Trial Number ####

A CROSSOVER TRIAL FOR ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS:

CASAL TRIAL

A Study from UW Biostatistics 524

Sponsored by

Biostatistics 524

Department of Biostatistics, School of Public Health

University of Washington

Co-Sponsored by:

None

Protocol Chair(s):

Juliana Bonilla-Velez, MD

Seattle Children's Hospital

Seattle, WA, United States

[DRAFT] Version [3.0]

[6/1/21]

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS

TABLE OF CONTENTS

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS

LIST OF ABBREVIATIONS AND ACRONYMS

AE	**Adverse Event**
ASA	**Acetylsalicylic acid or Aspirin**
CBC	**Complete Blood Count**
DSMB	**Data Safety and Monitoring Board**
HNLM	**Head and Neck Lymphatic Malformation**
iCOO	**Infant with Clefts Observation Outcomes**
LM	**Lymphatic Malformation**
PedsQL	**Pediatric Quality of Life Inventory**
PI3K	**Phosphatidylinositol 3-kinase**
PIK3CA	**Phosphatidylinositol-4,5-bisphospate 3-kinase, catalytic subunit alpha**
PT	**Prothrombin Time**
aPTT	**Activated Partial Thromboplastin Time**
SAE	**Significant Adverse Event**

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS

PROTOCOL TEAM ROSTER

Juliana Bonilla-Velez, MD
Protocol Chair
4800 Sand Point Way NE
Box 356515
Seattle, WA 98105
bonillav@uw.edu
617-290-0144

Hu, Hantong
Biostatistician, Co-Investigator
Department of Epidemiology
University of North Carolina, Chapel Hill
3207 Michael Hooker Center
Chapel Hill, NC 27599
hantongh@uw.edu
919-491-5588

Lois, Alex
Co-Investigator
Department of Surgery
University of Washington School of Medicine
1959 NE Pacific Street
Box 356410
Seattle, WA 98195-6410
Phone: 206-598-3300
alexlois@uw.edu
262-496-9503

Wu, Yunhan
Biostatistician, Co-Investigator
Department of Biostatistics
Magnusonn Health Sciences Center – T wing
1959 NE Pacific St
Seattle, WA 98195
yunhanwu@uw.edu
984-888-7123

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS: A CROSSOVER TRIAL

A Study from UW Biostatistics 524

Sponsored by

Biostatistics 524
Department of Biostatistics, School of Public Health
University of Washington

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by Biostats 524. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by trial network policies. Any presentation, abstract, or manuscript will be submitted to the ASA trial Manuscript Review Committee for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Juliana Bonilla-Velez

Name of Investigator of Record

_____X_____ 5/17/21

Signature of Investigator of Record Date

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS: A CROSSOVER TRIAL

A Study from UW Biostatistics 524

Sponsored by

Biostatistics 524
Department of Biostatistics, School of Public Health
University of Washington

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by Biostats 524. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by trial network policies. Any presentation, abstract, or manuscript will be submitted to the ASA trial Manuscript Review Committee for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Alex Lois

Name of Investigator of Record

_____X_____ 5/26/21

Signature of Investigator of Record Date

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS: A CROSSOVER TRIAL

A Study from UW Biostatistics 524

Sponsored by

Biostatistics 524
Department of Biostatistics, School of Public Health
University of Washington

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by Biostats 524. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by trial network policies. Any presentation, abstract, or manuscript will be submitted to the ASA trial Manuscript Review Committee for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Hantong Hu

Name of Investigator of Record

_____X_____ 5/26/21

Signature of Investigator of Record Date

Trial Number ####

ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS: A CROSSOVER TRIAL

A Study from UW Biostatistics 524

Sponsored by

Biostatistics 524
Department of Biostatistics, School of Public Health
University of Washington

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by Biostats 524. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by trial network policies. Any presentation, abstract, or manuscript will be submitted to the ASA trial Manuscript Review Committee for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Yunhan Wu

Name of Investigator of Record

_____X_____ 5/26/21

Signature of Investigator of Record Date

Trial Number ####
ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS:
A CROSSOVER TRIAL

SCHEMA

Purpose: To assess the effectiveness of acetylsalicylic acid in the management of symptomatic lymphatic malformations of the head and neck in pediatric patients

Design: A double-blinded, placebo-controlled randomized trial with crossover.

Study Population: Patients with symptomatic lymphatic malformation of the head and neck, ages 2-17.

Study Size: 96 patients: 48 assigned to treatment, 48 assigned to control

Treatment Regimen: Oral aspirin 30-50mg/kg/day rounded to the nearest half tablet (81mg) or equivalently dosed recal suppository

Study Duration: 6 years - 5 year accrual period followed by 12 month follow-up period; Individual patients will be follow for 13 months; 1-month screening period, 6-month randomization period, 6-month crossover period

Primary Objectives:

- Examine the efficacy of acetylsalicylic acid or aspirin (ASA) in producing improvement in a composite outcome in pediatric patients (age 2-18 years) with lymphatic malformations (LM) of the head and neck. The composite outcome consists of:
    - Biomarker:
        - LM size reduction on magnetic resonance imaging (MRI)
    - Caregiver-reported outcome measure of patient symptoms and function
        - Lymphatic malformation function assessment
        - Infant with Clefts Observation Outcomes (iCOO)
        - Pediatric Quality of Life Inventory (PedsQL)

Secondary Objectives:

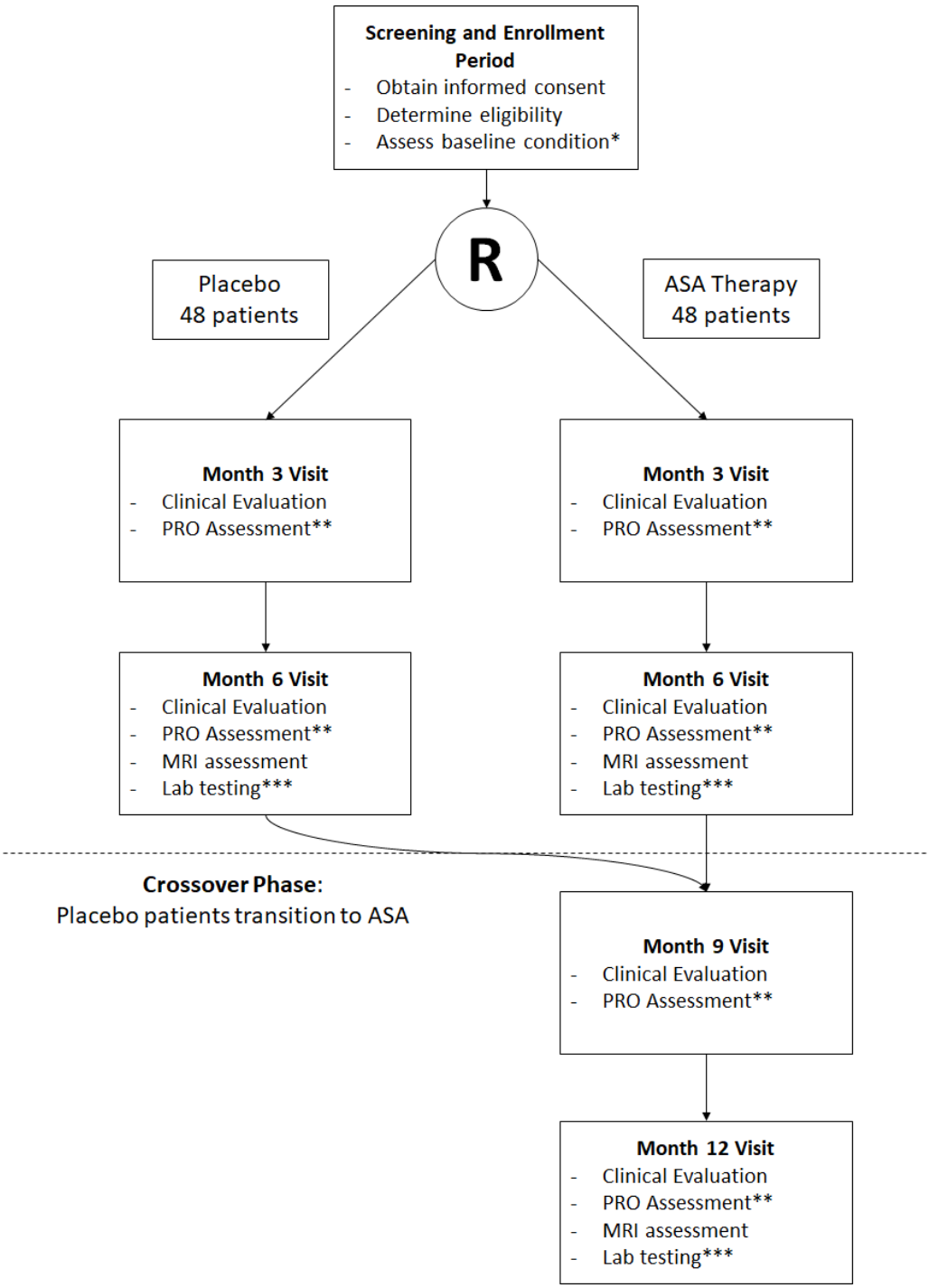
- Assess the safety of aspirin in treating LM in a pediatric population as defined by the occurrence of complications related to ASA therapy.
- Assess patient ability to adhere to drug treatment.
- Examine the impact of drug treatment on healthcare utilization and time in healthcare.
- Assess improvement in visualized size and appearance of the LM using clinical photography.
- Examine the efficacy of ASA in producing meaningful change in the individual components of the composite marker.

