Title:	**VATCH (Vascular Anomaly Analysis for Therapy Choice)** Sub-protocol 2 – Phase II Study of Alpelisib Treatment in Subjects with TIE2/PIK3CA pathway Driven Vascular Anomalies
Short Title	Alpelisib in TIE2/PIK3CA pathway Vascular Anomalies
Drug or Device Name(s):	Alpelisib tablet/capsule
FDA IND	IND Exempt (as determined by the FDA)
Regulatory Sponsor:	
eIRB Number	Pending
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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
DDE	Direct Data Entry
ddPCR	Droplet digital polymerase chain reaction
DICOM	Digital Imaging and Communications in Medicine
DILI	Drug-Induced Liver Injury
DMEG	Dysplastic Megalencephaly
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
FAO	Fibroadipose hyperplasia or Overgrowth
FDA	Food and Drug Administration
G1	Gap-1
GCP	Good Clinical Practice
GI	Gastrointestinal
GT	Gastric Tube
HDL	High density lipoprotein
HHML	Hemihyperplasia Multiple Lipomatosis
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 Representative
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
MCAP	Megalencephaly-Capillary Malformation
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
M-CM	Megalencephaly-Capillary Malformation
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
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)
PIK3CA	Phosphatidylinositide 3-kinase p110 alpha
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
RR	Response Rate
SAE(s)	Serious adverse event(s)
SAS	Statistical adverse event(s)
SC	Subcutaneous
SD	Stable Disease
SOP	Standard operating procedure
SR	Substantial Response
TIE2/TEK	Thyrosine Kinase endothelial
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

PIK3CA and TIE-2/TEK pathway driven vascular anomalies represent an extremely heterogenous group of disorders (ranging from small, isolated overgrowth to life-threatening extensive vascular malformations) that in the past were treated aggressively with surgical and endovascular procedures. With recent phenotype genotype discovery, more directed therapy with PIK3CA inhibitors has shown promising results, although data is limited. Alpelisib is a PIK3CA inhibitor, orally bioavailable, developed initially for malignant disorders with PIK3CA variants.

Objectives

Primary Objectives are:

1) To determine the proportion of subjects with objective beneficial response to alpelisib 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 alpelisib in children and young adults with PIK3CA/TIE2/TEK driven VA.

Secondary and exploratory objectives include biomarker analysis, duration of response, and tolerability of alpelisib over time in subjects with PIK3CA/TIE2/TEK 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 2 and will enroll 53 evaluable and eligible subjects with VA phenotypes and genotype alterations of the PIK3CA/TIE-2/TEK pathway. Subjects will be included that are deemed to need systemic medical treatment.

Study Interventions and Measures

The PIK3CA inhibitor alpelisib will be administered in this protocol for subjects with PIK3CA/TIE2/TEK 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

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.

PROTOCOL SYNOPSIS

Study Title	VATCH (Vascular Anomaly Analysis for Therapy Choice) – Sub-protocol 2 – Phase II Study of Alpelisib Treatment in Subjects with TIE2/PIK3CA 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 alpelisib in subjects with PIK3CA/TIE-2/TEK pathway driven vascular anomalies (VA). These diseases are rare and there is much heterogeneity of phenotype thus an innovative assessment of response will be used based on: radiology assessment, Patient Reported Outcome (PRO) Measurements, and Clinical Benefit Assessments (CBAs).
Study Objective(s)	**Primary** • To determine the proportion of subjects with objective beneficial response to alpelisib at the end of cycle 6 using individualized response criteria based on radiologic assessment, Patient Reported Outcomes (PROs), and Clinical Benefit Assessment (CBA). • To determine the safety of oral alpelisib in children and young adults with PIK3CA/TIE-2/TEK pathway driven vascular anomalies. **Secondary** • To assess the duration of response in subjects receiving alpelisib at the end of 12 and 24 cycles. • 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 PIK3CA and TIE-2/TEK somatic activating variations 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 suppression in subjects with PIK3CA/TIE-2/TEK pathway driven vascular anomalies. • To correlate cfDNA before and during pharmacologic suppression in subjects with PIK3CA/TIE-2/TEK pathway driven vascular anomalies.

	• To describe the distribution of genetic variants and their associated responses to alpelisib treatment in subjects with vascular and complex lymphatic anomalies.
Study Drug	Alpelisib tablet
Study Design	This is a Phase II multi-center non-randomized study to assess the safety and efficacy of alpelisib in PIK3CA/TIE-2/TEK driven vascular anomalies.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Signed informed consent and assent (when applicable) from the subject, parent/guardian or Legally Authorized Representative (LAR) must be obtained prior to any study related screening procedures. 2. Males or females age ≥ 2 years to ≤ 30 years at the time of informed consent with critical disease needed systemic medical therapy. 3. Documented laboratory validated pathogenic **or likely pathogenic** somatic activating variant in *PIK3CA* or somatic *TIE2/TEK* variant. Germline TIE2/TEK variants are acceptable. 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 a disease-related lesion or lesions which can be measured objectively via: a. Radiographic/imaging study OR b. Quantitative Clinical Benefit Assessments 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. 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 lower 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 ≥ 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
d. 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 > 75 x 10^9/L (independent of transfusions) exception is made for Kaposiform lymphangiomatosis subjects who have a baseline coagulopathy and thrombocytopenia
e. Additional Laboratory Assessments
    i. Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ Grade 1 according to NCI-CTCAE version 5.0 if judged clinically not significant by the investigator

ii. Potassium within normal limits, or corrected with supplements
iii. Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.5% (both criteria have to be met)
iv. Fasting Serum lipase ≤ ULN

8. 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.
9. Males and females of reproductive potential must agree to 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 that have received alpelisib previously either via Managed Access Program from Novartis or commercial supply are eligible to enroll IF they have been off alpelisib for at least 7 days and there is clinical progression/worsening while off treatment.

Exclusion Criteria

1. Subject with only epidermal nevus/nevi in the absence of other PIK3CA vascular anomaly/overgrowth
2. Debulking or other major surgery performed within 30 days, at time of informed consent.
3. 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
4. Sclerotherapy/embolization for vascular complications performed within 14 days before informed consent.
5. Subjects, who previously received systemic treatment including alpelisib and targeted topical therapy including *PIK3CA* inhibitors for their vascular anomaly (e.g.,mTOR inhibitors, AKT inhibitors, anti-angiogenic agents), may enter the study if the following criteria are met:
    a. Not simultaneously on another clinical trial;
    b. Off systemic previous systemic treatment for at least 30 days prior to consent;
    c. Off MTOR inhibitors for at least 14 days prior to initiation of alpelisib.
6. Participation in any other prior investigational study

within 4 weeks prior to study treatment start *and* within 5 half-lives of the investigational product, whichever is longer

7. 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.
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. Clinically significant heart disease not due to VA, including
    a. History of documented congestive heart failure (New York Heart Association functional classification III-IV);
    b. Clinically significant uncontrolled cardiac arrhythmias;
    c. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome;
    d. Corrected QT (QTcF) at screening: >450 ms.
10. Documented pneumonitis or interstitial lung disease not due to VA
11. History of acute pancreatitis within 1 year before informed consent or past medical history of chronic pancreatitis
12. Subjects with an established diagnosis of type I diabetes mellitus or uncontrolled type II diabetes mellitus
13. Impaired gastrointestinal (GI) function that may significantly alter the absorption of the study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
14. History of hypersensitivity to any drugs or metabolites of *PI3K* inhibitor or any of the excipients of alpelisib
15. Known history of Steven Johnson's syndrome, erythema multiform or toxic epidermal necrolysis
16. History of seizures or epilepsy on enzyme inducing antiepileptic drug(s); uncontrolled seizures are only allowed if due to *PIK3CA* variation
17. Concurrent severe and/or uncontrolled medical conditions not due to *PIK3CA* variation. Resolution of symptoms for at least 28 days must have occurred before consent

