	☐	☐	☐
AN3	———	☐	☐	☐	☐	☐
FATEXP41		☐	☐	☐	☐	☐
FATEXP40		☐	☐	☐	☐	☐

Parent Proxy Fatigue – Short Form 10a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
Pf4fatigue12r2	Being tired made it hard for my child to play or go out with friends as much as he/she would like.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 4
Pf4fatigue8r	My child felt weak.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf4fatigue3r	My child got tired easily.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2fatigue8r	Being tired made it hard for my child to keep up with schoolwork.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2fatigue4r	My child had trouble finishing things because he/she was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3fatigue7r	My child had trouble starting things because he/she was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3fatigue12r	My child was so tired it was hard for him/her to pay attention.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3fatigue8r	My child was too tired to do sports or exercise.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3fatigue4r	My child was too tired to do things outside	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf4fatigue4r2	My child was too tired to enjoy the things he/she likes to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 4

Pediatric Fatigue – Short Form 10a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
4239aR2r	Being tired made it hard for me to keep up with my schoolwork.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4212R1r	Being tired made it hard for me to play or go out with my friends as much as I'd like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4213R1r	I felt weak	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2876R1r	I got tired easily	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4221R1r	I had trouble finishing things because I was too tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4220R1r	I had trouble starting things because I was too tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4210R2r	I was so tired it was hard for me to pay attention	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4241R2r	I was too tired to do sports or exercise	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4208bR2r	I was too tired to do things outside.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4196R1r	I was too tired to enjoy the things I like to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

EDANX01		☐	☐	☐	☐	☐
EDANX40		☐	☐	☐	☐	☐
EDANX41		☐	☐	☐	☐	☐
EDANX53		☐	☐	☐	☐	☐

Early Childhood Parent Report Anxiety – Short Form 4a

Please respond to each question or statement by marking one box per row.

In the past 7 days		Never	Almost Never	Sometimes	Almost Always	Always
Pf2anxiety2r_ec	My child seemed scared or fearful.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1anxiety8r_ec	My child seemed nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1anxiety6r_ecr1	My child seemed fearful or worried when out in public.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
anx_ec5r2	My child was inconsolable when separating from me or other parent in a familiar setting	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Parent Proxy Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Almost Never	Sometimes	Often	Almost Always
Pf1anxiety8r	My child felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2anxiety2r	My child felt scared.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2anxiety9r	My child felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2anxiety1r	My child felt like something awful might happen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2anxiety5r	My child worried when he/she was at home	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1anxiety1r2	My child got scared really easily.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1anxiety3r	My child worried about what could happen to him/her.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2anxiety4r	My child worried when he/she went to bed at night	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pediatric Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
2220R2r	I felt like something awful might happen .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
713R1r	I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5044R1r	I felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3459bR1r	I worried when I was at home.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
227bR1r	I felt scared.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3150bR2r	I worried when I went to bed at night	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
231R1r	I worried about what could happen to me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2230R1r2	I got scared really easily.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Emotional Distress-Depression – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Early Childhood Parent Report Depressive Symptoms – Short Form 4a

Please respond to each question or statement by marking one box per row.

In the past 7 days

		Never	Almost Never	Sometimes	Almost Always	Always
Pf2depr3r_ec	My child seemed sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2depr10r_ec	My child was withdrawn	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2depr2r_ec	My child wasn't interested in doing things he/she usually likes	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
depr_ec4	My child acted sad during fun activities...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Parent Proxy Depressive Symptoms – Short Form 6a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
Pf2depr7r	My child could not stop feeling sad.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1depr7r	My child felt everything in his/her life went wrong	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1depr5r	My child felt like he/she couldn't do anything right.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2depr10r	My child felt lonely	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2depr3r	My child felt sad.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2depr6r	It was hard for my child to have fun.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pediatric Depressive Symptoms – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Almost Never	Sometimes	Often	Almost Always
488R1r	I could not stop feeling sad.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
461R1r	I felt alone.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5041R1r	I felt everything in my life went wrong....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5035R1r	I felt like I couldn't do anything right.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
711R1r	I felt lonely.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
228R1r	I felt sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
712R1r	I felt unhappy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3952aR2r	It was hard for me to have fun.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX VII: RADIOLOGY