Study Sites:

- Seattle Children's Hospital
- Additional study sites to be determined

Trial Number ####
ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS:
A CROSSOVER TRIAL

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1.0 INTRODUCTION

1.1 Background and Prior Research

Lymphatic malformations are rare, congenital, low-flow vascular lesions that arise from abnormal lymphatic system development, and are caused by somatic mosaic mutations in the phosphatidylinositol-4,5-bisphospate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene.[1,2] These gain-of function variants in *PIK3CA* result in constitutive activation of the phosphatidylinositol 3-kinase (PI3K) pathway.[2,3] The estimated incidence of lymphatic malformations is 1.2 to 2.8 per 10,000 live births, and can be detected in-utero.[4,5] Lymphatic malformations present most commonly in the head and neck, where their presence can compromise normal function, development and quality of life.[6] Clinically, the De Serres classification categorizes head and neck lymphatic malformations (HNLM) by their location (supra- or infrahyoid) and laterality (uni- or bilateral), resulting in five stages that correlate with symptom presence, degree of functional compromise, number of interventions, postoperative complications, malformation persistence and natural history.[7,8]

Patients with HNLM have great phenotypic heterogeneity manifested in their clinical presentation, symptom profile and functional impairment. HNLM primarily in the lateral neck (De Serres stage I and III) often present as large cystic masses that cause disfigurement, and sometimes can regress spontaneously within 3-9 months from diagnosis.[9,10] Bilateral, midface, suprahyoid HNLM (De Serres stage II, IV, V) cause facial disfigurement through soft and bony tissue asymmetry. The resulting facial disproportion (i.e. mandibular hypertrophy, malocclusion, macroglossia, etc.) causes dysfunction in mastication, dental hygiene, and swallowing, and affects psychological development and social and community interactions. In other cases, HNLM are diagnosed prenatally and the patient requires an EXIT-procedure (or ex utero intrapartum treatment procedure) for delivery to secure their airway at birth. In general, higher De Serres stage, i.e. more extensive, bilateral HNLM result in greater symptomatology and physiologic dysfunction.[6,11,12]

Management of HNLM in children is challenging. Treatment options include observation, medical therapies, surgery and/or sclerotherapy. Observation can be considered for patients without symptoms or functional compromise.[9] Spontaneous regression has been reported among patients being observed, especially with lateral macrocystic neck lesions.[10,11,13] Surgery and sclerotherapy are the most common treatments, but have limitations and can result in some degree of posttreatment persistence.[10,14-17] Lower stage macrocystic malformations (De Serres I-III) can respond well to observation, surgery or sclerotherapy.[16-19] Extensive, high stage (De Serres IV-V), mixed macro-microcystic malformations often have unpredictable and incomplete treatment responses resulting in persistent dysfunction and untreated symptoms, such as sleep apnea, dysphagia, pain, bleeding and inflammation.[16-19] There are currently no treatment guidelines for HNLM and optimal HNLM treatment is debated as much of the existing literature does not provide high-level evidence to support clinical decision-making.[14,20]

Now that the genetic driver of HNLM is known, targeted therapies that inhibit the phosphatidyl inositol 3-kinase (PI3K) pathway have emerged as a novel therapeutic modality for HNLM. Downstream PI3K pathway suppression with sirolimus (rapamycin) has been used off-label in HNLM treatment.[21] Sirolimus is the most commonly used agent in lymphatic malformations and other disorders of lymphangiogenesis.[21,22] Sirolimus inhibits mammalian target of rapamycin (mTOR), a component of the PI3K pathway, and has cytostatic, antiproliferative, and immunosuppressive properties.[23-25] While its exact mechanism of action in HNLM is unknown, Sirolimus is thought to reduce lymphangiogenesis and lymph leakage.[21,24-26] Treatment outcomes for patients with head and neck involvement have been retrospectively examined in one case series on 19 patients with previously treated extensive symptomatic malformations who were either refractory to therapy or the family desired medical therapy prior to considering further procedures.[22] The authors report the improvement in lesion size (on imaging) was modest for 12/19 (63%, <20% reduction), moderate in 3/19 (16%, 20-50% reduction) and significant in 4/19 (21%, >50% reduction) patients. Improvements in symptoms were measured by reduction of mucosal blebs (14/14 patients) and decreased rates of infection (6/6 patients). However, 17/19 patients had one or several adverse reactions (headache, mouth sores, eczema, rash, acne, nausea, emesis, diarrhea, neutropenia, fatigue, irregular menses, alopecia, joint pain, cellulitis treated with oral or intravenous antibiotics, transaminitis, elevated cholesterol and triglycerides) with two patients having to stop treatment. No opportunistic infections were reported, but all patients received antibiotic prophylaxis for pneumocystis jiroveci.[22] Thus, off-label use of Sirolimus for HNLM therapy has been used with some success but frequent adverse events. Use of this medication also requires close monitoring through hematology-oncology and frequent laboratory evaluations which can be particularly burdensome for children.

Direct inhibition of other components of the PI3K pathway are being examined as medical therapies in children with mosaic activating *PIK3CA* mutations. These include the AKT inhibitor miransertib[27] (NCT03094832, NCT03317366) and the PIK3CA inhibitor alpelisib (Figure 1). Alpelisib (BYL719) showed reduction of *PIK3CA*-induced overgrowth and reversal of other physiologic alterations in these conditions.[28] Alpelisib is being offered to some PIK3CA positive LM through compassionate use protocols (NCT03941782). These targeted therapies are not FDA approved for non-malignant PIK3CA induced conditions. These are currently under investigational use to determine the safety and efficacy in lymphatic disorders.