	18. Subject may not be pregnant or breast feeding. 19. Female subjects of childbearing age and male subjects who do not agree to abstinence or to a highly effective method of contraception (condoms and/or oral, injected or implanted hormonal methods of contraception, or placement of an intrauterine device or intrauterine system, or surgical sterilization for the duration of the study and for one week following discontinuation of alpelisib, or non-heterosexual partnerships) 20. Human Immunodeficiency Virus (HIV) infection by history or by eligibility testing 21. Concomitant treatment with Strong inducers of CYP3A4 (Appendix VI) 22. 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 53 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. Subjects without radiologically evaluable disease may have a CBA substituted for radiologic evaluation. -MRI evaluation will be at screening, and at the end of cycles 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
Statistical and Analytic Plan	For all the analyses, subjects who received any dose of alpelisib will be included in the analyses. For the primary efficacy analysis of objective response at the end of cycle 6, we will test a null hypothesis of response of 60% against an alternative hypothesis of response rate of 80%. We will follow the Simon's optimal two-stage design: an interim analysis will be conducted after 19 subjects have been observed for response, and if 11 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 53 evaluable subjects and at the end of the trial if 37 or more intermediate or substantial responses are observed, the treatment will be declared promising. This design provides >=90% power when the true response rate is 80% and yields a one-sided type I error of <=0.05 when the true response rate is 60%. For evaluating toxicity, a sample size of 53 provides 93% 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 10 observed toxicity events out of 53 subjects, the estimated toxicity rate is 19%, with the 95% exact confidence interval (CI) as 9% - 32%.
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:

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) and Complex lymphatic anomalies (CLA) are a group of malformations with highly variable presentations. Patients with vascular and lymphatic anomalies suffer from significant morbidity, disfigurement, and mortality with limited available systemic treatment options. The current systemic therapies utilized have limited evidence to support their efficacy and safety in part because of the highly diverse and variable diseases. This clinical heterogeneity reflects the complex genetic underpinnings of each subject's disease making the delivery of therapy targeted to individual subjects challenging.

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 PI3K/AKT/mTOR mammalian target of rapamycin (mTOR) signaling pathway plays a major role in the physiological processes regulating cellular growth, proliferation, angiogenesis, survival, and metabolism.[1-3] The hyper-activation of the PI3K/AKT/mTOR pathway results in dysregulation of cellular functions, leading to a competitive growth advantage. Somatic mutations and gains or losses in these genes are linked to different solid and hematological tumors as well as overgrowth syndromes.[4] *PIK3CA* encodes the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which transduces activation of tyrosine kinase growth factor and hormone receptors into activation of Protein Kinase B (AKT) and Mammalian Target of Rapamycin (mTOR) signaling to promote tissue growth. Patients who develop mosaic activating variants (typically somatic) in the *PIK3CA* gene can develop overgrowth of a particular section of the body, referred to as "PIK3CA-related overgrowth spectrum" (PROS).

PROS (FIG 1)[5,6] can encompass a range of clinical findings in which the core features are congenital or early-childhood onset of segmental/focal overgrowth with or without cellular dysplasia. The predominant areas of overgrowth include the brain, limbs, abdomen, chest, and face, and occur in an asymmetric distribution. A clinical spectrum is observed even though all the conditions are related to the PROS umbrella, where *PIK3CA* is the causative gene. PROS includes Fibroadipose hyperplasia or Overgrowth (FAO), Hemihyperplasia Multiple Lipomatosis (HHML), Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal (CLOVES) syndrome, macrodactyly, Fibroadipose Infiltrating Lipomatosis, and the related megalencephaly syndromes, Megalencephaly-Capillary Malformation (MCAP or M-CM) and Dysplastic Megalencephaly(DMEG). Vascular malformations may include capillary, venous, and less frequently, arterial or mixed (capillary-lymphatic-venous or capillary-venous-lymphatic) malformations. These may be in various locations (internal and/or external) and can cause various clinical issues, including swelling, pain, and occasionally localized bleeding

secondary to trauma. Lipomatous overgrowth may occur ipsilateral or contralateral to a vascular malformation. Intellectual disability may be a feature and appears to be mostly related to the presence and severity of seizures, cortical dysplasia (e.g., polymicrogyria), and hydrocephalus.

Endocrine issues affect a small number of individuals and most commonly include hypoglycemia (largely hypoinsulinemic hypoketotic hypoglycemia), hypothyroidism, and growth hormone deficiency. First clinical evidence of PROS usually occurs at birth or early in life (first 6-18 months of life). Affected areas generally keep growing throughout life, but at a slower pace after the subject reaches their third decade of life. Previously, there was no drug therapy for PROS, the treatment consisted of symptom management, mainly surgical interventions of overgrowth lesions that ultimately led to severe physical disabilities with unsatisfactory quality of life (QOL). The potential to modify and control disease progression is greatest during the rapid disease progression stage which occurs in early childhood. In more recent years, allosteric mTOR inhibitors such as sirolimus have been shown to slow the growth of cancers bearing *PIK3CA* variants.[7] Sirolimus also potently attenuates pathological AKT signaling and reduces cell proliferation in dermal fibroblasts derived from people with PROS and is currently being used in the treatment of PROS. Published reports of sirolimus therapy in PROS have suggested efficacy.[8-10] The use of Sirolimus and subsequent studies in participants with vascular anomalies and PROS support the hypothesis that agents targeting PI3K/AKT/mTOR pathway genes may be better candidates should be further explored in patients with specific PIK3CA mutations.

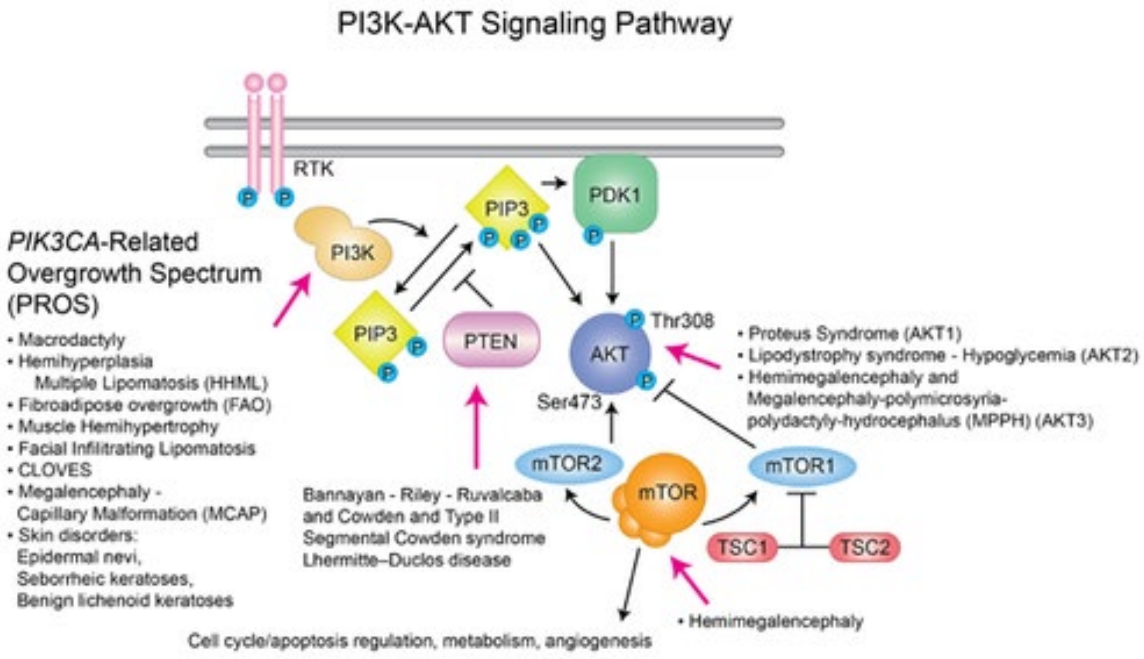

FIGURE 1: PI3K/AKT Pathway and Related Disorders

Venous Malformations (VM) can be caused by PIK3CA (20%) and TIE-2/TEK 80% of the time. They can be focal, multi-focal or extensive and can cause issues with pain, organ dysfunction, functionality and can lead to significant life-threatening complications such as bleeding and pulmonary emboli. The mTOR inhibitor sirolimus has been used in prospective studies revealing good efficacy and tolerability and this has been validated in animal models. (Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study.[11,12]
Many patients do not respond to sirolimus or lack durable responses, and this medication is known to be an immunosuppressant. Recently, alpelisib has been shown to be efficacious and safe in patients with complicated venous malformations.

