2.2.2 To determine the safety of oral sirolimus and IV vincristine in patients with high risk KHE. Toxicities will be assessed and recorded at specific intervals throughout therapy. Common Terminology Criteria for Adverse Events (CTCAE, version 4.0.3) will be used to categorize and grade all toxicities. Safety monitoring and stopping rules will be instituted to ensure that serious treatment-related toxicities are reported and study continuation re-evaluated.

2.3 Secondary Aims:

2.3.1 To determine the efficacy of these agents in the maintenance phase in patients with high risk KHE. Maintenance phase will last for 1 year and treatment change may occur for any patient that loses their response. (See research plan for details). Formal disease response will be assessed at end of maintenance courses 6 and 12 using radiographic, clinical and quality of life measures.

2.3.2 To determine the safety of these agents in the maintenance phase in patients with high risk KHE. Toxicities will be assessed and recorded at specific intervals throughout therapy. Common Terminology Criteria for Adverse Events (CTCAE, version 4.0.3) will be used to categorize and grade all toxicities with same monitoring.

2.3.3 To assess biomarker/genomic analysis on serum and tissue in children and adults with high risk KHE. Biomarkers in serum will be tested at baseline, end of induction, end of maintenance courses 6 and 12. Tissue availability will be more limited and will only be available at one time point.

3 BACKGROUND AND RATIONALE

3.1 Background and Significance:

Patients with Vascular Anomalies (VA) have a spectrum of diseases that can be broadly classified into vascular tumors and malformations (1, 2, 49) (Figure 1). Vascular tumors grow and spread through a proliferative process while vascular malformations enlarge through expansion of a developmental anomaly, with little cellular proliferative activity. Growth and/or expansion of VA cause clinical problems such as disfigurement, chronic pain, coagulopathies and bleeding, organ dysfunction and occasionally death. Individuals with VA often experience progressive clinical symptoms with worsening quality of life. Although limited treatment options are available, their efficacy has not been validated in prospective clinical trials and is usually based on case reports. Thus there are no validated standards of care for these patients (3).

Figure 1: Classification of Vascular Anomalies

ISSVA classification for vascular anomalies ©
(Approved at the 20th ISSVA Workshop, Melbourne, April 2014)

Overview table

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined °**	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

° **defined as two or more vascular malformations found in one lesion**
* **high-flow lesions**

Kaposiform hemangioendotheliomas (KHE) and tufted angiomas (TA) are rare tumors of vascular origin**.** There are no national registries documenting numbers of KHE patients but from extrapolating data at the 2 largest vascular anomaly centers in the U.S., the prevalence appears to be 0.91/100,000 children with an estimated total number of diagnosed cases in the US of 760 in 2011. These tumors pose difficult dilemmas for the practitioner particularly in regards to there being limited treatment options and a lack of validated biological markers. For example, KHE and TA can cause a coagulopathy known as Kasabach-Merritt Phenomenon (KMP) which has a mortality rate of 20 – 30% (4-7). A number of therapies have been reported via case reports but none have been uniformly effective. Steroids are often used as a first line therapy with varying results. (8, 9) Interferon has been used but has significant neurological side effects (10-12). Antifibrinolytic agents (e-aminocaproic acid or tranexamic acid) have been used with mixed responses, as have antiplatelet agents such as aspirin, or dipyridamole (13). Chemotherapy with agents such as cyclophosphamide, vincristine, and actinomycin has been used with variable responses as well (14-15). Other medical options that have been used include radiation therapy, compression therapy, and embolization therapy. We initially reported a case of refractory KHE with KMP whose hematologic parameters responded to sirolimus (16). Since that time, other cases have been reported that have improved outcome, at least in the short term (17).

We initially reported the use of sirolimus in the treatment of a 9 month old with refractory KHE with KMP on palliative treatment that had a hematologic recovery in 3 weeks to sirolimus and significant improvement in her clinical symptoms and quality of life (17). She began treatment in July 2007and has not suffered any long term effects. Since that time, other cases have been reported with excellent short term efficacy (18). Presently, 13 KHE patients are enrolled on SIR-DA-0901 (FDA Grant#

6.3 Randomization

The initial treatment assignment will be made using a response adaptive randomization algorithm: patients will be randomized in a 1:1 ratio (with equal probability) for the first 10 and in a skewed ratio for the rest to favor the better performing treatment arm by adjusting the treatment allocation ratio based on response data observed on previously accrued patients. The response data observed on previously enrolled patients will be available in a real time and continuously analyzed by the study statistician for treatment assignment of each newly enrolled patient. Clinical trial designs using such adaptive randomization algorithm are known to increase patient benefits over the course of trials without undermining the scientific rigor (39). We specifically will use the doubly adaptive biased coin design with a target allocation given by an urn model (40, 41).

Because of the time it takes to measure treatment response, we will modify the dynamic randomization in the following manner. Rather than using all previously enrolled patients response information to randomize the next patient, we will only base new randomization on the information from those previous patients who have had treatment response information available at the time of next randomization. Specifically, the probability of assigning a new patient to Sirolimus group is $\frac{1}{1+\frac{N_{m,A}}{N_{m,B}}\left(\frac{1-\hat{p}_{m,A}}{1-\hat{p}_{m,B}}\right)^2}$, where $N_{m,A}$ and $N_{m,B}$ are the number of numbers of patients who have been enrolled in Sirolimus and Vincristine respectively. $\hat{p}_{m,A}$ and $\hat{p}_{m,B}$ are respectively Sirolimus and Vincristine group observed response rates up to that time point.

6.4 INDUCTION

Arm 1: Vincristine + Steroid Taper
Arm 2: Sirolimus + Steroid Taper

6.4.1 **Steroid Taper –** Steroids may be started prior to study enrollment. All participants will continue to receive steroids during the Induction period. The steroid (prednisolone or equivalent) taper will begin following enrollment during 2 courses of the induction period along with either vincristine or sirolimus.