Protocol Name	Sequences	Est time	Coverage/ Contrast	Tech notes	Nursing/Child Life notes	Sedation/Anesthesia notes	Supporting evidence
VASCULAR MALFORMATION, EXTREMITY	Radiologist must define coverage area either based on localizer or prior studies. 1. Cor/Sag** T1 FSE 2. Cor/Sag** STIR 3. Axial T2 FS radial k-space filling sequence 4. Axial VIBE pre-contrast 5. Cor** time-resolved angiography (Temp. res.: 2.5 s; 20 phases) 6. Axial VIBE post-contrast. 7. If lesion is peri-articular or intra-articular: sagittal 3D GRE (DESS) to see hemosiderin deposition in synovium. 8. Axial DWI, b=0, 150, 300, 600, 800 **Planes must be prescribed to allow optimum visualization of the lesion	5 min 5 min 5 min 4 min 3 min 4 min 5 min (31 min)	ROI Radiologist must define coverage area either based on localizer or prior studies. **Contrast:** Standard (gadavist)	If focal lesion, place marker over site. Planes must be prescribed to allow optimum visualization of the lesion; discuss with radiologist.	**Study time:** 30 minutes (non-sedated) 45 minutes (sedated) **Position:** Always supine **Music/video**: Always possible (According to magnet) **IV site/size**: No preference **Power injection:** Mandatory **NPO:** N/A	**Sedation/Anesthesia:** Second PIV for contrast	Protocols from Boston Children's and Sick KIds

					Oral prep: N/A **Medications:** none		
Chest Vascular Malformation	1. Coronal T1 FSE 2. Coronal STIR 3. Axial T2 FS BLADE 4. Axial T1 FS volume-interpolated GRE ***Dynamic Contrast*** 5. Coronal time-resolved MR angiography (Temp Res: 2.5 s; 20 phases) 6. Axial T1 FS volume-interpolated GRE GD+ 7. Coronal T1 FS spoiled GRE GD+ 8. Axial DWI, b=0, 150, 300, 600, 800 ***OPTIONAL*** Delay Axial T1 FS spoiled GRE GD+	3 m 5 m 4 m 30 s 3 m 30 s 3 m (19') 3 m 5 m (27')	**From/To:** Include the entire lesion (might extend into neck and/or abdomen) **Contrast:** Standard (gadavist)	Temp resolution for TWIST if inside the thoracic cage (outside can be higher ~3.5)	**Study time:** 1 hour **Position:** Always supine **Breath holds:** None **Music/video:** Always possible (According to magnet) **IV site/size:** no preference **Power injection**: Always	**Sedation/Anesthesia:** Second PIV for contrast	Flors L, Leiva-Salinas C, Maged IM, et al. MR imaging of soft-tissue vascular malformations: diagnosis, classification, and therapy follow-up. Radiographics. 2011;31(5):1321-1341

					NPO: N/A **Oral prep:** N/A **Medications:** none		
VASCULAR MALFORMATION, BODY	**1. Axial T1 FSE** **2. Axial T2 FS radial k-space filling sequence** **3. Axial T1 FS stack stars volume-interpolated GRE pre-contrast** **4. Cor time-resolved MRA (Temp. res.: 2.5 s; 20 phases)** **5. Axial T1 FS stack stars volume-interpolated GRE post-contrast** **Axial DWI, b=0, 150, 300, 600, 800**	3 min 4 min 30 s 3 min 30 s 5 min 5 min (21 min)	**From: lung bases** **Through: pelvis** **Contrast:** Standard (gadavist)	Coach breath holding If focal lesion, place marker over site. Arms up whenever possible	**Study time:** 30 minutes (non-sedated) 45 minutes (sedated) **Position:** Always supine **Breath holds:** Up to 30 seconds (practice and let tech know if child is able) **Music/video:** Always possible (According to magnet) **IV site/size:**	**Sedation/Anesthesia:** Second PIV for contrast	Protocols from Boston Children's and Sick KIds