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: Alpelisib (Vijoice®)

Alpelisib (BYL719) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib has demonstrated antitumor activity in a variety of cancer cell lines, specifically those with *PIK3CA* variants and in xenograft models with mutated or amplified *PIK3CA*.[13] Human clinical studies also demonstrated the antitumor activity of alpelisib, especially in tumors with *PIK3CA* alterations, with a well charaterized safety profile.[14,15] Alpelisib is a first-in-class α-specific phosphatidylinositol 3-kinase inhibitor approved for the treatment of patients with estrogen receptor–positive metastatic breast cancer. Alpelisib demonstrated efficacy in a mouse model of PROS/CLOVES, which was followed by the use of alpelisib in patients with PROS under a compassionate use program consisting of 19 patients with PROS disorders led to substantial clinical improvement and a radiological response in all patients.[16] Children (<18 years) received alpelisib at 50 mg per day orally; adult participants received 250 mg per day orally. Disease evaluation was performed at baseline, then after 3 and 6 months of treatment. There was clinical improvement with partial or complete recovery from PROS-related complications (for instance, chronic gastrointestinal bleeding, disseminated intravascular coagulation, scoliosis, cognitive function and changed behavior) and with

changes in concomitant medication (for instance, cessation of strong analgesics, heparin, steroid treatment in participants who received these medications because of PROS-related complications). There have been subsequent case reports describing the successful use of alpelisib in patients with CLOVES and other PROS.[17,18] In summary, the PI3K/AKT pathway, which is dysregulated in PIK3CA-related overgrowth spectrum, is frequently activated through mutations in *PIK3CA*, thus, inhibition of PIK3CA by alpelisib is a rational approach for the therapeutic intervention in such diseases.

2.1.1 Rationale for Dose/Age

Drug dosing is based on two studies, EPIK-P1, NCT 04285723, and EPIK- P2, NCT04589650. The EPIK-P1[40] study was a non-interventional, site-based, medical chart review of patients > or = 2 years with PROS with severe/life-threatening conditions who received at least dose of alpelisib at least 24 weeks before the study cut-off date. On April 05, 2022, alpelisib received accelerated approval from the US FDA for the treatment of adult and pediatric patients aged ≥2 years with severe manifestations of PROS who require systemic therapy[41]. From this study, dosing for the present EPIK-P2[42]: a Phase II double-blind study with an upfront, 16-week randomized, placebo-controlled period to assess the efficacy, safety, and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS) was used. The same dosing per age will be used for this study.

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 by PIK3CA/TIE-2/TEK - pathway alteration. The phenotype and clinical characteristics will be heterogenous between subjects. The optimal measure of disease response in subjects with complex vascular anomalies has not been established. Current practice includes decreases in size of the VA, according to the subject perception, a physical exam, or radiographic (most commonly MRI) evaluations, laboratory assessments and other clinical testing 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 infection, 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 alpelisib 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 after approval from study PI or co-PI. These three components will be performed at discrete time points to quantitatively determine the individualized response to alpelisib therapy for subjects with vascular anomalies driven by PIK3CA/TIE-2/TEK alterations. Similar response criteria have been used in other studies. [28] 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 TIE2/TEK suppression

The angiopoietin-TIE2/TEK signaling pathway is critical for blood and lymphatic development and maintenance.[43-46]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 ECs, and in lymphatic ECs may activate lymphangiogenesis. [47,48] Elevated levels of Ang-2 and low Ang-1 levels have been found in KLA as well as other CLAs.[45] 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 x2 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 Alpelisib 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

Alpelisib is effective and safe for subjects with the diagnosis of vascular anomalies and overgrowth syndromes caused by somatic activating variants in PIK3CA and TIE-2/TEK genes.

3.2 Primary Objectives

- To determine the proportion of subjects with an objective beneficial response to alpelisib 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 alpelisib in children and young adults with PIK3CA/TIE2/TEK pathway driven vascular anomalies at the end of 6 cycles.

3.3 Secondary Objectives

- To assess the duration of response in subjects receiving alpelisib 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 PIK3CA and TIE-2/TEK somatic activating 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 with before and during pharmacologic suppression in subjects with PIK3CA/TIE-2/TEK pathway driven vascular anomalies.
- To correlate cfDNA before and during pharmacologic suppression in subjects with PIK3CA/TIE-2/TEK pathway driven vascular anomalies.
- To describe the distribution of genetic anomalies and their associated responses to alpelisib treatment in subjects with PIK3CA and TIE-2/TEK activating variants

4 INVESTIGATIONAL PLAN

4.1 General Schema of Study Design

This study is a single-arm, open-label investigational Phase II study of alpelisib administered orally on a continuous 28-days, for up to 24 total cycles in subjects ages 2 years to 30 years. 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 Le Cras'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 III).

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

Samples that are not immediately analyzed 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)

Alpelisib should be taken once daily with food, at approximately the same time each day. If a dose of alpelisib is missed, it can be taken immediately after food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, alpelisib should be taken at the usual time. If the subject vomits after taking the alpelisib dose, the subject should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Alpelisib is available as 50, 125, and 200mg tablets and will be dosed mg/day and not adjusted for body weight or body surface area.

4.3.1 Dosing

For subjects 18 years and older, alpelisib will be administered at 125mg daily (with the potential to increase up to a maximum dose of 250 mg orally once daily) on a continuous dosing schedule and can be adjusted for toxicity per the recommendations in this treatment plan. Alpelisib cannot be combined with other investigational agents as there are no safety data available.

For subjects 6-17 years of age, alpelisib will be administered at 50mg daily (with the potential to increase up to a maximum dose of 200 mg orally once daily) on a continuous dosing schedule and can be interrupted for toxicity per the recommendations in this treatment plan. Alpelisib cannot be combined with other investigational agents as there are no safety data available.

For subjects 2-5 years of age, alpelisib will be administered at 50 mg orally once daily on a continuous dosing schedule and can be interrupted for toxicity per the recommendations in this treatment plan. Alpelisib cannot be combined with other investigational agents as there is no safety data available. Alpelisib should be swallowed whole (tablets should not be chewed, crushed [with the exception of crushing under water to create an oral suspension], or split prior to swallowing. Tablets that are broken, cracked, or otherwise not entact should not be ingested and are to be returned to site staff. For participants who are unable to swallow, alpelisib can be administried as a drinkable suspension by crushing tablets under water with a spoon.

Refer to Section 10 for dose modifications for toxicity.