Steroid Taper Schedule

Table 2

Steroid Dose	Duration
2mg/kg/day divided BID	2 weeks
1.5 mg/kg/day divided BID	2 weeks
1.0 mg/kg/day divided BID	2 weeks
0.5 mg/kg/day QD	1 week
0.5 mg/kg/day QOD	Every other Day – 1 week

	Trough levels	
Loading Dose	Anytime between Day 10-14*	Continue Weekly trough level monitoring until 2 consecutive trough levels are stable**.
Stable levels**	Each course ***	• If trough levels within target range – continue same sirolimus dose • If trough levels are outside of target range after consultation with study Pharmacologist – Dose Adjustment
Dose adjustment	7-14 days following dose adjustment	Continue Weekly monitoring until trough levels are stable**.
Toxicity	At time of toxicity	See section 8.1

* Children up to age 2 will have loading dose trough sirolimus levels drawn beginning at Week 1 (Days 6-9) or, at the discretion of the investigator. Trough levels may be drawn at 2 time points (12 hours apart) during Week 1 to determine an individualized PK (count business days only).

** Stable Level is defined as 2 consecutive trough levels that are within target range. After the pharmacologist verifies the trough is within target range, the pharmacologist recommendation for the second level should be received within 7 business days.

*** Trough levels are to be drawn at the beginning of each course (defined as first 5 days) if stable during the prior course (does not have to be repeated if trough level recommendation was obtained within 7 business days prior to start of next course).

If unable to achieve a target trough sirolimus levels within 4 weeks, patients may be asked to have a mini-PK collection of 2 blood draws, in addition to a trough level, in order to better estimate the participant's recommended dose. The mini-PK collection will be at: 1 hour and 3 hours after a sirolimus dose.

6.7 Hematologic Response Assessment –Induction (all participants)

During the induction phase, time to hematological recovery will be measured to assess response. Hematologic response will be defined as a platelet count >100,000/µl or an increase in platelet count of 2 times the baseline (whichever is greater) and fibrinogen of > 150mg/dl. Hematologic response must be documented within 7 days prior to completion of induction course 2 or earlier if failure is suspected. Platelet count and fibrinogen levels must meet these parameters on 2 consecutive lab measurements with a minimum of 1 day between evaluations. Baseline is initial laboratory evaluation without transfusions; lab results performed outside of enrolling site may qualify as baseline as long as supporting documentation is provided. Study treatment will be continued during the period of hematologic response assessment. Hematologic response can NOT be assessed within 24 hours of a platelet or cryoprecipitate infusion (Section 7.1).

moved by two days per course.

6.10.3 **Pharmacokinetically Guided Dosing** – The target sirolimus trough level is 10-15ng/ml. Sirolimus dosing will be individually guided using real-time drug concentrations measurements in combination with a Bayesian population model-based target optimization approach (43)

The dosing of sirolimus will be guided by pre-dose concentration measurements (trough). Each participant will have sirolimus serum levels measured according to the timeline listed below. Analysis for sirolimus level will occur at each participating site, or at a local laboratory using a validated assay approved by the study Pharmacologist. Regardless of collection and analysis site, the study Pharmacologist or designee will perform all modeling and make recommendations for dose adjustment. Trough levels will be taken as listed below:

Table 5

Sirolimus	**Frequency of Trough levels**	**Action**
Loading Dose	Anytime between Day 10-14*	Continue Weekly trough level monitoring until 2 consecutive trough levels are stable**.
Stable levels**	Each course ***	• If trough levels within target range – continue same sirolimus dose • If trough levels are outside of target range after consultation with study Pharmacologist – Dose Adjustment
Dose adjustment	7-14 days following dose adjustment	Continue Weekly monitoring until trough levels are stable**.
Toxicity	At time of toxicity	See section 8.1

* Children up to age 2 will have loading dose trough sirolimus levels drawn beginning at Week 1 (Days 6-9) or, at the discretion of the investigator. Trough levels may be drawn at 2 time points (12 hours apart) during Week 1 to determine an individualized PK.

** Stable Level is defined as 2 consecutive trough levels that are within target range. After the pharmacologist verifies the trough is within target range, the pharmacologist recommendation for the second level should be received within 7 business days.

*** Trough levels are to be drawn at the beginning of each course if stable during the prior course (does not have to be repeated if trough level recommendation was obtained within 7 days prior to start of next course).

If unable to achieve a target trough sirolimus levels within 4 weeks, patients may be

asked to have a mini-PK collection of 2 blood draws, in addition to a trough level, in order to better estimate the participant's recommended dose. The mini-PK collection will be at: 1 hour and 3 hours after a sirolimus dose.

6.11 Response Assessment – Maintenance (All Participants)

The optimal measure of disease response in patients with complex vascular anomalies has not been established. Current practice includes changes in physical exam, radiologic 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, as determined radiologically and clinical changes or quality of life measures. For these reasons we have elected to assess **formal disease response** using three distinct methods:

1. Radiologic evaluation
2. Clinical measures of disease (cytopenias, coagulopathies, other clinically relevant radiologic evaluation beyond the lesion of interest such as chest X-rays), and/or parameters for grading functional impairment – (Functional Assessment - Appendix V)
3. Quality of life measures

Formal Responses will be assessed three times during the study: prior to initiation of study treatment (baseline), and at the end of courses 6 and 12 following the start of Maintenance. Disease assessments may be performed at any time during maintenance if clinically indicated. Participants with disease worsening as defined as "progressive disease" or "loss of response" based upon any one of the above methods will be permitted to change treatment. If worsened disease is based on laboratory parameters we suggest a repeat of laboratory evaluations to confirm. Refer to Section 11 for definitions of responses.

6.12 Treatment Change (During Maintenance)

Treatment change is permitted one time during the study. If participant has changed treatment at the start of maintenance and has 'progressive disease' or 'loss of response', off treatment criteria will have been met. If treatment change occurs during maintenance, treatment on the new arm will begin within 7 days of documentation of disease worsening. Functional Assessment and Quality of Life measures are to be repeated at the time of treatment change unless performed within the last 7 days.