Acetylsalicylic acid (ASA or aspirin) is an anti-inflammatory medication that suppresses the PI3K pathway in two places: upstream through COX- 2/PGE-2 pathway inhibition, and downstream through reduction of mTOR signaling (Figure 1).[29-31] Along with PI3K pathway suppression ASA could reduce inflammation which frequently causes HNLM symptoms that are often managed with antibiotics and corticosteroids.[32-34] Epidemiologic and experimental studies report daily ASA use in patients with sporadic cancers and tumors containing *PIK3CA* mutations prevent new tumor growth, reduce tumor growth and metastasis and sometimes improves survival.[35-38] In children, low dose ASA is safely used as primary therapy in multiple pediatric diseases, such as Kawasaki disease,[39] rheumatoid arthritis, and others.[40-43] It has been proposed as a prophylactic strategy in some hereditary cancer syndromes such as Lynch Syndrome and Constitutional Mismatch Repair Deficiency Syndrome.[44-46] The risk of Reye's syndrome is limited to the use of

ASA to treat acute febrile viral illnesses in children, and recent data suggest that susceptibility to Reye's syndrome is determined by a detectable inherited metabolic disorder.[47-49] Given this evidence as well as the relatively small risk associated with ASA therapy, we hypothesized that ASA could be a beneficial low-risk targeted HNLM therapy and described our initial experience treating pediatric HNLM patients with ASA.[50] We performed a retrospective analysis of patients treated with ASA at a single institution over 8 years. Patients with symptomatic HNLM, manifested as oral pain or localized mucosal blebs; recurrent pain or swelling with upper respiratory infections (acute exacerbations); or sudden or persistent LM swelling were offered ASA. Patients and/or caregivers were counselled regarding the genetic etiology of HNLM and all available treatments (observation, surgery, sclerotherapy, or sirolimus) and ASA therapy as an alternative to standard treatment based on its anti-inflammatory effects and inhibition of the PI3K pathway. Fifty-three patients were offered treatment with ASA of which 23 accepted and initiated therapy. Patients willing to trial ASA therapy were more likely to have extensive/recalcitrant HNLM compared to those who declined ASA [history of EXIT procedure ($p=0.033$), high De Serres stage (IV-V or bilateral distribution, $p=0.004$), oral cavity location ($p=0.039$), history of ≥2 invasive treatments ($p=0.015$), and tracheotomy ($p=0.004$)]. ASA treatment seemed to provide some degree of symptomatic benefit to 78% of patients in terms of reducing swelling (14, 61%), pain (9, 39%), bleeding (4, 17%), and visible blebs (1, 4%).). The majority of patients had a reduction in the size of the HNLM [partial response (14, 61%), complete response (4, 17%), and none worsened]. This small pilot study suggested that ASA could be an acceptable option for some patients, especially those with malformations that are extensive and in locations that were recalcitrant to prior invasive therapy. ASA appeared to be safe and well tolerated, with few reported side effects. The only adverse reaction noted was oral bleeding, which occurred in three of seven patients with oral cavity LM and stopped with medication cessation.

1.2 Rationale

The discovery of the genetic origin of HNLM has revolutionized the field. Suppression of the PI3K pathway has emerged as a potential therapeutic strategy that can offer symptomatic relief and improvement in function particularly for patients on whom other treatment modalities have suboptimal outcomes. Sirolimus has been used with some success but at considerable risk of

adverse effects and requires close clinical and laboratory monitoring. Novel PI3K inhibitors are being studied but are early in the therapeutic pipeline and their safety and efficacy are currently unknown. ASA has been used to treat pediatric conditions for decades and has a known safety profile in children. Mechanistically it provides both upstream and downstream inhibition of the PI3K pathway and preliminary pilot data is suggestive of some degree of improvement in symptoms and size of HNLM. Thus, a trial to test the safety and efficacy of ASA in the management of HNLM is needed.

We propose a phase II randomized clinical trial to test the safety and efficacy of ASA for the treatment of pediatric HNLM. Given that there is no prior data from experimental studies on patients with HNLM and some patients can exhibit spontaneous regression, patients will be randomized to ASA vs. placebo. ASA will be prescribed following weight-based recommendations based on Kawasaki disease (30-50 mg/kg/day, rounded to half or whole 81 mg tablets).

Demonstrating safety and efficacy of ASA for HNLM would have great implications for our patients. It would offer a therapeutic alternative of a medication that has been in the market for decades and for which we have a good understanding of the intended and off-target effects. It would provide a medication that can be administered in children without the need for laboratory surveillance which is particularly burdensome in this population. ASA is affordable and widely accessible worldwide, which would offer access to medical therapy to children with HNLM particularly in developing countries, where access to other therapeutic modalities or clinicians with expertise in vascular anomalies can be limited. Use of ASA has the potential to change the treatment paradigm for children with HNLM across the globe.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

The primary objective of this study is to examine the efficacy of aspirin (ASA) in producing clinical improvement in pediatric patients (age 2-18 years) with lymphatic malformations (LM) of the head and neck. Clinical improvement is defined by improvement in a composite outcome measure consisting of a biomarker of treatment response and three patient/caregiver-reported outcome measures of patient symptoms and function. The components of this composite outcome include:

- Biomarker:
    - LM size reduction on magnetic resonance imaging (MRI)
- Caregiver-reported outcome measure of patient symptoms and function
    - Lymphatic malformation function assessment
    - Infant with Clefts Observation Outcomes (iCOO)
    - Pediatric Quality of Life Inventory (PedsQL)

Primary outcome assessment of the randomization phase of the trial will occur at 6 months. Primary outcome assessment of the cross-over phase will occur at 12 months of clinical follow-up. Interval outcome assessment will occur at 3,6, and 9 month clinic visits. Caregiver reported outcome measures will be assessed at each clinical encounter with the use of a patient/caregiver completed survey. MRI, clinical photograph, and laboratory testing will be performed at 6-month intervals to assess LM size and extent.

2.2 Secondary Objectives

The secondary objectives of this study are several. The first is to examine the safety of aspirin in treating LM in a pediatric population as defined by the occurrence of complications related to ASA therapy. We will monitor for a number of predefined morbidity events (a subset of which are significant adverse events [SAEs] for data safety monitoring board reporting [DSMB]) including complications from medications including allergic reactions and side effects such as bleeding that would require cessation of the drug. The second will assess patient ability to adhere to drug treatment using both self-report and weighing of pill bottles at clinical follow-up. The third will examine the impact of drug treatment on healthcare utilization and time in healthcare as measured by days missed from work/school, ED/hospital encounters, LM-associated diagnostic testing and therapeutic interventions (including the need for surgical intervention as the result of disease progression), and out of pocket costs of therapy. Fourth, we will assess improvement in external size of LM using clinical photography. Finally, we examine the efficacy of ASA in producing meaningful change in the individual components of the composite marker including: LM size on MRI, lymphatic malformation function assessment score, iCOO score, and PedsQL inventory score.

2.3 Study Design

The intervention under investigation is aspirin (ASA) administered using weight-based dosing. Patients will receive 30-50mg/kg/day rounded to the nearest half or whole tablet. Children unable to take oral tablets will be offered rectal formulations.

This study will be a phase IIb, superiority, multicenter, double-blinded, randomized control trial comparing aspirin to placebo for the management of symptomatic lymphatic malformations of the head and neck. Due to the rarity of this disease process, this study will incorporate a cross-over trial design to maximize statistical power. After enrollment, patients will be randomized to either aspirin therapy or placebo. At study enrollment patients will undergo a baseline medical evaluation consisting of physical exam, laboratory studies, and imaging. Laboratory studies will include a standard complete blood count (CBC), coagulation studies (including a d-dimer, fibrinogen, PT and aPTT), and a blood smear to evaluate for the presence of blood dyscrasia, bleeding diathesis, and platelet disorders that would preclude from aspirin therapy and trial participation. Baseline imaging will consist of MRI and clinical photographs to determine baseline measurements for LMs. At study enrollment patients/caregivers will be asked to complete a baseline survey that includes the lymphatic malformation function assessment,

Infant with Clefts Observation Outcomes (iCOO), Pediatric Quality of Life Inventory (PedsQL), and demographic information. Patients will then be randomly allocated to ASA or placebo. Patients and clinical providers will be blinded to treatment allocation with only study coordinators having access to blinding schema.