4.4 Follow-up Phase

Subjects who have stopped alpelisib 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 the 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 53 evaluable subjects are enrolled. It is expected that approximately 61 subjects will be enrolled to produce 53 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 53 evaluable subjects in total. The study will enroll both adult and pediatric subjects ≥2 years 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 years to ≤ 30 years at the time of informed consent with critical disease needed systemic medical therapy.
3. Documented laboratory validated pathogenic **or likely pathogenic** somatic activating variant in *PIK3CA* or somatic *TIE2/TEK* mutation. Germline TIE2/TEK variants are acceptable. 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 Clinical Benefit Assessments measurement (Appendix IX) 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 lower 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 ≥ 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
d. 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 > 75 x 10^9/L (independent of transfusions) exception is made for Kaposiform lymphangiomatosis subjects who have a baseline coagulopathy and thrombocytopenia
e. Additional Laboratory Assessments
    i. Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ Grade 1 according to NCI-CTCAE version 5.0 if judged clinically not significant by the investigator
    ii. Potassium within normal limits, or corrected with supplements
    iii. Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.5% (both criteria have to be met)
    iv. Fasting Serum lipase ≤ ULN

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 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 that have received alpelisib previously either via Managed Access Program from Novartis or commercial supply are eligible to enroll IF they have been off alpelisib for at least 7 days and there is clinical progression/worsening while off treatment.

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. Subject with only epidermal nevus/nevi in the absence of other PIK3CA vascular anomaly/overgrowth
2. Debulking or other major surgery performed within 30 days, at time of informed consent.
3. 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
4. Sclerotherapy/embolization for vascular complications performed within 14 days before informed consent.
5. Subjects, who previously received systemic treatment including alpelisib and targeted topical therapy including *PIK3CA* inhibitors for their vascular anomaly (e.g.,mTOR inhibitors, AKT inhibitors, anti-angiogenic agents), may enter the study if the following criteria are met:
    i. Not simultaneously on another clinical trial;
    ii. Off systemic previous systemic treatment for at least 30 days prior to consent;
    iii. Off MTOR inhibitors for at least 14 days prior to initiation of alpelisib.
6. Participation in any other prior investigational study within 4 weeks prior to study treatment start *and* within 5 half-lives of the investigational product, whichever is longer
7. 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.
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. Clinically significant heart disease not due to VA, including
    a. History of documented congestive heart failure (New York Heart Association functional classification III-IV);
    b. Clinically significant uncontrolled cardiac arrhythmias;
    c. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome;
    d. Corrected QT (QTcF) at screening: >450 ms.
10. Documented pneumonitis or interstitial lung disease not due to VA
11. History of acute pancreatitis within 1 year before informed consent or past medical history of chronic pancreatitis
12. Subjects with an established diagnosis of type I diabetes mellitus or

uncontrolled type II diabetes mellitus

13. Impaired gastrointestinal (GI) function that may significantly alter the absorption of the study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
14. History of hypersensitivity to any drugs or metabolites of *PI3K* inhibitor or any of the excipients of alpelisib
15. Known history of Steven Johnson's syndrome, erythema multiform or toxic epidermal necrolysis
16. History of seizures or epilepsy on enzyme inducing antiepileptic drug(s); uncontrolled seizures are only allowed if due to *PIK3CA* variant
17. Concurrent severe and/or uncontrolled medical conditions not due to *PIK3CA* variant. Resolution of symptoms for at least 28 days must have occurred before consent
18. Subject may not be pregnant or breast feeding.
19. Female subjects of childbearing age and male subjects who do not agree to abstinence or to a highly effective method of contraception (condoms and/or oral, injected or implanted hormonal methods of contraception, or placement of an intrauterine device or intrauterine system, or surgical sterilization for the duration of the study and for one week following discontinuation of alpelisib, or non-heterosexual partnerships)
20. Human Immunodeficiency Virus (HIV) infection by history or by eligibility testing
21. Concomitant treatment with Strong inducers of CYP3A4 (Appendix VI)
22. 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 somatic *PIK3CA* or somatic *TIE2/TEK* 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 • Hemoglobin A1C
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. To be completed at screening and to be repeated at investigator discretion only if clinically indicated.
    - 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 6, 12, 18, 24, 30, 36, and end of study (not triplicate). To be repeated at investigator discretion only if abnormal at screening.
- Individualized Response Criteria
    - Radiologic assessment (within 4 weeks of enrollment)

- Imaging modality of choice based on underlying vascular anomaly (MRI, MRL, US, X-rays, CT scan)

- Patient Reported Outcome (PRO) Measurement

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 **(4 items)**	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 IX.

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 VII. 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 persons who can get pregnant of childbearing age subjects of childbearing potential: serum or urine pregnancy testing
- Collect unused study drug and diary

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 VA except for agents known to have significant interactions with Alpelisib as

noted in Section 7.3. 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 PROS-related lesion volume reduction should be avoided. Systemic therapy targeting PI3K/AKT/mTOR pathway other than alpelisib and/or any investigational/not approved medication for PROS 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 PROS.

The subject must discontinue from specific treatment with small molecules (such as mTOR inhibitors, AKT inhibitors, MEK inhibitors) for PROS before any of study related assessments and at least 4 weeks before study treatment start. An exception is made for MTOR inhibitors that should be discontinued at least 2 weeks before study treatment start because of drug half-life.

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 alpelisib) 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 the Section 7.2.1and Section 7.3 below).
- Treatment for concomitant medical conditions, adverse events (see prohibited and cautioned medications in the Section 7.2.1and Section 7.3 below)
- Supplemental nutrition (enteral, parenteral)
- Routine vaccinations
- Supportive care use of anticoagulants and compression garments is allowed. Subjects must have been using these interventions in an unchanged manner for 3 months before study enrollment

7.2.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution are described below and listed in Appendix V. This list is not comprehensive and is only meant to be used as a guide.

These medications should be excluded from subject use if possible. If they must be given based on the investigator's judgment, then use with caution and consider an alpelisib interruption, as appropriate, if the concomitant medication is only needed for a short time.

Medications to be used with caution (Appendix V):

- **CYP2C9 substrates with narrow therapeutic index (NTI) (e.g., anticoagulants):** *In vitro* evaluations indicated that pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. In the absence of clinical data, caution is recommended with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may reduce the clinical activity of such drugs. Alternatively, therapeutic anticoagulation may be accomplished using low- molecular weight heparin or Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors.
- **CYP2B6 sensitive substrates or CYP2B6 substrates with NTI:** Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In the absence of clinical data, sensitive CYP2B6 substrates (e.g., bupropion, evafirenz) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such drugs.
- **Selected CYP3A4 substrates:** Alpelisib can be co-administered with sensitive CYP3A4 substrates (e.g., midazolam) and CYP3A4 substrates with narrow therapeutic window (e.g., fentanyl). Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism Systemic exposures of such CYP3A4 auto-inhibitors and auto-inducers may be either decreased or increased depending on the drug and nature of auto-perpetrator potential, respectively, when alpelisib is co-administered, based on PBPK simulations.
- Please refer to the latest version of alpelisib Investigator's Brochure for additional information pertaining to alpelisib.

7.2.1.1 Oral Anti diabetics

Subjects who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association)/EASD (European Association for the Study of Diabetes) guidance. It is recommended to start treatment with metformin. Metformin is not recommended in subjects below the age of 10 years, metformin extended release (XR) is not recommended in pediatric subjects below the age of 18 years. Consultation with a diabetologist is needed to find the optimal individualized treatment for hyperglycemia, especially in pediatric subjects under 10 years old (where international or local guidelines may apply). Subjects receiving oral anti-diabetics which are predominantly metabolized by

CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored with respect to their effectiveness as alpelisib was found to be an inducer of CYP2C9 in vitro.

7.2.1.2 Corticosteroids

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes). Hyperglycemia is a common adverse event for PI3K inhibitors like alpelisib; corticosteroids should therefore be used with caution and subjects should be closely monitored.

7.2.1.3 Gastric protection agents

Alpelisib is characterized by a pH-dependent solubility. Therefore, acid reducing agents (ARAs, e.g., proton-pump inhibitors, H2-antagonists and antacids) may alter the solubility of alpelisib and hence its bioavailability. A drug-drug interaction study in human healthy volunteers confirmed that co-administration of alpelisib with the H2-antagonist ranitidine after a meal lead to a decrease in exposure by only ~20%, considered not to be clinically relevant. Alpelisib can be co-administered with any ARAs.