6.13 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for up to 14 courses (inclusive of Induction and Maintenance) or until one of the following criteria applies:

- Intolerable toxicity (leading to treatment interruption for more than 4 weeks)
- Refusal of further protocol therapy by patient and/or parent/guardian

be removed from protocol therapy. The listing of medications in Appendix II lists medications to avoid/ use caution with when taking sirolimus.

Enzyme inducing anticonvulsants: Patients may not be taking enzyme–inducing anticonvulsants, and may not have received these medications within 1 week of entry, as these patients may experience different drug disposition. These medications are listed in Appendix II.

7.3.3 Vaccinations- Patients receiving immunosuppressants, including sirolimus and vincristine, should not be administered live vaccines. All other vaccines are permitted and highly suggested.

8 DOSE MODIFICATIONS/DOSE DELAYS

Patients entered on the trial will be carefully monitored for the development of sirolimus-related toxicities and vincristine-related toxicities. This study will utilize the CTCAE of the National Cancer Institute for reporting of AEs. A copy of the current version of the CTCAE version 4.03 can be downloaded from CTEP: http://ctep.cancer.gov/reporting/ctc.html

8.1 Sirolimus Arm

Any patient experiencing a Grade 3 or 4 toxicity that is possibly, probably, or definitely related to sirolimus should have the drug held and a sirolimus trough level obtained as soon as possible. Other toxicities requiring dose adjustments will be defined based on categorization of toxicity and sirolimus trough levels.

8.1.1 Hematological Toxicity - If a patient experiences ≥Grade 3 neutropenia (ANC <750), anemia (Hgb <8), the sirolimus will be withheld. Patients should continue to be seen and have complete blood counts measured, in addition trough sirolimus levels will be obtained every week until recovery (≤Grade 1) is documented. See section 8.1.3 Table 6 for details on sirolimus trough target adjustments.

8.1.2 Non-Hematological Toxicity - During All Courses for toxicities attributable (possibly, probably, definitely) to sirolimus:

If a patient experiences a non-hematological toxicity as defined below, sirolimus will be withheld. Patients should continue to be seen and have appropriate labs/observations, in addition to trough sirolimus levels, obtained at least weekly until recovery (≤Grade 1) is documented. See section 8.1.3 Table 6 for details on sirolimus target adjustments.

Sirolimus-related (possibly, probably, or definitely) toxicities Requiring Dose Adjustments/Interruptions or other interventions

- Grade 3 or Grade 4 non-hematological toxicity **(*)**

- Grade ≥2 serum creatinine elevation
- Grade ≥2 allergic reaction
- Grade ≥2 hypertension
- Grade ≥1 non-hematologic toxicities related to sirolimus that are intolerable to the patient
- Any ≥ Grade 2 non-hematological toxicity that persists for ≥7 days without resolution (return to less than Grade 2 or baseline) and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption and/or dose reduction (see Table 6).

(*) The only non-hematological toxicities that are *excluded* from requiring dose adjustments/interruptions or other interventions are the following:

- Grade 3 nausea and vomiting of less than 3 days duration
- Grade 3 transaminase elevations that return to levels that meet initial eligibility criteria within 7 days of study drug interruption and that do not recur upon study re-challenge with study drug
- Grade 3 GGT elevation
- Grade 3 lymphopenia

8.1.3 Dose Modification Algorithm for Toxicity - All recommendations for dose modifications will be made by the coordinating center after analysis of blood samples for sirolimus levels at local laboratory. New doses will be communicated to the treating institution by the CCHMC Pharmacologist or designee. The table below will be used to modify sirolimus dose for patients who develop toxicity.

All toxicities should recover to baseline or < Grade 2 prior to resuming sirolimus dosing.

Table 6

Sirolimus Trough Levels at time of Toxicity	**Dose Adjustment**	
	Toxicities attributable to sirolimus (possibly, probably, or related)	***Other explanation for toxicity (i.e., viral infection)***
>15ng/mL (target trough 10-15ng/mL)*	Resume at modified dose for target trough goal of 10-15ng/mL	Resume therapy at same dose (targeted trough level of 10-15ng/mL)
Between 10-15ng/mL	25% sirolimus dose reduction – resume at target trough goal of 7-10ng/mL	Resume therapy at same dose (targeted trough level 10-15ng/mL).
>10ng/mL (target trough 7-10ng/mL)*	Resume at modified dose for target trough goal of 7-10 ng/mL	Resume at same dose (targeted trough level 7-10ng/mL)
Between 7-10ng/mL	50% sirolimus dose reduction –	Resume at same dose (targeted

        - Arm 2 (Sirolimus) - Electrolytes including BUN, creatinine, **fasting glucose**, blood chemistry including albumin, total protein, alkaline phosphatase, uric acid, phosphorous and **fasting serum** lipid profile (triglycerides, total cholesterol, HDL and LDL), SGOT, SGPT, and bilirubin (total and direct).
    - Any laboratory assessments may be performed more frequently if clinically indicated.
- Disease Assessments – Baseline, at the end of maintenance courses 6 and 12.
    - Hematologic response – Occurs within 7 days of completion of Induction course 2. This may occur sooner if hematologic failure is suspected to assess response including platelet count and fibrinogen levels. See Section 6.7 and 7.1 regarding platelet transfusions and cryoprecipitate infusions.
    - Imaging analysis at time of treatment change
    - Assessment of functional impairment (Appendix IV) – to be repeated at time of treatment change
    - Health-related quality of life and pain assessments – to be repeated at time of treatment change
    - Disease assessments may be repeated any time if clinically indicated.

9.4 Off treatment (completion of study drug assessments)

Assessments as described in Section 9.1 and 9.2 are to be performed at time of study drug discontinuation for any reason.

9.5 Follow up Assessments

All patients who complete the study or have a response (defined as stable disease or better), regardless of treatment arm, will continue to be followed for growth and complications of the vascular tumor and protocol therapy related toxicities for a total of 5 years from the date of study enrollment. Following completion of study therapy, patients will be followed at a minimum interval of every 6 months. Follow up visits may occur at participants home institutions or they may return to the study site at a minimum of every 6 months for their routine follow up care. Participants should return to the study site on an annual basis for a follow up visit. See section 6.14 for further information for follow-up criteria.