					No preference **Power injection:** Mandatory **NPO:** N/A **Oral prep:** N/A **Medications:** none		
MRL	**1. T2 SPACE coronal** **2. Coronal TWIST*** **3. Post Gd coronal 3D IR FLASH (sequential after each access injection)** ***With slow injection of Gd into sequential access sites (nodes, liver, and mesentery) 0.2 mmol/kg diluted to allow appropriate volume**		**Chest & abd** **TWIST with 1-1.5 mm slices, every 8-12 s for 30 phases** **IRFLASH with respiratory navigation**				European Radiology (2019) 29:5190–5196
Brain	**1. Axial diffusion** **2. T1 3D GRE volumetric / MPRAGE Sag, with axial reformations** **3. TSE T2 axial** **4. FLAIR axial**						

	5. **TSE T2 coronal** 6. **Pre-gad SE T1 axial with fat sat** 7. **TWIST MRA** 8. **Post-gad SE T1 axial with fat sat**						
Face	1. **HASTE ax & cor** 2. **Sag T1** 3. **Ax T2 fat sat** 4. **Ax STIR** 5. **Ax diffusion** 6. **Cor T2** 7. **Pre-gad ax T1 FS** 8. **Axial TWIST** 9. **Post gad Sag, Ax & Cor T1 fat sat**						
Neck	1. **HASTE ax & cor (not done on follow up studies)** 2. **Sag T1** 3. **Ax STIR** 4. **Ax diffusion** 5. **Cor fat sat T2 Dixon** 6. **Axial TWIST** 7. **Post gad Ax & Cor T1 fat sat Dixon**						
Orbits	1. **Small FOV sag & ax T1 thin section** 2. **TSE T2 Ax (with fat sat)** 3. **TSE T2 Cor with fat sat** 4. **Ax diffusion** 5. **Pre-gad ax T1 FS**						

	6. Axial TWIST **7. Post gad SE T1 ax & cor with fat sat thin sections**						

APPENDIX VIII: BLOOD SAMPLING

Blood will be collected into the following tubes:

1. **Blue top (sodium citrate) for plasma – 4.5 mL tube**
2. **Red top for serum – 6.0 mL tube**
3. **Purple top (EDTA) for DNA – 6.0 mL tubes**
4. Cell- free DNA collection tube **– 8.5ml tubes**
5. **Tubes will be filled to capacity if possible and the order of priority if blood volume is limited is 1-5.**

For blood-derived plasma and serum (tubes 1. and 2), the plasma and serum must be separated as soon as possible and frozen at -70F. Tubes should be shipped on dry ice overnight to the biorepository. EDTA tubes (#3) and cfDNA tubes *#4) can be shipped by FedEx or other express services in room temperature to: Division of Pulmonary Biology, Cincinnati Children's Children's Hospital R40153333 Burnet Avenue, Cincinnati 45229.

Samples sent to Dr. Hakon Hakonarson's lab should be sent to:

Center for Applied Genomics (CAG)

Leonard Madlyn Abramson Research Center

3615 Civic Center Blvd, Lab 1014, 10th Floor

Attn: James Snyder

APPENIX IX: ROADMAP

Trametinib in the Treatment of _____

Cycle _____		
	_____	_____
	Patient Name	DOB

Dosing guidelines: 0.025 mg/kg/dose (or 0.0125mg/kg/dose for critically ill subjects, infants < 10kg at enrollment		
Drug	**Dosage**	**Route**
Trametinib		