7.3 Prohibited medication

The following medications are prohibited during treatment with alpelisib (Appendix VI):

This list is not comprehensive and is only meant to be used as a guide.

- **Strong inducers of CYP3A4:**
  Co-administration of alpelisib with a strong CYP3A4 inducer may decrease alpelisib concentration, which may decrease alpelisib activity. Avoid coadministration of alpelisib with strong CYP3A4 inducers.

- **Inhibitors of BCRP:**
  Co-administration of alpelisib with a BCRP inhibitor may increase alpelisib concentration, which may increase the risk of toxicities. Avoid the use of BCRP inhibitors in subjects treated with alpelisib.

- **Bisphosphonates:**
  Zoledronic acid or other bisphosphonates administration will not be allowed during the alpelisib treatment period due to increased risk of osteonecrosis.

- **Herbal Medications:**

  The use of herbal preparations/medications and dietary supplements (except for vitamins) are prohibited throughout the study, as a potential drug-drug interaction is possible. Herbal medication include but are not limited to St. John's Wort (Hypericum perforatum), and Avasimibe or BCRP inhibitors such as Curcumin.Medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential

for complex interactions. Subjects must stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

- **Other investigational and antineoplastic therapies**

  In addition, the subject should discontinue from specific treatment with small molecules (such as mTOR inhibitors, AKT inhibitors) and/or anti angiogenic agents for PROS before any of study related assessments or at least 4 weeks before study treatment starts whichever comes first.

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 Assesments

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 section6.1 Screening Assessments
ECG[4]: repeat during study if abnormal at screening or as clinically indicated per treating team (not triplicate)
X[4]: can repeat during study if abnormal at screening or by decision of the treating team (not triplicate)
Radiologic assessment[5]: At screening and at the end of every 6 cycles on treatment are mandatory. Following radiologic assessments as per decision of local treating team
X[6]: Within 4 weeks (28 days) of screening
Optional Biologic Studies[7]: As outlined in section 6.1 Screening Assessments
X[8]: All labs, physical exams, and vital signs, must be done within 14 days of starting Alpelisib
X[9]: 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.

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 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 IX) Examples of testing or assessments that can be followed to complete this grading scale include: o Pulmonary function testing o Lymphedema staging o Laboratory parameters o Bleeding assessment o PLE grading o Effusion assessment o Infection rates o Seizure grading o Photography o Videos o 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(if applicable) 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 IV).

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. [32] 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. [35-37 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 8-3. In 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 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	PROMIS Scale v1.2 -	PROMIS Early Childhood	PROMIS Parent Proxy Scale v1.0	PROMIS Pediatric Scale

Health Subscale	Global Health	Parent-Report Scale v1.0 - Global Health 8a	- Global Health 7+2	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 IX.

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 PIK3CA inhibitor alpelisib administered once a day on a continuous dosing schedule to subjects with PIK3CA 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[29,30].

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 alpelisib in children and young adults with PIK3CA and TIE-2/TEK activating variants in subjects. The primary efficacy endpoint is objective response at the end of cycle 6 and the primary safety endpoint is toxicity of alpelisib. Secondary endpoints include objective response at the end of cycle 12, safety and tolerability of alpelisib over time, duration of response, and biomarker measures.

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 60% against an alternative hypothesis of response rate of 80%. We will follow the Simon's optimal two-stage design: an interim analysis will be conducted after 19 subjects have been observed for response, and if 11 or fewer response is observed, the trial will be stopped for futility; otherwise the trial will continue to enroll a total of 53 evaluable subjects and at the end of the trial if 37 or more responses are observed, the treatment will be declared promising. This design provides >=90% power when the true response rate is 80% and yields a one-sided type I error of <=0.05 when the true response rate is 60%.

For evaluating of toxicity, a sample size of 53 provides 93% 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 10 observed toxicity events out of 53 subjects, the estimated toxicity rate is 19%, with the 95% exact confidence interval (CI) as 9% - 32%.

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 infection, Pneumocysitis jirovecii pneumonia, Grade 2 pneumonitis, Grade 4 rash, Grade 4 hyperglycemia, Grade 4 diarrhea, 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 6% if the underlying true toxicity rate is 10%, the probability of early stopping will be 65% if the underlying true toxicity rate is 20%, and the probability of early stopping will be 97% 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
37-43	9
44-50	10
51-53	11

9.3 Statistical Analyses Plan

For all the analyses, subjects who received any dose of alpelisib 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 alpelisib. We will use binomial distributions to estimate the response and the toxicity rates with their 95% exact CIs. For the secondary efficacy endpoint of response at the end of cycle 12, 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 the radiologic assessment, PROMIS Patient Reported Outcome measurement, 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 PROMs 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

Dose escalation for response optimization purpose is considered in this study.

Dose escalation is allowed:

Decision to escalate the dose for response optimization purpose will be done by the investigator based on local assessment of lesion response and overall clinical response. Escalation will be allowed, when:

- The subject does not meet criteria for lesion response based on local assessment and there are no safety/tolerability concerns which may preclude from treatment continuation at a higher dose level.
- The subject, in the opinion of the investigator, did not derive sufficient clinical benefit (based on overall clinical response assessed by the investigator) from previous treatment regardless of meeting criteria for lesion response and there are no safety/tolerability concerns which may preclude from treatment continuation at higher dose level.

Dose escalation is allowed at a minimum of 12-week intervals.

Subjects ages 6 years or older, dose escalations are possible from cycle 3 visit onwards as following:

- Subjects 18 years or older: from 125 mg to 200 mg, from 200 mg to 250 mg once daily p.o.
- Subjects aged 6-17: from 50 mg to from 125 mg, to 200 mg once daily p.o.

Table 10-1 Dose escalation for alpelisib ages 18+

Alpelisib dose level	Dose (18+)	Number of tablets & strength
Starting	125 mg/day	1 x 125 mg tablet
Dose level 1	200 mg/day	1 x 200mg tablet
Dose level 2	250 mg/day	1 x 200mg tablet + 1 x 50mg

Table 10-2 Dose escalation for alpelisib ages 6-17

Alpelisib dose level	Dose (Ages 6-17)	Number of tablets & strength
Starting dose	50 mg/day	1 x 50 mg tablet
Dose level 1	125 mg/day	1 x 125 mg tablet

Dose level 2	200 mg/day	1 x 200 mg tablet

10.1.2 Dose Reduction

Dose reduction and/or interruption is allowed in all age groups at any time for reasons of tolerability and safety.

Generally, when dose reduction is permitted as per toxicity management guidance, maximum 2 consequent dose reductions are possible. When the subject experiences safety concerns at starting dose level, only one dose reduction is permitted. Depending on the dose of alpelisib, the investigator should follow the general guidance for alpelisib dose reductions sequential steps as described in Table 10-4 and Table 10-5.

For subjects aged 2-5, if starting dose is not tolerated, dose reduction is not allowed. Subject will hold or completely stop the alpelisib in case of toxicities.

Investigators should exercise caution and consider dose interruption for safety reasons, especially in subjects who experience adverse events of grade 3 and higher, regardless of their apparent relatedness to study medication, and in subjects experiencing recurrent or prolonged adverse events. This is particularly important for pediatric subjects. A combined approach of drug interruption with subsequent re-initiation of study medication at a reduced dose may be pursued.

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.

The sections below provide specific guidance for management and study drug modification in the event of: QTcF prolongation, skin toxicity, hyperglycemia, pneumonitis, diarrhea and stomatitis/oral mucositis.

When minor or major surgical invasive procedure is planned, the investigator may make a decision to interrupt study medication based on clinical condition of the subject.