9.6 Correlative Studies (Biomarkers) - Optional Serum, plasma and Tissue (archival) collection

Correlative molecular biology studies will be conducted as part of the current trial. All patients should be approached for consent to all of these biology studies. Patients may participate in the treatment portion of this trial without consenting to the biology studies. Following completion of biomarker analysis at CCHMC, any remaining samples will be stored in the vascular tissue repository at CCHMC with participant consent.

Biomarker analysis

Biomarker analysis will be conducted on blood samples (serum and plasma) and tissue (when available) at baseline (blood and tissue), at the end of induction course 2, and at the end of maintenance courses 6 and 12 (following initiation of induction and maintenance). The change in levels of these vascular markers will be analyzed in LeCras' laboratory at CCHMC using ELISA. Analysis will include VEGF-A, -C, -D, Pleiotrophin, IGF-1, Endothelin-1, Thrombospondin and Angiopoietin-1, and-2 and future biomarkers of interest in this class of patients. Control serum and plasma from age and sex matched non-malformation patients may be obtained from left-over clinical samples or tissue repository. Tissue analysis (expression of the vascular markers) will include phosphorylated Akt, phosphorylated ERK-1/2, and mTOR and phosphor-S6 kinase, as well as biomarkers VEGF-A, -C, -D, Pleiotrophin, IGF-1, Endothelin-1, Thrombospondin and Angiopoietin-1, and-2 and future biomarkers of interest in this class of patients. There is limited information on biomarker analysis in this population of patients.

9.6.1 Sample Collection

Tissue:

Archival tissue may be submitted to satisfy this correlative study. In the event tissue is available at another institution, the enrolling site should work with the institution to obtain the tissue samples, either snap-frozen or in paraffin block, or as prepared slides (10 unstained sections, if available. Sites should contact the coordinating center if fewer sections are available for submission). In the event no archival tissue is available and the patient has a cutaneous lesion, if consent is indicated on the study consent form, a 6 mm punch biopsy may be obtained to satisfy this correlative study.

Processing: For patients undergoing punch biopsy, the coordinating center should be contacted prior to the procedure to obtain further processing instructions.

Labeling: All tissue samples should be labeled with the subject's study ID number, initials, and the date of collection.

Shipping: See shipping instructions on the tissue specimen transmittal form.

9.6.2 Blood Biomarkers analysis:

Time point: Baseline, at end of induction and end of maintenance courses 6 and 12.

Sample collection: 1-6 ml of blood will be collected in a serum and plasma separator tubes

Processing:

- Specimens collected at CCHMC need to be received at LeCras' laboratory within 45 minutes of being drawn.
- Serum collection and processing: Collect 1-6 ml blood in serum separator tube (red top). Centrifuge at 1800xG for 15 minutes. Transfer serum to a 2-5 ml polypropylene cryogenic vial. Freeze and store at -80℃ until shipped.
- Plasma collection and processing: Collect 1-6 ml blood in a plasma separator tube (sodium citrate tube). Centrifuge at 1800xG for 15 minutes. Transfer plasma to a new tube and

The optimal measure of disease response in patients with complex vascular anomalies has not been established. Current practice includes changes in physical exam, radiologic 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 radiologically and clinical changes or quality of life measures. For these reasons we have elected to assess disease response using three distinct methods:

11.1.1 Response by Imaging:

For each imaging assessment time point (at baseline and end of maintenance courses 6 and 12), initial radiologic response will be reviewed by each site's radiologist. If the radiologist identifies an area of possible disease progression while evaluating the imaging, the imaging will be reviewed by the identified site study radiologist prior to dispensing drug.

MRI should be used as the radiologic study of choice. MRI will be performed using a 1.5 or 3.0 Tesla system with standard MRI protocols (Appendix III) to assess vascular anomaly response. In rare cases where the patient may have a contraindication to MRI, contrast-enhanced CT should be performed. 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 the target lesion at baseline and during follow up. To improve reliability and consistency of response assessments all imaging will be centrally reviewed at BCH. Screening scan will be sent to BCH immediately for review to confirm eligibility. All scans will be sent by disc at the end of maintenance for assessment. If there is any question about radiologic disease response at any time during maintenance, the scans will be reviewed by the site radiologist and BCH study radiologist.

11.1.2 Quality of Life Assessments (QOL):

This study will evaluate the effects of disease and treatment with sirolimus on the health related quality of life (HRQOL) in children and young adults. QOL measurements in this population are complicated by the range of age of affected individuals (infants to young adults) and the lack of validated QOL scales for patients with vascular anomalies. However, there exist generic scales used to quantitate QOL in pediatric and adult patients with good reliability and validity for a variety of chronic diseases.

The Pediatric Quality of Life Inventory (PedsQL 4.0) will be used to assess the QOL of children from 3 to 18 years of age. (46) The infant PedsQL is a tool to assess QOL in patients under the age of 2 years. The PedsQL is a brief standardized multidimensional pediatric QOL scales consisting of both child self-report and parent proxy-report measures and includes

generic and disease specific modules. It consists of a 23-item core measure of global QOL that has four subscales: physical functioning, emotional functioning, social functioning, and school functioning. Based on the standard error of the mean, Varni has also defined minimum changes in total score as clinically meaningful (4.4 change in the child self-report and 4.5 change in the parent proxy report). Changes in total scores with maintenance therapy will be used to quantitate the effects of this drug on health related quality of life in the pediatric population. A brief description of the QOL scales being used in this protocol is attached in Appendix V.

The Functional Assessment of Chronic Illness Therapy (FACIT) system will be used to assess health-related QOL (47) in adult patients (19-31 years of age). Specifically, this study will utilize a 27-item generic core (FACT-G) that includes 4 core subscales - physical well-being, emotional well-being, social well-being, and functional well-being. The FACT-G is a brief, reliable, and valid QOL measure, which is sensitive to clinical change and has been used with patients with cancer and a variety of other chronic illnesses (48). Based on the standard error of the mean, the minimally clinically important difference in FACT-G scores is 3.99.