Patients will return to the clinic at three-month intervals for ongoing clinical assessment and completion of interval survey administration. At three-month intervals patients will repeat the patient reported outcome assessments. At the six-month clinic follow-up patients will be evaluated for clinical improvement as measured by the primary endpoint, as well as, repeat laboratory evaluation with CBC and coagulation panels to monitor platelet counts and clotting times. Patients will undergo follow-up MRI testing and clinical photography in addition to patient reported outcome assessment and laboratory testing. At six months after study randomization, trial crossover will occur. Patients initially randomized to aspirin therapy will continue aspirin until study completion. Patients initially randomized to placebo will crossover to aspirin therapy. Study participants will continue this treatment assignment until completion of the study at 12 months. Analyses will be divided into two phases: phase I, evaluating initial randomization period (occurs at 6 months) and phase II, evaluating the crossover trial period. Of note, participants that experience a complete clinical response will be allowed to discontinue their assigned therapy prior to study completion, due to the rarity of LM recurrence after resolution. Patients will still be required to complete clinical follow-up according to the study schedule after medication discontinuation.

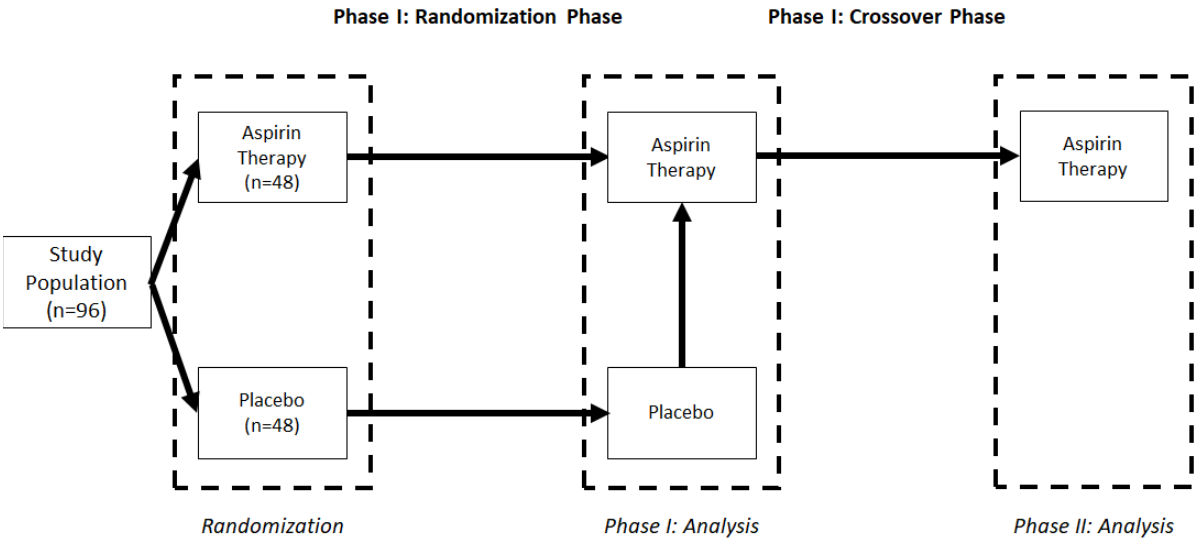


Figure 1. Diagram of Study Phases

3.0 STUDY POPULATION

A total of 96 patients diagnosed with a symptomatic LM of the head and neck, regardless of deSerres stage, will be included in this study. Participants will be selected for the study

according to the criteria in Section 3.1 and 3.2 [and the guidelines in Section 3.4]. They will be recruited, screened, and enrolled as described in Section 3.3 [and assigned to a study treatment/product/intervention group as described in Section 7.4]. Issues related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively.

3.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for inclusion in this study:

- Pediatric patients, ages 2-17 years
- Diagnosed with symptomatic LM of the head a neck (International Society for the Study of Vascular Anomalies [ISSVA] Class IIa)
- Presentation to/actively followed by one of the participating clinical sites

3.2 Exclusion Criteria

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

- Pediatric patients less than 2 years of age
- Adult patients, age equal or greater than 18 years
- Prior/ongoing treatment with ASA
- Ongoing treatment with sirolimus or other medications that act on the PI3K signaling pathway
- Planned surgery of the head and neck
- Prior/ongoing treatment for malignancy
- Contraindication to ASA therapy (e.g. increased risk for Reye's syndrome, arteriovenous malformations, coagulopathy, thrombocytopenia, blood dyscrasias)
- Patients diagnosed with PIK3CA-related overgrowth spectrum (PROS) groups lesions including:
    - 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 / Facial Infiltrative Lipomatosis
    - Megalencephaly-Capillary Malformation (MCAP or M-CM)
    - Dysplastic Megalencephaly (DMEG)
    - Klippel-Trenaunay syndrome

3.3 Recruitment Process

Patients will be identified through otolaryngology, vascular anomaly and general pediatric clinics at participating sites. Research coordinators will be embedded in the clinics and will also monitor for patients who have been treated for symptomatic lymphatic malformations of the head neck but are not currently followed at participating sites. All patients meeting inclusion

criteria and not having exclusion criteria will be reviewed with the site principal investigator and surgical staff to ensure eligibility. Once eligibility has been confirmed, patients will be approached for participation in the trial. Eligible patients will be offered standard educational materials that explain the burdens of trial participation and informed consent materials detailing the risks and benefits of trial participation. Following adequate time to review informational materials, patients will be asked to participate in the trial.

3.4 Co-Enrollment Guidelines

Patients that choose to participate in the CASAL trial will be barred from participating in any other investigational trial relating to the management of symptomatic lymphatic malformations.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain him/her for 12 months of follow-up in order to minimize possible bias associated with loss-to-follow-up. *S*tudy site staff are responsible for developing and implementing local standard operating procedures to target this goal. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit
- Thorough explanation of the importance of ongoing participation from all study participants to the overall success of the study.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about investigational treatments for symptomatic LMs and explain the purpose of research into new treatments for LMs and the importance of completing research study visits.

3.6 Participant Withdrawal

Regardless of the participant retention methods just described, participants may voluntarily withdraw from the study for any reason at any time. The Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, DAIDS Medical Officer, SDMC Protocol Statistician, and CORE Protocol Specialist.

- Participants that require urgent/emergent surgery that cannot be delayed until after the completion of the study period, and thus may require pausing/discontinuation of ASA therapy will be withdrawn from the study.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/ECs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Section 5.6) of participants who terminate from the study prior to Day 364, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY TREATMENT/PRODUCT/INTERVENTION

4.1 Treatment/Product/Intervention Formulation/Content

Study medications will be produced by Bayer AG. Aspirin will be administered in two formulations 1) oral tablets for participants able to swallow pills and 2) rectal suppositories for those unable to swallow pills. The placebo formulations will also be produced by Bayer AG and will be identical to aspirin formulations with the exclusion of the active ingredient (acetylsalicylic acid).

- Aspirin
    - Oral tablets - 81 mg, non-enteric coated
    - Rectal suppository - available in 1200 mg; 600 mg; 325mg; 300 mg; 125 mg doses
- Placebo
    - Oral tablets
    - Rectal suppository

4.2 Treatment/Product/Intervention Regimen(s)

Participants able to take oral formulations will receive either ASA dosed at 30-50mg/kg/day rounded to the nearest half or whole tablet or the equivalent number of placebo tablets to take daily. Those unable to take oral tablets will receive a rectal suppository formulation corresponding to 30-50mg/kg/day. Those assigned to placebo will receive the equivalent number of placebo suppositories.

4.3 Treatment/Product/Intervention Administration

Medications (ASA and placebo) will be dispensed in 90-day supply at 3-months intervals.

4.4 Treatment/Product/Intervention Supply and Accountability

The site pharmacist must maintain complete records of all study drugs/products received from the Clinical Research Products Management Center and subsequently dispensed to study participants. All unused supplies must be returned to the Clinical Research Products Management Center after the study is completed or terminated.

4.5 Adherence Assessment

Adherence will be assessed at 3-month intervals. Monitoring will consist of redundant measures of adherence including both weighing pill bottles/medication vials and recording the amount of remaining medication (i.e. suppositories for patients taking rectal formulations and remaining tablets for those able to take pills).