Dose reduction sequential steps are described in the Table 10-4 and Table 10-5; guidelines and criteria for dose reduction/interruption/re-initiation are provided in the following Sections (10.1.3.1-10.1.3.7).

Table 10-4 Dose reduction sequential steps for alpelisib in ages 18+

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
125 mg daily p.o	50 mg daily p.o	Not allowed
200 mg daily p.o	125 mg daily p.o	50 mg daily p.o
250 mg daily p.o	200 mg daily p.o	125 mg daily p.o

Table 10-5 Dose reduction sequential steps for alpelisib in ages 6-17

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
50 mg daily p.o	50 mg every other day p.o	Not allowed
125 mg daily p.o	50 mg daily p.o	50 mg every other day
200 mg daily p.o	125 mg daily p.o	50 mg daily p.o

10.2 Management of adverse effects

10.2.1 Dose adjustments for QTcF prolongation

The Fridericia QT correction formula (QTcF) should be used for clinical decisions. When QTcF > 500 ms or > 60 ms change from baseline (≥ Grade 3) is detected on at least two separate ECGs, the investigator should follow criteria for interruption and re-initiation of study treatment as per Table 10-6 below.

Table 10-6 Criteria for interruption and re-initiation of alpelisib treatment due to QTcF prolongation

If QTcF > 500 ms or > 60 ms change from baseline (≥ Grade 3) is identified:

- Assess the quality of the ECG recording and the QT value and repeat if needed
- If deemed necessary, consult with a cardiologist (or qualified specialist) to confirm ECG diagnosis

If QTcF prolongation is confirmed:

- Interrupt study treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
- Review concomitant medication use for other causes for QT prolongation (refer to crediblemeds.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check study drug dosing schedule and treatment compliance
- Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 ms or < 60 ms change from baseline

After resolution to ≤ 480 ms / 60 ms change from baseline, re-introduce treatment at a reduced dose (if possible), and increase ECG monitoring

If QTcF prolongation recurs (> 500 ms / 60 ms change from baseline, i.e., ≥ Grade 3) after treatment re-introduction, discontinue subject from study.

10.2.2 Guidelines for the treatment of alpelisib induced skin toxicity

Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. Dermatologist consult is mandated for serious cutaneous reactions (i.e., fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM). Dose modification guidelines are described in Table 10-7.

Table 10-7 Criteria for interruption and re-initiation of alpelisib treatment due to skin toxicity

Worst toxicity-CTCAE Grade (value)	**Dose Modifications for alpelisib**
Skin and subcutaneous tissue disorders	
Grade 1 (<10% body surface area (BSA) with active skin toxicity*)	**Maintain dose level** Initiate topical corticosteroids 3-4 times daily, preferred compounds to use are triamcinolone, betamethasone as long as skin toxicity is active, for a duration of maximum 28 days. For subjects with symptoms like burning and/or pruritus add a non-sedating anti-histamine; consider adding a sedating anti-histamine at night. If active rash is not resolved within 28 days of appropriate treatment, consider adding low dose systemic corticosteroid

Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level** Initiate topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone as long as skin toxicity is active, during max. 28 days Consider adding systemic corticosteroids in adult subjects. The optimal doses of systemic steroids in pediatric subjects should be defined individually after a consultation with a dermatologist according to the local label. If rash resolves to ≤ G1 within 10 days, the systemic corticosteroid may be discontinued. For subjects with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine; consider adding a sedating anti-histamine at night
Grade 3 (>30% BSA with active skin toxicity*)	**Omit alpelisib** dose until rash /skin toxicity is no longer active but fading (G1), skin biopsy may be considered if part of local practice • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days • Add systemic corticosteroids If rash resolves to ≤ G1 within 10 days, systemic corticosteroid may be discontinued For subjects with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine during day time; consider adding a sedating antihistamine at night Re-start alpelisib dose once rash/skin toxicity is no longer active but fading (G1): • at same dose in case of first occurrence, at reduced dose level in case of second

	occurrence • If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon rechallenge with alpelisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued. • For subjects with symptoms like burning, stinging and/or pruritus an antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue subject from alpelisib • Mandated to consult a dermatologist. Photographs and skin biopsy** may be considered if part of local practice. Treatment may follow guidelines for Grade 3 above with the exception of rechallenge. Additional measures may be taken as per local treatment guidance
Any Grade of Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis or other SJS/TEN-like severe skin reactions	• Permanently discontinue subject from alpelisib • Consult dermatologist, ensure documentation by imaging like photographs and consider skin biopsy** if part of local practice. • Follow local treatment guidelines for SJS/TEN
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy. ** Skin biopsy: skin biopsy can be performed as clinically indicated and assessed locally; no skin samples will be sent for central assessment	

10.2.3 Guidelines for the treatment of alpelisib induced hyperglycemia

Always consider consultation with a diabetologist, particularly for pediatric subjects, and recommend/reinforce lifestyle changes as per American Diabetes Association (ADA), i.e., exercise

and dietary advice (e.g., small frequent meals, low carb, high fiber, balancing carbs over the course of the day. Three small meals and two small snacks rather than one large meal).

The table below provides dose management recommendations. The preferred option for treating alpelisib-induced hyperglycemia, in subjects over 10 years old, is metformin, given its wide availability and well characterized safety profile. However, in case of intolerance, unavailability or unsuitability of metformin (e.g., in very young subjects), it is needed to consult a diabetologist to find the optimal individualized treatment for hyperglycemia, especially in pediatric subjects under 10 years old (where international or local guidelines may apply). Other insulin sensitizers such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors may be used for the treatment of alpelisib-induced hyperglycemia in adult subjects. Dose modification guidelines are described in Table 10-8.

Table 10-8 Criteria for interruption and re-initiation of alpelisib treatment due to hyperglycemia

Worst toxicity-CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For subjects with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this applies only for findings > 140 mg/dL (7.7 mmol/L)	**Maintain dose level** and remind subject on lifestyle changes. • If FPG < 140 mg/dl, consider adding metformin as per guidance below or in cooperation with diabetologist (for children<10 years old, a consultation with diabetologist to individualize treatment is required). • If FPG 140-160 mg/dl, start/intensify metformin as per guidance below or in cooperation with diabetologist (for children<10 years old, a consultation with diabetologist to individualize treatment is required). Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated,

	reduce to prior tolerated dose. Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until FPG is within baseline values.
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	**Maintain dose level** and remind subject of lifestyle changes, exclude confounding factors like e.g., urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. If FPG is still rising on maximum tolerated dose of metformin or persistently >160mg/dl (>8.9 mmol/L), add an insulin-sensitizer, e.g., pioglitazone 30 mg (max. dose). Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	Omit alpelisib and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g., urinary tract infection and consider consultation with a

	diabetologist. Administer intravenous hydration and intervention for electrolyte/ketoacidosis/ hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. • If FPG resolves to ≤ Grade1 within 3-5 days, while off program treatment and on metformin, re-start alpelisib and reduce by 1 dose level, continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl • If FPG does not resolve to Grade1 within 3-5 days while off program treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g., urinary tract infection, permanently discontinue subject from alpelisib treatment.
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	Omit alpelisib, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors (e.g., urinary tract infection). Should consult with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-

	check within 24 hours. • If grade improves then follow specific grade recommendations • If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue subject from alpelisib.
A diabetologist consultation should always be considered. In cases where there is rapidly increasing serum glucose suspicious of severe clinical presentation and/or diabetic ketoacidosis without obvious confounding factors, a diabetologist should be consulted with consideration of potential hospitalization and close monitoring.	

10.2.4 Guidelines for treatment of alpelisib induced pneumonitis

An early consultation with a pulmonologist is recommended at any suspicion of pneumonitis for an appropriate evaluation and management**.** Dose modification guidelines are described in Table 10-9.