Quality of Life assessments will be used in determining disease response as outlined in section11.2. For Peds-QL, the patient's self-report will be used when appropriate. If the patient's self-report is not available or other circumstances such as developmental delays, mental retardation, psychosis, or other apparent psychiatric issue, that in the opinion of the investigator would impair the subject's ability to complete the scale accurately, then the proxy report will be used instead at the discretion of the investigator. Likewise, a proxy-report will be used over the patient's self-report as appropriate based on the developmental age of the patient. This determination will be made by the investigator at the baseline QOL time point and will remain consistent for all other QOL time points. In the event that there is neither a consistent parent nor proxy report, the QOL assessments will not be used as a measure of disease response.

Pain will be assessed as an exploratory outcome and is not part of the response criteria for this study. Minimal clinically meaningful values have not been established for these variables; however given the importance of pain from the patient's perspective, we will include its assessment. Pain will be measured using the FLACC pain questionnaire for infants and older subjects unable to complete their age appropriate pain questionnaire, the PedsQL Pediatric Pain Questionnaire (49) for children and the short-form McGill Pain Questionnaire (50) for adults.

11.1.3 Clinical criteria and functional impairment:

The degree of impairment of organ function caused by the vascular anomalies has been used historically to assess disease response to therapy. Currently, there are no validated scales, specific to vascular anomalies, to assess functional impairment. We therefore, have developed

once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

12.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.3.1 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

12.2 Documentation and reporting of non-serious AEs or SARs

The severity of toxicities will be graded in accordance with the Common Terminology Criteria for AE (CTCAE) version 4.0.3. Grade 2 AEs deemed possible, probable or definitely attributed to study

event to the BCH IRB and BCH DSMB center program DSMB within 72 hours after the sponsor is made aware of the event.

12.5.3 Unexpected Grade 3 serious adverse events at least possibly attributable to the research will be reported to the BCH IRB per institutional policies.

12.5.4 Pfizer Reporting Requirements:

Notify Pfizer Drug Safety of all SAEs using the safety reporting form provided by Pfizer. Pfizer: Fax: (866) 997-8322

12.6 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 STATISTICAL ANALYSIS PLAN

13.1 Sample size and power calculation:

This is a two treatment arm randomized multi-center two-phase (induction/maintenance) clinical trial using the doubly adaptive biased coin design with a target allocation given by an urn model (40, 41) to continuously skew the randomization ratio to favor the better performing treatment arm. Patients will be randomized to receive either sirolimus or vincristine in the beginning of induction phase, and will be switched to the treatment they were not initially assigned to only if they fail to attain hematologic response (an increase of platelet count of >100,000 /µl or an increase in platelets of 2 times the baseline, whichever is greater, and a fibrinogen > 150 mg/dl; platelet and fibrinogen levels must meet these parameters on two consecutive lab measurements with a minimum of one day between evaluations). The primary efficacy endpoint is attainment of hematologic response by the end of the induction period.

We plan to enroll n=50 evaluable patients over a 4 year period from up to 8 participating institutions. In the study SIR-DA-0901 we observed the median time to hematologic response was 3 weeks and we anticipate 74%~90% response rate for the sirolimus treatment arm, whereas 20%~40% for the vincristine, depending on the underlying time to response mechanism and preliminary data. Based on a computer simulation study and assuming a response rate difference of 40% or greater, we anticipate the proposed sample of n=50 in total under the doubly adaptive biased coin design will provide 73%~90% power to detect a significant higher hematologic response rate of the sirolimus treatment arm. The simulation study also suggests that on average ≥20% more patients will be treated with the

more efficacious sirolimus treatment arm compared to the conventional fixed design.

In this adaptive design we will not conduct an interim analysis or stop the trial early. The adaptive design will treat more subjects with the sirolimus treatment arm by design in the case that the sirolimus treatment arm is more efficacious. We also do not expect any serious adverse events attributable to sirolimus. Therefore, futility may be the only legitimate reason to stop the trial early. However, the small total sample size limits the power of the interim analysis to test for the futility of sirolimus and splitting the type I error rate between the interim and the final analysis will lead to reducing the power of the final analysis without any substantial chance of early stopping for futility.

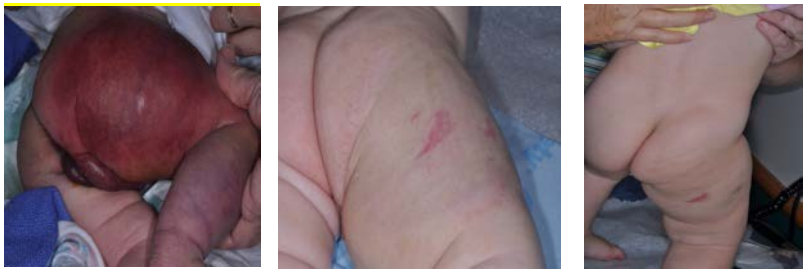
An early stopping rule will be invoked to prevent further accrual of patients onto the study in the event that Sirolimus or Vincristine is associated with a higher than acceptable rate of severe toxicity (10%) with severe toxicity (defined as Grade 4 infection, pneumocystis carinii pneumonia, Grade 2 pneumonitis, Grade 4 rash, Grade 4 hypertension, or Grade >2 allergic reaction) identified during the Induction period (the first 2 courses). We adopt a dynamic stopping rule based on cumulative number of patients enrolled into each treatment group. Enrollment to a treatment will be stopped, if the number of severe toxicity AE reaches a threshold defined in the table. This threshold is defined such that the 95% lower confidence bound of severe toxicity exceeds acceptable 10% rate, for either of the treatment groups. The stopping rule has high probability of stopping early if the probability of severe toxicity is moderately great (≥20%) and low probability of stopping if the underlying probability of severe toxicity is ≤10%.

A graph is also given below to visually show threshold as a function of total number enrolled in a particular treatment group. If the cumulative number of aforementioned severe toxicity AE reaches or exceeds the red line, the enrollment to that treatment will be stopped. New enrollment to the study will only be into the other group at that point.