4.6 Toxicity Management

Although drug toxicity is not expected, adverse events including: bleeding events and anaphylaxis can occur in rare cases. In the event of an adverse event, in addition to event reporting described in Section 6.0, clinical staff will review all adverse events to determine if another cause for the adverse event can be identified. In the absence of another explanatory cause, study treatment will be discontinued. Dosage adjustments will not be made. Patients will continue to be followed until study completion.

4.7 Concomitant Medications

Enrolled study participants may continue use of all concomitant medications — except those listed under criteria for exclusion or treatment discontinuation — during this study (Section 3.2).

All concomitant medications taken or received by participants within the 4 weeks prior to study enrollment will be reported on applicable study case report forms. In addition to prescribed and over-the-counter medications, vitamins, herbal remedies, and other traditional preparations will be recorded. Alcohol and recreational or street drug use will be recorded in clinical progress notes if needed for interpretation/documentation of observed participant health status. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable study case report forms.

5.0 STUDY PROCEDURES

Please see Appendix A for a supplementary table detailing study visit procedures.

5.1 Screening (0 to 28 Days Before First Study Visit)

Before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from every participant. A copy of the signed and dated ICF must be given to the participant.

The following procedures are to be conducted at screening.

- Obtain the participant’s demographic information.
- Obtain any medical history of clinical significance.
- Obtain details of any medication currently taking.
- Ensure all of the inclusion criteria and none of the exclusion criteria are met.
- Schedule an appointment for the participant to return for the next study visit.

5.2 Visit 1 (Day 1 / Month 0)

- Obtain demographic information and medical history if different from screening period.
- Perform physical examination including vital signs (heart rate, blood pressure, temperature, and respiratory rate).
- Obtain the participant’s randomization number and study intervention allocation.

- Collect a blood sample.
- Collect questionnaires on Lymphatic malformation function assessment, Infant with Clefts Observation Outcomes (iCOO), and Pediatric Quality of Life Inventory (PedsQL)
- Shoot clinical photographs of participant's LM.
- Perform an MRI on participant's LM.
- Explain the e-diary technologies available for this study, and assist the participant in downloading the study application onto the participant's or participant's parents or legal guardian's device. Provide instructions on e-diary completion and ask the participant to complete the e-diary until study ends.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the symptoms detailed in Section 6 and consent form.
- Dispense allocated drugs to the participant and provide instructions on dosage.
- Schedule an appointment for the participant to return for the next study visit.

5.3 Visit 2 (Day 91 / Month 3)

- Record AEs as described in Section 6.
- Perform physical examination including vital signs (heart rate, blood pressure, temperature, and respiratory rate).
- Collect questionnaires on Lymphatic malformation function assessment, Infant with Clefts Observation Outcomes (iCOO), and Pediatric Quality of Life Inventory (PedsQL)
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the symptoms detailed in Section 6 and consent form.
- Dispense allocated drugs to the participant and provide instructions on dosage.
- Schedule an appointment for the participant to return for the next study visit.

5.4 Visit 3 (Day 183 / Month 6)

- Record AEs as described in Section 6.
- Perform physical examination including vital signs (heart rate, blood pressure, temperature, and respiratory rate).
- Collect a blood sample.
- Collect questionnaires on Lymphatic malformation function assessment, Infant with Clefts Observation Outcomes (iCOO), and Pediatric Quality of Life Inventory (PedsQL)

- Shoot clinical photographs of participant's LM.
- Perform an MRI on participant's LM.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the symptoms detailed in Section 6 and consent form.
- Dispense allocated drugs to the participant and provide instructions on dosage.
- Schedule an appointment for the participant to return for the next study visit.

5.5 Visit 4 (Day 273 / Month 9)

- Record AEs as described in Section 6.
- Perform physical examination including vital signs (heart rate, blood pressure, temperature, and respiratory rate).
- Collect questionnaires on Lymphatic malformation function assessment, Infant with Clefts Observation Outcomes (iCOO), and Pediatric Quality of Life Inventory (PedsQL)
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the symptoms detailed in Section 6 and consent form.
- Dispense allocated drugs to the participant and provide instructions on dosage.
- Remind the participant to bring the e-diary to the next visit.
- Schedule an appointment for the participant to return for the next study visit.

5.6 Visit 5 (Day 364 / Month 12)

- Record AEs as described in Section 6.
- Perform physical examination including vital signs (heart rate, blood pressure, temperature, and respiratory rate).
- Collect a blood sample.
- Collect questionnaires on Lymphatic malformation function assessment, Infant with Clefts Observation Outcomes (iCOO), and Pediatric Quality of Life Inventory (PedsQL)
- Shoot clinical photographs of participant's LM.
- Perform an MRI on participant's LM.
- Ask the participant to contact the site staff or investigator immediately if the participant experiences any of the symptoms detailed in Section 6 and consent form.
- Check the participant's e-diary.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Study oversight will be conducted by a data safety monitoring board [DSMB] for the purpose of monitoring adverse events and ensuring participant safety. Protocol chair(s), study site investigator(s), biostatisticians, and other study team members will cooperate closely to monitor participant safety and respond to occurrences of adverse events or serious adverse events in a timely manner.

The study site investigators will play the primary role in monitoring for and recording all adverse events that occur during the duration of the study. Participants of both the treatment group and control group will be closely monitored for adverse events. The protocol team will be unblinded to review safety data and make decisions regarding trial termination in the event of safety related issues. The recruitment of new participants will be suspended if more than one study participant in the treatment arm experiences a SAE (as defined in section 6.2.2) that could be plausibly related to aspirin treatment without another attributable cause. The protocol team then will review all pertinent safety data and determine whether to continue the trial. A decision to stop the trial may be made by the protocol team at this time.

6.2 Adverse Event Definitions and Reporting Requirements

6.2.1 Adverse Event

We define an adverse event (AE) as the occurrence of any unfavorable or unintended symptoms that are plausibly associated with the use of aspirin treatment. Specifically, attention will be paid to the following short list of non-life-threatening side effects: headache, mouth sores, eczema, rash, acne, nausea, emesis, diarrhea, neutropenia, fatigue, irregular menses, alopecia, joint pain, cellulitis treated with oral or intravenous antibiotics, transaminitis or elevated cholesterol and triglycerides. The list of AEs could also be found in the appendix table. Investigating whether the AEs occur more frequently in the aspirin group compared with placebo group is a prespecified aim of the trial.

Study team members will ensure that study participants could reach DSMB anytime during the day via a 24-hour telephone number. Instructions will also be given for study participants to report any AEs they may experience to study clinician. In the case of life-threatening events, study participants will not follow the standard procedure and they should directly contact immediate emergency care.

Study clinicians will be properly trained to detect, report and document any events that could be categorized as an AE, particularly when the study participants are not certain about the

condition. In addition, the study clinicians will be instructed to avoid a leading manner when inquiring about the adverse events.

Participants experiencing AE will be followed clinically until the incident resolves and the patient returns to their baseline health status. In the case of an AE evolving into SAE, the study clinicians will properly record the progression and handle the event as described in Section 6.2.2.

In the event a participant experiences an AE or a SAE, expedited review of the event and its resolution may be requested by the DSMB at any time.

6.2.2 Serious Adverse Event

Serious adverse event (SAE) will be defined per U.S. Code of Federal Regulations (CFR) 312.32 and International Conference on Harmonization (ICH), “Good Clinical Practice: Consolidated Guidance” (E6) and “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” (E2A), as AE occurring at any dose that: Results in death, is life-threatening, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or requires inpatient hospitalization or prolongation of existing hospitalization.

In the scope of our clinical trial, we define two specific SAEs:

1. Severe allergic reactions to aspirin requiring intervention.

2. Serious bleeding requiring blood transfusion or procedural intervention.

Although there will be screening for aspirin allergies prior to initiating the treatment for all study participants, monitoring for severe allergic reactions to aspirin remains a necessary precaution for the clinical trial. Other SAEs, including but not limited to death, are deemed less likely to occur during the course of the study, but any and all SAEs that meet the general definition above will be recorded and their relationship to treatment will be assessed.

This study will be subject to suspension or early termination if the number of participants experiencing SAEs in the treatment arm triggers the stopping rule.