Table 10-9 Management of pneumonitis related to alpelisib with or without other agents in combination

Pneumonitis	Recommended Investigations	Management of Pneumonitis	Program Treatment Modification
Any Grade	Obtain appropriate imaging (e.g., high resolution CT scan) Consider broncho-alveolar lavage (BAL) and biopsy, if clinically appropriate Infectious causes of interstitial lung disease should be ruled out	Follow institutional practice for management of pneumonitis (e.g., Treatment with high dose corticosteroids; concurrent antibiotic therapy if infectious causes are suspected). Consultation with a pulmonologist is highly recommended	Immediately interrupt alpelisib for any case of suspected pneumonitis. For all subjects with confirmed pneumonitis alpelisib should be permanently discontinued

10.2.5 Guidelines for the treatment of alpelisib induced diarrhea

Mild to moderate diarrhea has been reported in studies of single agent alpelisib. Severe diarrhea and its clinical consequences including dehydration and acute kidney injury, have been reported in subjects treated with alpelisib. Based on the severity of the diarrhea, alpelisib may require dose interruption, reduction, or discontinuation.

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, subject education as well as proper management of alpelisib-induced diarrhea is mandatory. For pediatric subjects, early detection and treatment of diarrhea is particularly important to avoid dehydration, and consultation with a gastroenterologist is recommended. The investigators and care givers should ensure appropriate hydration and nutrition of the subjects experiencing diarrhea; standards of local practice to be applied. In pediatric subjects the investigator may consider immediate dose interruption and initiation of anti-diarrhea treatment at occurrence of the first episode of diarrhea, and should ensure, that subjects and care givers are guided how to control diarrhea in timely manner. Dose modification guidelines are described in Table 10-10.

The following algorithm for treatment and management of diarrhea is based on Wadler et al 1998 [38], Kornblau et al 2000 [39].

Table 10-10 Criteria for interruption and re-initiation of alpelisib treatment due to diarrhea

Worst toxicity-CTCAE Grade	**Dose Modifications for alpelisib**
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at same dose
≥ Grade 3	Omit dose until resolved to ≤ Grade 1, then reduce 1 dose level

Subject history of diarrhea

- At baseline, the subject's history of diarrhea should be reviewed and the subject (and caregiver) should be appropriately informed of potential alpelisib-induced diarrhea and its management
- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions
- Stop all diarrheogenic agents, otherwise exclude from program
- Instruct subjects regarding risk of developing diarrhea
- Perform baseline clinical/laboratory studies (e.g., one could rule out carrier state of *Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium* which can lead to opportunistic infections in immunosuppressed subjects)
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 10-10).

First report of diarrhea:

- Obtain history of onset and duration of diarrhea

- Description of number of stools and stool composition (e.g., watery, blood, mucus in stool)
- Assess subject for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)
- Proactively look for occurrence of diarrhea. If no problems occur, instruct the subject and care-giver to call when a problem does arise

Management of diarrhea

General Recommendation

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g., Metamucil®) and stool softeners (e.g., docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g., bananas, rice, apple sauce, toast)

It is recommended that subjects are treated with loperamide (refer to the local label). Subjects and caregivers should be instructed on the use of loperamide in order to manage signs or symptoms of diarrhea at home. Subjects should be instructed to start oral loperamide at the first sign of loose stool or symptoms of abdominal pain (initial administration for adults: 4 mg, then 2 mg every 4 hrs to a maximum of 16 mg/day; for children below 12 years, depending on age: 1-2 mg up to 4 times a day). These instructions should be provided at each visit and the treating physician should ensure that the subject understands the instruction. At each visit, subjects should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the treating physician should question the subject regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea.

Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide, however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the subject's response to treatment should be observed and appropriately documented.

Treatment of diarrhea CTCAE Grade 1 or 2

Diarrhea CTCAE Grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hrs. (maximum of 16 mg/day) or after each unformed stool). Dosage and dosage schedule for pediatric subjects should be individualized according to the local loperamide label.

12-24 hours later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hours diarrhea-free interval

Diarrhea unresolved

- Persisting diarrhea CTCAE Grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of subjects condition to rule out dehydration, sepsis, ileus, medical check and selected workup if subject does not need hospitalization (see section Diarrhea workup below). Observe subject for response to antidiarrheal treatment.
- Persisting diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of subjects condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe subject for response.

After 12-24 hours:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs. diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (CTCAE Grades 1 and 2), after 48hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.
- If diarrhea still persisting and progressed to CTCAE Grades 3 and 4, employ measures described below.

Treatment of diarrhea CTCAE Grade 3 or 4

Severe diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of subjects condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup below).

Observe subject for response.

After 12-24 hours:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 jig tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE Grade 3 or 4 still persists subjects should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE Grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 jig TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolves.

Diarrhea workup

Perform appropriate tests.[27]

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed subjects), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures:

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis

- Sigmoidoscopy - reassessment of colitis

Table 10-11 NCI CTCAE version 5.0 grading of diarrhea for subjects without Colostomy

Toxicity				
Diarrhea	Increase of < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care Activity of Daily Living (ADL)	Life-threatening consequences; urgent intervention indicated
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements.				

10.2.6 Guidelines for the treatment of alpelisib induced stomatitis/oral mucositis

For pediatric subjects, early consultation with a dentist is recommended on suspicion of alpelisib-induced stomatitis for appropriate evaluation and management. Dose modification guidelines are described in Table 10-12.

Table 10-12 Criteria for interruption and re-initiation of alpelisib treatment due to stomatitis

Worst toxicity- CTCAE Grade (value)	Dose Modifications for alpelisib
Grade 1/Tolerable Grade 2	Maintain dose level Non-alcoholic or salt water mouth wash
Intolerable Grade 2 or Grade 3	First occurrence: hold until ≤ Grade 1 and reduce 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ Grade 1 and reduce 1 dose level.
Grade 4	Permanently discontinue subject from alpelisib

10.2.7 Guideline for treatment of alpelisib induced pancreatitis

If acute pancreatitis is diagnosed, initiate appropriate treatment and follow dose modification guidelines described in the Table 10-13.

Table 10-13 Criteria for interruption and re-initiation of alpelisib treatment due to pancreatitis.

Worst toxicity-CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 2 (enzymatic elevation or radiologic findings only)	Maintain dose level. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3	Omit dose until resolved to Grade ≤ 1, then resume treatment at decrease 1 dose level. Only 1 dose reduction is allowed. If toxicity recurs, permanently discontinue subject from alpelisib
Grade 4	Permanently discontinue subject from alpelisib

10.2.8 Investigations: alpelisib dose modifications

Recommendations for dose reduction or dose interruption of alpelisib in the management of changes in the investigations when they are considered adverse events are summarized in the Table 10-14 and Table 10-15.

Clinical judgment of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each subject based on individual benefit/risk assessment.

- Dose reduction will be allowed after which treatment must be discontinued as indicated in Table 10-14 and Table 10-15.

After treatment is resumed at a lower dose:

- If the same toxicity reoccurs with the same severity, treatment must be discontinued.
- Once the AE has resolved and alpelisib dose has been reduced, the investigator may consider a dose re-escalation only if it may be needed to provide optimal clinical benefit (based on overall response assessment) and if there are no safety/tolerability concerns which may preclude from treatment continuation at higher dose level.

Table 10-14 Criteria for interruption and re-initiation of alpelisib treatment: Investigations (hematologic)

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	• Maintain dose level. • Maintain dose level and monitor as clinically indicated.
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	• Omit dose until resolved to ≤ Grade 1, then resume at the next
Grade 4 (ANC < 0.5 x 10^9/L)	• Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level.
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	• Omit dose until resolved, then decrease 1 dose level. Discontinue from study in the event of recurrence
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	• Maintain dose level. • Maintain dose level and monitor as clinically indicated.
Grade 3 (PLT < 50-25 x 10^9/L)	• Omit dose until resolved to ≤ Grade 1, then resume at the next
Grade 4 (PLT < 25 x 10^9/L)	• Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level.