Number of patients enrolled to a particular treatment group	Stop enrollment If at least this many patients experienced severe toxicity AE cumulatively	Probability of stopping at this stage if the true toxicity rate is 10%	Probability of stopping at this stage if the true toxicity rate is 20%
2	2	0.01	0.04
3	2	0.028	0.104
4	3	0.004	0.027
5	3	0.009	0.058
6	3	0.016	0.099
7	3	0.026	0.148
8	3	0.038	0.203
9	4	0.008	0.086

5RO1FD003712-04) (Figure 2 and Table 1). Twelve patients completed drug therapy and are in follow up. All twelve patients had a partial response to treatment (improvement of quality of life, organ function and radiologic imaging). Of the twelve patients who completed treatment, 8 were females and 5 were males. The average age at the start of treatment was 11 months with a range of 3 weeks to 3 years. Eleven patients presented at the time of diagnosis with KMP. Of the eleven, 3 had resolution of KMP prior to starting study but all were on steroid therapy and unable to wean treatment because of reoccurrence of KMP. When sirolimus was started all of these patients were weaned off steroids without reoccurrence of KMP. Of the 8 patients with KMP at study initiation, all had resolution of KMP with an average time to hematologic recovery of 3 weeks. One patient with multifocal KHE of the bone without KMP was taken off of study secondary to disease progression. This patient had been given a "wash-out period" (removal from previous therapy for 2 weeks prior to starting protocol). She was in severe pain from the beginning of the study, and also had multifocal bone disease which is extremely rare and perhaps has a different clinical spectrum than unifocal KHE. The "wash out" requirement was subsequently removed from the study. There were limited Grade III or IV toxicities in this group of patients, none of which required dose reduction or withdrawal from study. There have been no drug related infections and no obvious long term effects. Although we are presently evaluating this data, our preliminary conclusion is that sirolimus appears to be an effective and well-tolerated agent for high-risk KHE patients who otherwise have very limited options for treatment.

Figure 2. One patient's results with sirolimus.



a. Enrollment b. 6 months on study c. 12 months on study

Stop	

6.5 Arm 1: Vincristine + Steroids (Induction)

6.5.1 **Administration** - Vincristine will be administered weekly for 2 courses (one course is 28 days) by central venous catheter (recommend PICC line) per institutional guidelines. Vincristine administration may be moved by one day per course. The vincristine dose used for this study is based upon weight with 10 kg as a cut-off.

Vincristine Dose

- 0.05 mg/kg/dose IV – for participants less than or equal to 10 kg
  OR
- 1.5 mg/m^2/dose IV – for participants greater than 10kg

6.6 Arm 2: Sirolimus + Steroids (Induction)

6.6.1 **Administration –** Sirolimus will be administered at a dose of 0.8 mg/m^2/dose for participants <6 months of age and 1mg/m^2/dose for participants ≥6 months of age twice a day on a continuous dosing schedule. One course will be 28 days, measured by a 24 hour clock, rather than calendar days, to accommodate instances when the first dose of a course is the evening dose. Previous studies support the role of therapeutic monitoring and dose adjustment, and the importance of twice daily dosing given the more rapid drug metabolism in pediatric patients (42). Sirolimus will be administered as an oral (liquid) preparation in this study.

6.6.2 **Pharmacokinetically Guided Dosing** – The target sirolimus trough level is 10-15ng/ml. Sirolimus dosing will be individually guided using real-time drug concentrations measurements in combination with a Bayesian population model-based target optimization approach (43)

The dosing of sirolimus will be guided by pre-dose concentration measurements (trough) collected prior to either the AM or PM sirolimus dose. Each participant will have sirolimus serum levels measured according to the timeline listed below. Analysis for sirolimus level will occur at each participating site, or at a local laboratory using a validated assay approved by the study Pharmacologist. Regardless of collection and analysis site, the study Pharmacologist (Sander Vinks, PharmD, PhD, FC at Cincinnati Children's Hospital Medical Center (CCHMC)) or designee will perform all modeling and make recommendations for dose adjustment. Trough levels will be taken as listed below:

Table 3.

Sirolimus	**Frequency of**	**Action**

6.8 Treatment Change (Induction)

Participants who fail to achieve hematologic response by the end of induction (2 courses of therapy) will change to the other treatment arm for the start of Maintenance. **Although participants are expected to finish their assigned induction period, a participant may switch treatment arm (change treatment) prior to the end of the induction period if it is in the best interest of the participant's safety and well-being and hematologic failure is documented. Such participant will be considered a treatment failure (a non-responder will be counted as failure and the participant will change to the other therapy, but will be counted in the intent to treat group).** Treatment change is permitted one time during the study. Maintenance should be initiated within one week following documentation of hematologic failure for patients who change treatment. Functional assessments (Appendix V) and Quality of Life Questionnaires will be repeated prior to start of new treatment arm. These will serve as the baseline for the subsequent assessments obtained during maintenance.

6.9 MAINTENANCE (12 courses)

Study treatment (all participants) will be continuous between the periods of Induction and Maintenance. For participants who change treatments prior to start of maintenance, study treatment should begin within one week after documentation of hematologic failure.

6.9.1 Arm 1: Vincristine

6.9.2 **Administration** – Participants randomized to Arm 1 and have achieved hematologic recovery as defined in Section 6.7 will continue to receive vincristine on the schedule outlined in Table 4. Participants randomized to Sirolimus for induction and who have failed to achieve hematologic recovery as defined in Section 6.7 will change treatment to Arm 1 and receive Vincristine as outlined in Table 4. Vincristine will be administered by central venous catheter (recommend PICC line) per institutional policy during Maintenance for a total of 12 courses (48 weeks).