6.2.3 Frequency and Time Frame for Collecting AEs and SAEs

After the written informed consent are obtained from each study participant (or the parents or legal guardians of participants who cannot consent for themselves), the study clinicians will actively monitor and record all AE and SAE occurrences from patients, regardless of their treatment arm.

The exact time window for adverse event monitoring will be from visit 1 at time -1 month and visit 6 at month 12 after treatment initiation. The entire time period for recording AEs and SAEs will be for approximately one year and a month. The time period of observation for participants

who experience AE or SAE may be extended if the AE or SAE has not completely resolved by the final clinical visit, even if this extends beyond the study observation period or the anticipated date of study completion..

After the study period, the investigators will not be required to actively inquire about AE or SAE from participants. However, any AE or SAE possibly related to the treatment after the study period will also be documented and reported to the DSMB if reported to the study team.

6.2.4 Adverse Event Reporting Requirements

All occurrences of AE and SAE during the active monitoring period will be reported to the DSMB.

Any case of SAE will be properly recorded and a report will be filed to the DSMB via a SAE report form. In all circumstances, the report should be delivered to the designated personnel within 24 hours when the occurrence was received by the study clinicians. All expedited AE should also follow similar procedures.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

We would like to propose a phase II superiority cross-over randomized controlled trial to examine the safety and efficacy of ASA to treat pediatric patients with head and neck lymphatic malformations.

7.2 Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective to examine the safety and efficacy of ASA to treat pediatric patients with head and neck lymphatic malformation, the following endpoint will be assessed:

- LM size reduction on magnetic resonance imaging
- Lymphatic malformation function assessment
- Infant with Clefts Observation Outcomes (iCOO)
- Pediatric Quality of Life Inventory (PedsQL)

Our primary outcome, patient clinical improvement, is defined by improvement in a composite outcome measure consisting of a biomarker of treatment response and three patient/caregiver-reported outcome measures of patient symptoms and function above. Note that the primary outcome is binary, either improvement or no improvement. The status of improvement could only change from no improvement to improvement but not the other direction since we consider LM as relapse-free.

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to examine the safety and efficacy of ASA to treat pediatric patients with head and neck Lymphatic Malformation, the following endpoints will be assessed:

- Predefined morbidity events (a subset of which are significant adverse events [SAEs])
- Individual components of the composite marker: LM size on MRI, lymphatic malformation function assessment score, iCOO score, and PedsQL inventory score.
- Patient ability to adhere to drug treatment using both self-report and weighing of pill bottles
- Patient healthcare utilization and time in healthcare (days missed from work/school, ED/hospital encounters, LM-associated diagnostic test and therapeutic interventions, and out of pocket costs of therapy)

7.3 Accrual, Follow-up, and Sample Size

7.3.1 Sample Size Calculation

Our primary outcome is binary (patient clinical improvement: Yes/No). We define experiencing improvement as an event. We expect the proportion of events for the ASA group is [0.5], and the proportion of events for the placebo group is [0.2]. The effect size would be [0.3].

We calculate our sample size using Fisher's Exact Test. We choose power=0.9 to maintain a low false negative rate. We let type 1 error = 0.1, since we desire a slightly less stringent criteria for false positives in phase-2b trial. With the above choice, the sample size for this trial is N = [96].

7.3.2 Accrual and Follow-up Plan

Given the rarity of LM we anticipate a 60 month accrual and 12 months additional follow-up after accrual ends. The total time is 72 months.

7.4 Random Assignment / Study Arm Assignment

Randomization Scheme: Participants will be randomized to either treatment group (30-50mg/kg/day of ASA) or placebo group using permuted blocks randomization.

Blocking Scheme: We choose randomly permuted blocks to guarantee balanced allocation and double-blinding. Block sizes are 2 and 4 with pre-specified proportions of 2:1.

We will set a fixed seed first. Then, participants will be randomized to either treatment group (30-50mg/kg/day of ASA) or placebo group using randomly permuted blocks within each stratum. Block sizes are 2 and 4 with pre-specified proportions of 2:1. The size of blocks are randomly chosen from the available block sizes.

7.5 Blinding

Throughout the study, sponsor and designee, the Investigator and the study participants will be blinded to the treatment assignment. The ASA tablets and the matching placebo tablets have been manufactured to be identical in size and appearance.

7.6 Data Analysis

7.6.1 Primary Analyses

Our primary outcome is patient clinical improvement, defined by improvement in a composite outcome measure consisting of a biomarker of treatment response and three patient/caregiver-reported outcome measures of patient symptoms and function as described above. Thus the primary outcome is binary.

Primary Outcome, Null Hypothesis: For pediatric patients with head and neck lymphatic malformations and selected in our trial, ASA 30-50mg/kg/day and the same dose of Placebo do not differ in the proportion of patient clinical improvement over the 12 months of individual follow up, at significance level (alpha) of 0.1.

Primary Outcome, Alternative Hypotheses: For pediatric patients with head and neck Lymphatic Malformations and selected in our trial, ASA 30-50mg/kg/day has a greater proportion of patient clinical improvement over the 12 months of individual follow up when compared to the same dose of Placebo, at significance level (alpha) of 0.1.

As we have a dichotomous primary outcome, we selected a Chi-squared test to examine the null and alternative hypotheses. Our test achieves a type I error rate 0.1 so that there is a 10% chance that we reject the null hypothesis even when ASA is not associated with clinical improvement.

7.6.2 Secondary Analyses

Our secondary outcomes are:

- Safety of aspirin in treating LM (occurrence of complications related to ASA therapy)
- Individual components of the composite endpoint
- Patient adherence to drug treatment
- Patient healthcare utilization

- Change on clinical photography

We will examine whether the SAEs occurrence has different frequency between treatment and control group. We define a binary outcome for SAEs, where 1 represents occurrence of at least one SAEs and 0 if no SAEs occur. Since we expect the occurrence for SAEs to be rare and our sample size is small, we will use Fisher’s exact test for analysis.

We conduct statistical tests for each of the individual biomarkers/endpoints. The list of outcomes: LM size on MRI, lymphatic malformation function assessment score, iCOO score, and PedsQL inventory score, are all continuous so we will use a two-sample t-test to assess statistical significance for each outcome. Note that the p-values are for reference only, since we are not adjusting for multiple comparisons. Confidence intervals for each outcome crossed with the treatment group will also be produced.

We will report adherence based on self-report and weighing of pill bottles at clinical follow-up. No formal statistical analysis will be performed. A frequency table will be presented about proportions of adherence for both treatment and control arms.

We assess patient healthcare utilization and time in healthcare by reporting summary statistics. We produce estimates for mean and standard deviation for continuous outcomes including days missed from work/school, number of ED/hospital encounters and out of pocket costs of therapy. We provide frequency tables for other categorical outcomes.

7.7 Baseline Characteristics

Summary statistics for baseline demographic variables will be provided to assess appropriateness of randomization. We will report age, sex, race, language preference, stage of LM, whether the patient received head/neck surgery and whether the patient received prior PIK3CA therapy. For continuous variables, we exhibit mean and standard deviation and for categorical variables, we display frequency for each category.