Weight: _____ kg **Height: _____cm** **BSA: _____m^2**

To begin cycle: Absolute Neutrophil Count >1,000 and Platelets >75,000

Date Due	Date Received	Week	Day	Dose given _____	Comments
		1	1		
			2	–	
			3	–	
			4	–	
			5	–	
			6	–	
			7	–	
		2	8	–	
			9	–	
			10	–	
			11	–	
			12	–	
			13	–	
			14	–	
		3	15	–	
			16	–	
			17	–	
			18	–	
			19	–	
			20	–	
			21	–	
		4	22	–	
			23	–	
			24	–	
			25	–	
			26	–	
			27	–	
			28	–	
			29/1		

Each Cycle = 28 days

Observations:

APPENDIX X: CLINICAL BENEFIT OF ASSESSMENT

Clinical Benefit Assessment (CBA)

Please assess each pertinent criterion for your patient. Each patient should have at least 2 pertinent criteria to be placed on study. Pertinent criteria should be Grade 2 or greater for each criteria category chosen. Base your assessment on the last 7 days of the patient's clinical status. Your assessment should be based on the patients underlying vascular anomaly diagnosis, not side effects of the drug. Grade 5 for all criteria is death.

Cardiac:

Grade 0	Normal
Grade 1	Mild asymptomatic diagnostic finding; no intervention required
Grade 2	Moderate asymptomatic or symptomatic diagnostic findings; outpatient interventions (cardiac medications)
Grade 3	Symptomatic, requiring intervention; hospitalization; responsive to therapy
Grade 4	Symptomatic, requiring aggressive intervention; not responsive to therapy

Pulmonary:

Grade 0	Normal
Grade 1	Mild asymptomatic diagnostic finding; no intervention required
Grade 2	Moderate symptomatic diagnostic finding, outpatient interventions (medications, O2, CPAP etc.)
Grade 3	Symptomatic, requiring intervention, hospitalization; responsive to therapy
Grade 4	Symptomatic, requiring aggressive intervention; hospitalization; not responsive to therapy

Skin:

Grade 0 Normal

Grade 1 Asymptomatic clinical changes of color, texture, warmth

Grade 2 Symptomatic skin lesions without breakdown

Grade 3 Skin breakdown with bleeding; pain and or infection

Grade 4 Life-threatening consequences; major invasive intervention indicated

Proptosis/enophthalmos:

Grade 0 Normal

Grade 1 Asymptomatic, intervention not indicated

Grade 2 Symptomatic and interfering with function, but not interfering with ADL

Grade 3 Symptomatic and interfering with ADL

Grade 4 Loss of vision

Obstruction of Visual Axis:

Grade 0 No obstruction of visual axis

Grade 1 Eyelid dysfunction a symptomatic but not interfering with ADL; no astigmatism

Grade 2 Symptomatic; interfering with ADL; causing amblyopia or astigmatism

Grade 3 Intervention indicated (medical and or surgical)

Grade 4 Loss of vision

Obstruction of airway:

Obstruction of: (select one or more)

- Bronchus
- Larynx
- Pharynx
- Trachea

Grade 0	No obstruction of airway
Grade 1	Asymptomatic obstruction on exam, endoscopy, or radiograph
Grade 2 distress;	Symptomatic (e.g., noisy airway breathing), but causing no respiratory medical management and/or IR intervention indicated
Grade 3 stent,	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., laser, IR intervention, surgical removal, may need Tracheotomy)
Grade 4	Life-threatening airway compromise; tracheotomy or intubation indicated, need for ventilatory support

Hemorrhage/Bleeding From VA:

Grade 0	No hemorrhage/bleeding from VA
Grade 1	Mild without transfusion, no anemia
Grade 2	Moderate without transfusion but anemia, or interference of ADL
Grade 3	Transfusion indicated, procedural intervention required and or hospitalization required
Grade 4	Catastrophic bleeding, requiring major non-elective intervention

Thrombotic Event from VA:

Grade 0	No thrombotic event from VA
Grade 1	Phleboliths present on clinical or radiographic exam but asymptomatic
Grade 2	Phleboliths present on clinical or radiographic exam and symptomatic. Superficial phlebitis requiring medical management (anti-inflammatory agents or prophylactic anticoagulation.
Grade 3	Superficial phlebitis requiring medical management (treatment anticoagulation); Deep/Large Venous Thrombosis without Acute decompensation but in need of medical management
Grade 4	Life threatening Venous Thrombosis with Acute decompensation requiring intensive intervention and hospitalization