Vincristine Dose

- 0.05 mg/kg/dose IV – for participants less than or equal to 10 kg
  OR
- 1.5 mg/m^2/dose IV – for participants greater than 10kg

Vincristine administration schedule:

Vincristine will be administered weekly for 2 courses (Maintenance Courses 1-2). After 2 courses vincristine will be administered every two weeks for 5 courses (Maintenance Courses 3-7). Treatment will then be every 3 weeks for 5 courses (Maintenance Courses 8-12). Doses held/ missed for toxicity will not be made up. Vincristine administration may be

Table 4

Frequency	**Duration – 48 weeks**
Weekly	Maintenance Courses 1-2 (8 doses)
Every 2 weeks	Maintenance Courses 3-7 (10 doses)
Every 3 weeks	Maintenance Courses 8-12 (6 doses)

Frequency	Weekly (+/- 2 days)							
Maintenance Course	Course 1				Course 2			
Week	1	2	3	4	5	6	7	8
Vincristine	•	•	•	•	•	•	•	•

Frequency	Every 2 weeks (+/- 2 days)																			
Course	Course 3				Course 4				Course 5				Course 6				Course 7			
Week	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Vincristine		•		•		•		•		•		•		•		•		•		•

Frequency	Every 3 Weeks (+/- 2 days)																			
Course	Course 8				Course 9				Course 10				Course 11				Course 12			
Week	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Vincristine			•			•			•			•			•			•		

6.9.3 **Monitoring** – Laboratory assessments and toxicity monitoring will occur as outlined in Section 9.

6.10 Arm 2: Sirolimus

6.10.1 **Administration –** Participants randomized to Arm 2 for Induction and who have achieved hematologic recovery as defined in Section 6.7 will continue to receive sirolimus. Participants currently receiving sirolimus will continue at their current dose unless the criteria for dose adjustment as described in Section 6.10.3 are met.

6.10.2 Sirolimus Administration for Treatment Change to Arm 2- Participants originally randomized to Arm 1 that fail to achieve hematologic recovery will then switch to Arm 2 and will be administered sirolimus at a dose of 0.8 mg/m^2/dose for participants <6 months of age and 1mg/m^2/dose for participants ≥6 months of age twice a day on a continuous dosing schedule. Sirolimus dosing will be monitored pharmacokinetically to achieve serum trough levels for sirolimus between 10-15ng/ml.

- Physician determines it is in the best interest of the patient
- Progressive Disease or loss of response following change of treatment
- End of Protocol defined therapy
- Complete response to therapy*
  * If there is a Complete Response (CR) prior to completion of 12-24 weeks of therapy (3-6 courses), all study drugs will be stopped.
- Continuation of sirolimus or vincristine off study will be up to the patient's primary physician.

Participants who are off protocol therapy will be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent is withdrawn.

6.14 Duration of Follow-Up

All patients who complete the study or have a response (defined as stable disease or better), regardless of treatment arm, will continue to be followed for growth and complications of the vascular tumor and therapy-related toxicities for a total of 5 years from the date of study enrollment. Following completion of study therapy, patients will be followed at a minimum interval of every 6 months. Follow up visits may occur at participants home institutions or they may return to the study site for their routine follow up care. Participants should return to the study site on an annual basis during follow-up.

Patients who stop study treatment early for any reason and did not have a documented response to sirolimus or vincristine (defined as stable disease or better) will be followed for 30 days from the last dose of study treatment or until toxicities resolve to baseline or less than or equal to Grade 1.

6.15 Off Study Criteria

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission
- Complete Follow up as defined in Section 6.14
- Five years from protocol enrollment

	resume at target trough goal of 5-7ng/mL	trough level 7-10ng/mL)
>7 (target trough 5-7ng/mL)*	Resume at modified dose for target rough goal of 5-7 ng/mL	Resume at same dose (targeted trough level 5-7ng/mL)
Between 5-7ng/mL	Remove from treatment	Remove from treatment
* If sirolimus trough level is above target range at time of toxicity; therapy may resume when trough level is within target range.		

8.1.4 Interventions for Hyperlipidemia/Hypertriglyceridemia

Hyperlipidemia has been reported as an AE in at least 10% of patients treated with Sirolimus. As per the recent American Heart Association Scientific Statement on Cardiovascular Risk Reduction in High Risk Pediatric Patients, Tier III (65) management of hyperlipidemia should occur for patients with a fasting LDL cholesterol > 160 mg/dL. Age appropriate dietary restrictions should be enforced. Consult with your pediatric dietary and/ or nutrition services.

Table 7

Event	**Action**
Hyperlipidemia	
Fasting LDL >160 mg/dL and Patient ≥ 10 years old	• Diet (Nutritionist counseling – 30% of calories from fat, avoidance of trans-fats for 6 months) and exercise – Repeat Fasting LDL in 3 months. • If fasting LDL cholesterol is still >160 mg/dL, continue diet and exercise and initiate a triglyceride-lowering agent such as an HMG-CoA reductase inhibitor (pravastatin, atorvastatin, or fluvastatin). Patients should avoid drugs that inhibit or induce CYP3A4. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other AEs as required in the product data sheets for HMG-CoA reductase inhibitors. Continue to follow lipid panel every 8-12 weeks and adjust statins as necessary. • If fasting LDL cannot be maintained ≤ 160mg/dL despite medical intervention, or the patient cannot tolerate medical intervention, then the sirolimus target goal should be reduced to a target goal of 7-10 ng/mL. • If after 3 months, fasting LDL cholesterol is still >160 mg/dL, then the sirolimus target goal should be reduced again to a target goal of 5-7 ng/mL. • If after 3 months at this new target goal fasting LDL cholesterol is still >160 mg/dL, then the patient must be removed from protocol therapy.
Fasting LDL >160mg/dL and Patient <10 years old	• Diet (Nutritionist Counseling <30% of calories from fat, avoidance of trans-fats for 6 months). Repeat Fasting LDL in 3 months. • If fasting LDL cholesterol is still >160mg/dL, continue diet and exercise and consider cholestyramine resin. • If fasting LDL cannot be maintained ≤ 160mg/dL despite medical intervention, or patient cannot tolerate medical intervention, then the sirolimus target goal should be reduced to a target goal of 7-10ng/mL. • If after 3 months, fasting LDL cholesterol is still 160 mg/dL, then sirolimus target goal should be reduced again to a target goal of 5-7ng/mL. • If after 3 additional months at this new target goal fasting LDL cholesterol is still >160 mg/dL, then the patient must be removed from protocol

repeat centrifugation 1800xG for 15 minutes. Transfer plasma to a 2-5ml polypropylene cryogenic vial. Freeze and store at -80℃ until shipped

- Due to blood volume limits, collect blood for clinical labs, then biomarker samples with serum as first priority then plasma.
- Polypropylene cryogenic vials will be provided to participating institutions.