7.8 Tables

Table 1 Baseline characteristic by treatment arms

	Treatment Group	Placebo Group
Age		
Sex		
-Male		
-Female		
-Other		
Race		
-Asian		

-Black		
-White		
-Hispanic		
-Other		
Language		
-English		
-Spanish		
-Other		
LM Stage		
-De Serres stage I		
-De Serres stage II		
-De Serres stage III		
-De Serres stage IV		
-De Serres stage V		
Previous Head/Neck surgery		
-Yes		
-No		
Prior PIK3CA Therapy		
-Yes		
-No		

Table 2 Primary outcome by treatment arms

	Treatment Group	Placebo Group
Improvement		
Non-improvement		

Table 3 Secondary outcomes by treatment arms

	Treatment Group	Placebo Group
Individual components of primary outcome		
LM size on MRI		
Lymphatic malformation function assessment score		
iCOO score		
PedsQL inventory score		
Patient ability to adhere to drug treatment		
Self-report adherence to drug treatment		
Adherence to drug treatment by weighing of pill bottles		
Impact of drug treatment on healthcare utilization and time in healthcare		
Days missed from work/school		
ED/hospital encounters		
LM-associated diagnostic testing and therapeutic interventions		

Out of pocket costs of therapy		
Safety of ASA therapy		
At least one SAEs		
Headache		
Mouth sores		
Eczema		
Rash		
Acne		
Nausea		
Emesis		
Diarrhea		
Neutropenia		
Fatigue		
Irregular menses		
Alopecia		
Joint pain		
Cellulitis treated with oral or intravenous antibiotics		
Transaminitis		
Elevated cholesterol and triglycerides		

8.0 Human Subjects Consideration

8.1 Ethical Review

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH GCP Guidelines
- Applicable laws and regulatory requirements

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

8.2 Informed Consent

Written informed consent will be obtained from each study participant (or the parents or legal guardians of participants who cannot consent for themselves). The informed consent document(s) must meet the requirements of local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

Each study site is responsible for developing a study informed consent form for local use, and must contain the standard information, including but not limited to the purpose of the study, the procedures to be followed, and the risks and benefits of participation, based on the template in Appendix B. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-

translation. Any change to the content of the consent must be approved by the Sponsor and the IEC / IRB prior to the form being used.

The investigator is responsible for explaining and ensuring the participant or the parents or legal guardians of participants fully understands the nature and purpose of the study.

The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study and given sufficient time to decide whether they wish to participate.

8.3 Potential Risks

This is a crossover study, so all of the participants will receive ASA at some time point. Those receiving ASA will have the following risks reported as side effects of ASA:

- Common (<10%): dyspepsia, increased bleeding tendencies, headache, abdominal pain, drowsiness, epigastric discomfort, heartburn, and nausea
- Rare (<0.1%): Aplastic anemia agranulocytosis, thrombocytopenia, anaphylactic reactions including shock, Steven-Johnson syndrome, Lyell's syndrome, erythema nodosum, erythema multiforme, hemorrhagic vasculitis, menorrhagia

As an FDA-approved medication, a complete list of possible side effects of ASA could be found in the US Food and Drug Administration database.

All of the participants will have the following risks caused by LM:

- Bleeding
- Difficulty in swallowing and/or breathing
- Rash
- Gastrointestinal upset
- Gastric Ulcer
- Bruising

To monitor the risk in this study, a Data and Safety Monitoring Board (DSMB) will review the information from the research study.

8.4 Potential Benefits

The target study population for this study is pediatric patients (age<18) with lymphatic malformations (LM) of the head and neck. The following benefits may accrue to participants:

- ASA may be an effective medication in reducing the LM size.

- ASA may be an effective medication in reducing pain caused by LM and consequently increasing quality of life.
- Standard care and surveillance for LM and MRI evaluation for LM size are applied to every participant throughout the study.
- Contributing to assessing the efficacy of a medication against LM, which currently had no effective and efficient treatment by medication only.

8.5 Incentive

Pending IRB/EC approval, participants and/or their parents or legal guardians will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Reimbursement amount and method of payment are specified in the consent form. Each site may provide different methods of payment.

Complimentary items are available for each study visit, such as free snacks and drinks, subject to availability of each study site.

Any type of injuries and/or diseases directly caused by this research study happened to the participant will be fully compensated in the form of treatment, either in the hospital where the study took place or in other hospitals. A referral will be offered as needed.

8.6 Confidentiality

Participants will be assigned a unique identifier after the randomization process. Any participant records, datasets, and/or any study-related information that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will be stored in a separate, locked file in an area with limited access.

Before the start of the study, each participant will be asked to complete a form allowing the Investigator to notify the participant's primary health care provider of his/her participation in this study. Medical information may be given to the participant's primary health care provider if necessary.

Participant's study information will not be released without the written permission of the participant. However, the participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Investigator and all study staff involved with this study may not disclose or use for any purpose other than performance of this study only. Prior written agreement from the Sponsor must be obtained for the disclosure of any confidential information to other parties.

8.7 Study Discontinuation

The study may be discontinued at any time by IRBs/ECs, and/or other government or regulatory authorities upon any regulation and ethical considerations.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the local laboratory (LL):

- Blood samples

Local laboratories will perform Chemistry, Hematology, and coagulation studies as indicated in Appendix I. Laboratories performing these tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant External Quality Assurance (EQA) programs.

Each study site will adhere to standards of good clinical laboratory practice, and local standard operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the CASAL Data Management System (CDMS) as described in the study-specific procedures manual.

9.2 Quality Control (QC) Procedures

9.2.1 Laboratory Quality Control and Quality Assurance Procedures

The clinical sites will document that their clinical laboratories are certified under the Continuous Laboratory Improvement Act of 1988 (CLIA-certified) and/or participate in DAIDS sponsored EQA programs. Given this study relies on routine laboratory testing, no additional QA procedures beyond standard laboratory operating procedures.

9.2.2 Quality Control for MRI Imaging

Radiologists at participating institutions will be provided with a standardized protocol for MRI interpretation and LM measurement. MRI evaluations will be randomly selected for review by the DSMB to ensure consistency in MRI interpretation.

9.3 Specimen Storage and Possible Future Research Testing

Study site staff will store all blood samples collected in this study at least through the end of the study. In addition, study participants will be asked to provide written informed consent for their blood samples to be stored after the end of the study for possible future testing. The specimens

of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

9.4 Biohazard Containment

As the transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and the Sponsor. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) prior to the implementation of the amendment.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such an amendment will be released by the Sponsor, agreed by the Investigator(s), and approved by the relevant IRB(s)/IEC(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the ICF have been approved by relevant IRB(s)/IEC(s) must be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the Investigator(s), and notified to the IRB(s)/IEC(s).

10.2 Protocol Compliance

The study will be conducted in full compliance with the protocol. In the case of noncompliance, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site Investigator to identify and report noncompliance to the Sponsor or its designee. Protocol deviations must be sent to the reviewing IRB/IEC per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB/IEC requirements.

10.3 Study Monitoring

It is the study monitor's responsibility to protect the rights of the participants, to verify compliance with research regulations and adherence to the protocol, and to confirm completeness, accuracy, and consistency of the data collected at each study site throughout the study.

During the study, a study monitor will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that the investigational team is adhering to the protocol and correctly recording study data.
- Record and report any noncompliance to the protocol.
- Confirm AEs and SAEs have been properly documented and confirm any SAEs that met criteria for reporting have been forwarded to the IRB/IEC.
- Inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms) if necessary.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice. The DSMB will also have responsibility for safety monitoring.

10.4 Study Activation and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Investigator and/or Sponsor may initiate study-site closure at any time, provided immediate notification to the IRBs/ECs, and/or other government or regulatory authorities and reasonable causes include but not limited to:

- Continuation of the study represents a significant medical risk and/or harm to participants.
- Failure of investigators, research staff, and/or study staff to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

In any case of study-site closure and study termination before planned study completion, investigators should inform the participant and should assure appropriate participant therapy and/or follow-up.

10.5 Retention of Study Records

The Principal Investigator must maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Study records include administrative documentation (e.g., protocol registration documents and all reports and correspondence relating to the study) and documentation related to each participant screened for and/or enrolled in the study (e.g., informed consent forms, locator forms, case report forms, notations of all contacts with the participant).The investigator will retain all study records for a period of at least 3 years after study completion. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 3 years.

If it becomes necessary for the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records. No records may be destroyed or transferred to another location or party without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.6 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

11.0 REFERENCES

1. Wassef M, Blei F, Adams D, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics.* 2015;136(1):e203-214.

2. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr.* 2015;166(4):1048-1054 e1041-1045.

3. Karakas B, Bachman KE, Park BH. Mutation of the PIK3CA oncogene in human cancers. *Br J Cancer.* 2006;94(4):455-459.

4. Harsha WJ, Perkins JA, Lewis CW, Manning SC. Pediatric admissions and procedures for lymphatic malformations in the United States: 1997 and 2000. *Lymphat Res Biol.* 2005;3(2):58-65.