Localized intravascular Coagulopathy (LIC) from VA:

Grade 0 No LIC

Grade 1 Normal Fibrinogen, normal platelet count, mildly elevated D-dimer (> normal less than 2x normal)

Grade 2 Mildly decreased fibrinogen (<150 mg/dl/ > 100 mg/dl), normal-low normal platelet count (> 100 10*3/ul), AND/OR moderately elevated D-dimer (> 2x normal, Less than 3 x normal)

Grade 3 Moderately decreased fibrinogen (< 100 mg/dl/>50 mg/dl), moderately decreased platelet count (<100 10*3/ul/>50 10*3/ul), AND/OR moderately elevated D-dimer (same as above

Requiring medical intervention but no replacement except during procedures

Grade 4 Significantly decreased fibrinogen (<50 mg/dl), moderately/significantly decreased platelet (< 100 10*3/ul), AND/OR critically elevated D-dimer requiring medical (> 4 x normal).

Requiring intervention and replacement

Grading System for severity of Kaposiform Lymphangiomatosis (KLA) and Kasabach Merritt Syndrome (KMP) like coagulopathy:

Grade 0 KLA without KMP

Grade 1 KLA with KMP without bleeding or blood product support

Grade 2 KLA with KMP with no active bleeding or DIC, intermittently receiving blood product support secondary to low numbers or need for procedures

Grade 3 KLA with KMP with active bleeding, bruising and needing blood product support

Grade 4 KLA with KMP/DIC/bleeding requiring aggressive medical care (mechanical ventilation, pressor support)

Grading of Hematological product support (Any Diagnosis):

Grade 0 No need for blood product support

Grade 1 One of the following hematological supports: PRBC, platelets, fibrinogen (cryoprecipitate)

Grade 2	Two of the following hematological supports: PRBC, platelets, fibrinogen (cryoprecipitate)
Grade 3	All three of the following hematological supports: PRBC, platelets, fibrinogen (cryoprecipitate)
Grade 4	All three of the following hematological supports: PRBC, platelets, fibrinogen (cryoprecipitate), AND at least one other means of hematological support (including factor support)

Grading of Thrombocytopenia (no transfusion within 1 week):

Grade 0	Normal platelet count
Grade 1	plat < 100 10*3 /ul without bleeding
Grade 2	plat < 50 10*3/ul without bleeding
Grade 3	plat < 20 10*3/ul without bleeding
Grade 4	Any thrombocytopenia with clinically significant bleeding

Grading of Fibrinogen: (no transfusion within 3 weeks):

Grade 0	Normal fibrinogen
Grade 1	Fibrinogen < 150 mg/dl without bleeding
Grade 2	Fibrinogen < 100 mg/dl without bleeding
Grade 3	Hypofibrinogenemia < 50 mg/dl without bleeding
Grade 4	Hypofibrinogenemia with clinically significant bleeding

Neurologic/Compression by paraspinal/spinal VA:

Grade 0	No neurologic/compression by paraspinal/spinal VA
Grade 1	Asymptomatic radiologic findings only
Grade 2	Symptomatic, but not interfering with ADL
Grade 3	Symptomatic and interfering with ADL needing intervention (medical, surgical, IR intervention)

Grade 4 Life-threatening; disabling; immediate intervention indicated (IR/surgical)

Neurologic CSF Leak (spinal or intracranial):

Grade 0 No CSF leak

Grade 1 Asymptomatic radiologic findings only

Grade 2 Symptomatic, but not interfering with ADL

Grade 3 Symptomatic and interfering with ADL needing intervention (medical, surgical, IR intervention

Grade 4 Life-threatening, disabling, immediate intervention indicated (IR surgical)

Liver dysfunction:

Grade 0 Normal

Grade 1 Asymptomatic

Grade 2 Jaundice

Grade 3 Asterixis

Grade 4 Encephalopathy

Abdominal compartment syndrome:

Grade 0 No abdominal compartment syndrome

Grade 1 Hepatomegaly

Grade 2 Mild hepatomegaly and abdominal distention

Grade 3 Moderate hepatomegaly and abdominal distention

Grade 4 Impairment of urine output or respiratory distress

Grade 5 Death

Bone involvement of VA:

Grade 0	No bone involvement of VA
Grade 1	Asymptomatic, radiologic findings only
Grade 2	Symptomatic, but not interfering with ADL, medication/intervention may be needed
Grade 3	Altered ADL secondary to symptoms: pain, fracture
Grade 4	Complete loss of function

Effusions caused by VA (pleural, cardiac, ascites):

Grade 0	No effusions caused by VA (pleural, cardiac, ascites)
Grade 1	Asymptomatic, radiologic findings only
Grade 2	Symptomatic, but not requiring immediate intervention
Grade 3	Requiring intervention, fluid removal, tube drainage, fluid replacement
Grade 4	Requiring ventilation or more aggressive surgical support

Lymphedema caused by VA:

Grade 0	No lymphedema caused by VA
Grade 1	Intermittent swelling, when swelling skin will “pit”, Relief and reduction with elevation
Grade 2	Tissue is firmer, less pitting, no relief with elevation
Grade 3	Hard (fibrotic) skin, thickening of surface, Increase in circumference
Grade 4	All of the above with skin breakdown with or without infection

AVM Skin Involvement:

Grade 0	No skin discoloration or stain
Grade 1	Skin discoloration or stain, warmth, shunting on Doppler
Grade 2	Enlargement, pulsation-thrill, bruit with or without minor ulceration or pain

Grade 3 Moderate ulceration, bleeding, or pain

Grade 4 Severe ulceration, bleeding, pain, or other significant morbidity

Physical Disability:

Grade 0 No disability

Grade 1 Mildly impaired, Performs ADLs

Grade 2 Moderately impaired, Needs help with some ADLs

Grade 3 Severely impaired, needs help with all ADLs

Grade 4 Unable to perform any intentional physical activity

Protein Losing Enteropathy (PLE)

Grade 0 No PLE

Grade 1 Mildly abnormalities in lab work (Albumin, TP, Alpha -1 anti-trypsin etc.)

Grade 2 Moderate abnormalities in lab work, no replacement needed, may need low-fat diet

Grade 3 Significant impairment in lab work, need for replacement, strict low-fat diet, MRL intervention

Grade 4 Hospitalization, Requiring replacement and intervention (MRL with treatment, surgical procedures)

Hypoglycemia

Grade 0 No hypoglycemia

Grade 1 Mildly impaired, Episodes but limited intervention

Grade 2 Moderately impaired, Need for frequent interventions

Grade 3 Severely impaired, need for frequent glucose monitoring and IV replacement

Grade 4 Hypoglycemic events requiring hospitalization

Seizures

Grade 0	No need for antiepileptic medication
Grade 1	Seizures controlled on medication
Grade 2	Seizures partially controlled on medication
Grade 3	Seizures poorly controlled needing medication adjustment
Grade 4	Seizures uncontrolled or inadequately controlled on medication requiring hospitalization

ADL = Activities of Daily Life

KMP = Kasabach-Merritt Phenomenon

VA = Vascular Anomalies (vascular tumors and vascular malformations)

VM = Vascular Malformations

KLA = Kaposiform lymphangiomatosis

Open Endend Questions

1. How has your vascular anomaly gotten better since starting on medication? It is okay to write “none” if nothing has gotten better.
    a. How has the rest of your health gotten better since starting on medication in this study? It is okay to write “none” if nothing has gotten better.
2. How has your vascular anomaly gotten worse since starting on medication? It is okay to write “none” if nothing has gotten worse.
    a. How has the rest of your health gotten worse since starting on medication in this study? It is okay to write “none” if nothing has gotten better.
3. What else would you like us to know about your experience taking this medication