Table 10-15 Criteria for interruption and re-initiation of alpelisib treatment: Investigations (other)

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level.
2 – 3 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose leve If resolved in > 7 days, then decrease 1 dose level.
Grade 3 (> 3.0 – 6.0 x ULN)	• Permanently discontinue subject from study
Grade 4 (> 6.0 x ULN)	• Permanently discontinue subject from study
Investigations (Hepatic)	
Isolated total Bilirubin elevation (for subjects with Gilbert Syndrome these dose modifications apply to changes in direct	
Grade 1 (>ULN - 1.5 x ULN)	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.
Grade 3 (>3.0 - 10.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (>10.0 x ULN)	• Permanently discontinue.
Isolated AST or ALT elevation	
Grade 1 (>ULN - 3.0 x ULN) Grade 2 (>3.0 - 5.0 x ULN)	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (>5.0 - 20.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (>20.0 x ULN)	• Permanently discontinue.
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	• Maintain dose level.
Grade 2 (> 1.5 - 2.0 x ULN)	• Maintain dose level.

Grade ≥ 3 (> 2.0 x ULN)	• Omit dose until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level. • If resolved in > 14 days, then decrease 1 dose level. Note: • In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase)
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	• Maintain dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.
Grade 4	Permanently discontinue subject from alpelisib.

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 (alpelisib).

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/LARor 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 baseline, 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.

Alpelisib 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 at each study site by 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

TIE2/PIK3CA pathway Driven Vascular Anomalies are serious conditions with limited approval for pharmacological treatment targeting the underlying cause of the disease. Current therapy includes debulking surgery, amputation, and/or endovascular occlusive procedures which mainly addresses symptoms and complications of the disease. There is a high unmet medical need for an effective systemic treatment.

The main risks of this study are from alpelisib administration. The safety profile of alpelisib observed in EPIK-P1 was consistent with the mechanism of action of alpelisib and compares favorably with prior experience in clinical studies and post marketing exposure in the oncology setting. The most common AEs are Diarrhea (reported in 15.8% of all patients), hyperglycemia (12.3%) and aphthous ulcer (10.5%). All events were of grade 1/2 in severity and were effectively managed with appropriate treatment. No AEs led to treatment discontinuation and no deaths were reported during the study[40].

11.6 Potential Benefits of Trial Participation

Alpelisib is considered to be a promising treatment option for pediatric and adult subjects with a confirmed TIE2/PIK3CA variant. Treatment with alpelisib related to variant(s) in TIE2/PIK3CA gene may provide a clinical benefit compared to available treatment options. The participants enrolled in this study will receive alpelisib as active treatment for their disease. Based on published clinical data (Venot et al 2018)[16] and recent results from EPIK-P1[40] study, treatment with alpelisib 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 alpelisib 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.

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: PROMIS

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 III: 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 (cf) 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

APPENDIX IV: 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 **Oral prep:** N/A **Medications:** none	**Sedation/Anesthesia:** Second PIV for contrast	Protocols from Boston Children's and Sick KIds
Chest Vascular Malformation	1. Coronal T1 FSE 2. Coronal STIR 3. Axial T2 FS BLADE 4. Axial T1 FS volume-interpolated GRE ***Dynamic Contrast***	3 m 5 m 4 m 30 s	**From/To:** Include the entire lesion (might extend into neck and/or abdomen) **Contrast:**	Temp resolution for TWIST if inside the thoracic cage (outside can be	**Study time:** 1 hour **Position:** Always supine	**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

	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 30 s 3 m (19') 3 m 5 m (27')	Standard (gadavist)	higher ~3.5)	**Breath holds:** None **Music/video:** Always possible (According to magnet) **IV site/size:** no preference **Power injection**: Always **NPO:** N/A **Oral prep:** N/A **Medications:** none		follow-up. Radiographics. 2011;31(5):1321-1341

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:** No preference **Power injection:** Mandatory **NPO:** N/A **Oral prep:** N/A **Medications:** none	**Sedation/Anesthesia:** Second PIV for contrast	Protocols from Boston Children's and Sick KIds
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**		**Chest & abd** **TWIST with 1-1.5 mm slices, every 8-12 s for 30 phases** **IRFLASH with**				European Radiology (2019) 29:5190–5196

	mmol/kg diluted to allow appropriate volume		**respiratory navigation**				
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 V: MEDICATIONS TO BE USED WITH CAUTION

List of CYP450 substrates to be used with caution	
Category	**Drug names**
CYP2C9 substrates	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin and other coumarin-derivative anticoagulants
Sensitive substrates of CYP2C9	Benzbromarone, Celecoxib, Glimepiride, Glipizide, (R)/(S)-Ibuprofen, Lornoxicam, Meloxicam, Piroxicam, Tolbutamine, (S)-Warfarin
CYP2B6 substrates	
Narrow Therapeutic index substrates of CYP2B6	Meperidine
Sensitive substrates of CYP2B6	Bupropion, Efavirenz
Selected CYP3A4 substrates	
Narrow Therapeutic index substrates of CYP3A	Alfentanil, Diergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine
Sensitive substrates of CYP3A	Alfentanil, Atazanavir, Atorvastatin, Darunavir, Lumefantrine, Midazolam, Simvastatin, Triazolam
CYP3A4 substrates which are known or potential auto-perpetrators	Clarithromycin, Conivaptan, Encorafenib, Erythromycin, Diltiazem, Mifepriston, Ribociclib, Telthromycin, Troleandomycin, Verapamil

* *Substrates with narrow therapeutic index (NTI):* Drugs whose exposure-response indicates that increase in their exposure levels by the concomitant use of potent inhibitors may lead to serious concerns (e.g. Torsades de Pointes, QT prolongation).

** *Sensitive substrates:* Drug that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

CYP3A4 substrates which are auto-perpetrators: Based on Novartis internal assessment.

APPENDIX VI: PROHIBITED MEDICATION

List of prohibited medication	
Category	Drug Name
Strong CYP3A Inducers	Apalutamide, Avasimibe[1], Carbamazepine, Enzalutamide, Ivosidenib, Lumacaftor, Mitotane, Phenobarbital, Phenytoin, Rifabutin, Rifapentine, Rifampin (Rifampicin), St. John's wort (hypericum perforatum)[1]
BCRP inhibitors - Evidence for DDI potential shown in vivo	Protease Inhibitors (e.g., Atazanavir/ritonavir[1,2], , Lopinavir/ritonavir[1,2], Tipranavir/ritonavir[1,2], Tipranavir[2] , Paritaprevir[2]), Elvitegravir/cobicistat[1,2], Curcumin[1,2], Cyclosporine[1,2], Daclatasvir[1,2], Ledipasvir[2], Eltrombopag[1,2], Gefitinib[2], Lapatinib[1], Pantoprazole[1,2]
[1] Herbal product	
[1] Lee et al 2015 [2] Novartis PK Sciences DDI List (January, 2018)	

APPENDIX VII: MEDICATION DIARY

Alpelisib in the Treatment of _____

Cycle _____

_____ _____

Patient Name DOB

Drug	Dosage	Route	Day
Alpelisib			

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 VIII: ROAD MAP

Alpelisib in the Treatment of _____

Cycle _____		
	Patient Name	DOB

Dosing guidelines: Subjects 18 years and older: 125 mg daily (up to 250 mg daily), subjects 6-17 years of age: 50 mg daily (up to 200 mg daily), Subjects 2-5 years of age: 50 mg daily		
Drug	**Dosage**	**Route**
Alpelisib		

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 IX: 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