Labeling: All samples should be labeled with the subject's study ID number, initials, the date of collection and time point (baseline, end of induction, and end of maintenance courses 6 and 12

Shipping: See shipping instructions on the serum and plasma specimen transmittal form. Frozen serum and plasma samples should be shipped frozen on dry ice overnight by FedEx or another overnight service. Please email tracking number and time/date/place of shipping to: HVMCresearch@cchmc.org.

Ship frozen serum/plasma samples in dry ice by FedEx or other overnight carrier; First Priority Overnight to:

Megan Metcalf
Cincinnati Children's Hospital Medical Center
3333 Burnet Ave.
MLC 7015
Cincinnati, OH 45229
Pager: (513) 736-3010

10 DRUG INFORMATION

10.1 Sirolimus (Investigational Brochure).

Sirolimus (Rapamune) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The sirolimus: FKBP-12 complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. Following administration of sirolimus oral solution, sirolimus is rapidly absorbed, with a mean time-to-peak concentration of approximately 1 hour (range 1-3 hours). The systemic availability of sirolimus was estimated to be approximately 14% after the administration of sirolimus oral solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution; however, clinical equivalence has been demonstrated at the 2-mg dose level. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation to at least seven major metabolites. The parent drug contributes to more than 90% of the activity. The main route of elimination is through the feces (91%). The mean t 1/2 increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. Males have a 12% lower clearance of sirolimus than females after oral solution administration. No

a system of measurement which can be used across centers in a standardized manner (Appendix IV). This instrument has been adopted from the measures of organ function that have been validated in the quantification of AEs resulting from medical therapies or procedures (Common Terminology Criteria for AEs) and is currently in use In SIR-DA-0901 We will use these objective measures to quantify specific organ dysfunction resulting from vascular anomaly.

11.2 Disease Response

Response will be established by changes in at least 1 parameter at 6 and 12 courses after the initiation of maintenance using the following criteria:

Disease response – Complete Response (CR) and Partial Response (PR)

- **CR**
  - No evidence of disease on radiologic imaging and
  - No evidence of organ dysfunction due to disease and
  - Normalization of QOL criteria*
- **PR**
  - > 20 % reduction in volume by radiologic imaging, or
  - Improvement in target organ dysfunction by at least one grade, or
  - Improvement of proxy-report PedsQL by > 4.5; FACT-G by > 3.99*

Progressive disease

- > 20 % increase in target lesion volume by radiologic imaging, or
- Worsening in target organ dysfunction by at least one grade, or
- Worsening of Peds proxy-report PedsQL by > 4.5; FACT-G by > 3.99*

Stable disease: None of the above

Formal Responses will be assessed two times during maintenance at the end of courses 6 and 12 following start of Maintenance. Disease assessments may be performed at any time during maintenance if clinically indicated. Disease worsening as defined as “progressive disease” or “loss of response” based upon any one of the above methods will be permitted to cross-over. If worsened disease is based on laboratory parameters we suggest a repeat of laboratory evaluations to confirm.

* In the event there is an apparent discrepancy between the patient or parent proxy PedsQL score with either the investigator’s assessment of target organ dysfunction or response evident radiographically, the patient will remain on protocol therapy at the investigator’s discretion. In these particular instances, at the time of planned data analysis, the study statistician will determine if the patient should remain evaluable for overall response for the study.

medication and all Grade 3 and higher AEs, regardless of suspected causal relationship to study drug, will be recorded as AEs in the CRFs.

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

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 BCH or other nationally recognized pediatric standards may be used to determine the grade of the laboratory value.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least once a course.

Refer to the Manual of Operations for this clinical trial for more detail instructions regarding adverse event reporting.

12.3 Documentation of SAEs or Serious SARs

SAEs and Serious SARs will be recorded from the time of informed consent until 30 days after completion of study treatment.

12.3.1 SAE and Serious SAR reporting in the Follow Up Period

In the event that during the 5-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 patient continued therapy on marketed off-label sirolimus) attributable to sirolimus, 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.

12.4 Participating Site Responsibilities:

12.4.1 SAE/Serious SAR Reporting

All SAEs and Serious SARs, regardless of attribution or expectedness, must be reported to BCH verbally to coordinating center and Denise Adams within 24 hours of site awareness and followed with a FDA MedWatch 3500a Form. For participating sites, this form must be submitted to BCH within 3 days of learning of the event.

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

10	4	0.013	0.121
11	4	0.019	0.161
12	4	0.026	0.205
13	4	0.034	0.253
14	4	0.044	0.302
15	5	0.013	0.164
16	5	0.017	0.202
17	5	0.022	0.242
18	5	0.028	0.284
19	5	0.035	0.327
20	5	0.043	0.37
21	6	0.014	0.231
22	6	0.018	0.267
23	6	0.023	0.305
24	6	0.028	0.344
25	6	0.033	0.383
26	6	0.04	0.423
27	6	0.047	0.461
28	7	0.018	0.322
29	7	0.022	0.357
30	7	0.026	0.393
31	7	0.031	0.429
32	7	0.036	0.465
33	7	0.042	0.5
34	7	0.048	0.534
35	8	0.02	0.401
36	8	0.024	0.434
37	8	0.027	0.467
38	8	0.032	0.5
39	8	0.037	0.532
40	8	0.042	0.563
41	8	0.048	0.593
42	9	0.021	0.469
43	9	0.024	0.5
44	9	0.028	0.53
45	9	0.032	0.559
46	9	0.036	0.588
47	9	0.041	0.616
48	9	0.046	0.642
49	10	0.022	0.528
50	10	0.025	0.556