5. Longstreet B, Balakrishnan K, Saltzman B, Perkins JA, Dighe M. Prognostic value of a simplified anatomically based nomenclature for fetal nuchal lymphatic anomalies. *Otolaryngol Head Neck Surg.* 2015;152(2):342-347.

6. Kirkham EM, Edwards TC, Weaver EM, Balakrishnan K, Perkins JA. The Lymphatic Malformation Function (LMF) Instrument. *Otolaryngol Head Neck Surg.* 2015;153(4):656-662.

7. Bonilla-Velez J, Whitlock KB, Ganti S, et al. Active Observation as an Alternative to Invasive Treatments for Pediatric Head and Neck Lymphatic Malformations.

8. de Serres LM, Sie KC, Richardson MA. Lymphatic malformations of the head and neck. A proposal for staging. *Arch Otolaryngol Head Neck Surg.* 1995;121(5):577-582.

9. Bonilla-Velez J, Whitlock KB, Ganti S, et al. Active Observation as an Alternative to Invasive Treatments for Pediatric Head and Neck Lymphatic Malformations. *Laryngoscope.* 2020.

10. Perkins JA, Maniglia C, Magit A, Sidhu M, Manning SC, Chen EY. Clinical and radiographic findings in children with spontaneous lymphatic malformation regression. *Otolaryngol Head Neck Surg.* 2008;138(6):772-777.

11. Foley LS, Kulungowski AM. Vascular Anomalies in Pediatrics. *Adv Pediatr.* 2015;62(1):227-255.

12. Perkins JA, Tempero RM, Hannibal MC, Manning SC. Clinical outcomes in lymphocytopenic lymphatic malformation patients. *Lymphat Res Biol.* 2007;5(3):169-174.

13. Kato M, Watanabe S, Kato R, Kawashima H, Iida T, Watanabe A. Spontaneous Regression of Lymphangiomas in a Single Center Over 34 Years. *Plast Reconstr Surg Glob Open.* 2017;5(9):e1501.

14. Adams MT, Saltzman B, Perkins JA. Head and neck lymphatic malformation treatment: a systematic review. *Otolaryngol Head Neck Surg.* 2012;147(4):627-639.

15. Balakrishnan K, Menezes MD, Chen BS, Magit AE, Perkins JA. Primary surgery vs primary sclerotherapy for head and neck lymphatic malformations. *JAMA Otolaryngol Head Neck Surg.* 2014;140(1):41-45.

16. Bonilla-Velez J, Moore BP, Cleves MA, Richter GT. Surgical Resection of Macrocystic Lymphatic Malformations of the Head and Neck: Short and Long-Term Outcomes. *Int J Pediatr Otorhinolaryngol.* 2020;134:110013.

17. Richter GT, Friedman AB. Hemangiomas and vascular malformations: current theory and management. *Int J Pediatr.* 2012;2012:645678.

18. Renton JP, Smith RJ. Current treatment paradigms in the management of lymphatic malformations. *Laryngoscope.* 2011;121(1):56-59.

19. Perkins JA, Manning SC, Tempero RM, et al. Lymphatic malformations: review of current treatment. *Otolaryngol Head Neck Surg.* 2010;142(6):795-803, 803 e791.

20. Balakrishnan K, Bauman N, Chun RH, et al. Standardized outcome and reporting measures in pediatric head and neck lymphatic malformations. *Otolaryngol Head Neck Surg.* 2015;152(5):948-953.

21. Adams DM, Trenor CC, 3rd, Hammill AM, et al. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. *Pediatrics.* 2016;137(2):e20153257.

22. Strychowsky JE, Rahbar R, O'Hare MJ, Irace AL, Padua H, Trenor CC, 3rd. Sirolimus as treatment for 19 patients with refractory cervicofacial lymphatic malformation. *Laryngoscope.* 2018;128(1):269-276.

23. Morris RE. Rapamycins: Antifungal, antitumor, antiproliferative, and immunosuppressive macrolides. *Transplant Rev.*1992(6):39–87.

24. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc.* 2003;35(3 Suppl):7S-14S.

25. Wiegand S, Wichmann G, Dietz A. Treatment of Lymphatic Malformations with the mTOR Inhibitor Sirolimus: A Systematic Review. *Lymphat Res Biol.* 2018;16(4):330-339.

26. MacFarland SP, Sullivan LM, States LJ, et al. Management of Refractory Pediatric Kaposiform Hemangioendothelioma With Sirolimus and Aspirin. *J Pediatr Hematol Oncol.* 2018;40(4):e239-e242.

27. Biesecker LG, Edwards M, O'Donnell S, et al. Clinical report: one year of treatment of Proteus syndrome with miransertib (ARQ 092). *Cold Spring Harb Mol Case Stud.* 2020;6(1).

28. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature.* 2018;558(7711):540-546.

29. Din FV, Valanciute A, Houde VP, et al. Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. *Gastroenterology.* 2012;142(7):1504-1515 e1503.

30. Kaur J, Sanyal SN. PI3-kinase/Wnt association mediates COX-2/PGE(2) pathway to inhibit apoptosis in early stages of colon carcinogenesis: chemoprevention by diclofenac. *Tumour Biol.* 2010;31(6):623-631.

31. Uddin S, Ahmed M, Hussain A, et al. Cyclooxygenase-2 inhibition inhibits PI3K/AKT kinase activity in epithelial ovarian cancer. *Int J Cancer.* 2010;126(2):382-394.

32. Kim D, Benjamin L, Wysong A, Hovsepian D, Teng J. Treatment of complex periorbital venolymphatic malformation in a neonate with a combination therapy of sirolimus and prednisolone. *Dermatol Ther.* 2015;28(4):218-221.

33. Harsha WJ, Crawford JV, Sorensen DM. An unusual case of adult airway obstruction from a lymphovenous malformation. *Ear Nose Throat J.* 2008;87(7):402-404.

34. Levy G. Clinical pharmacokinetics of aspirin. *Pediatrics.* 1978;62(5 Pt 2 Suppl):867-872.

35. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol.* 2012;13(5):518-527.

36. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med.* 2003;348(10):891-899.

37. Dube C, Rostom A, Lewin G, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2007;146(5):365-375.

38. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med.* 2012;367(17):1596-1606.

39. Zheng X, Yue P, Liu L, et al. Efficacy between low and high dose aspirin for the initial treatment of Kawasaki disease: Current evidence based on a meta-analysis. *PLoS ONE.* 2019;14(5):e0217274.

40. Karimi M, Haghpanah S, Pishdad P, Zahedi Z, Parand S, Safaei S. Frequency of silent brain lesions and aspirin protection evaluation over 3 years follow-up in beta thalassemia patients. *Ann Hematol.* 2019;98(10):2267-2271.

41. Walsh S, Knofler R, Hahn G, et al. Childhood primary large vessel CNS vasculitis: single-centre experience and review of the literature. *Clin Exp Rheumatol.* 2017;35 Suppl 103(1):213-220.

42. Schmugge M, Speer O, Kroiss S, et al. Monitoring aspirin therapy in children after interventional cardiac catheterization: laboratory measures, dose response, and clinical outcomes. *Eur J Pediatr.* 2015;174(7):933-941.

43. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. *J Am Coll Cardiol.* 2011;58(6):645-651.

44. Israels SJ, Michelson AD. Antiplatelet therapy in children. *Thromb Res.* 2006;118(1):75-83.

45. Wood LE, Tulloh RM. Kawasaki disease in children. *Heart.* 2009;95(10):787-792.

46. Leenders E, Westdorp H, Bruggemann RJ, et al. Cancer prevention by aspirin in children with Constitutional Mismatch Repair Deficiency (CMMRD). *Eur J Hum Genet.* 2018;26(10):1417-1423.

47. Beutler AI, Chesnut GT, Mattingly JC, Jamieson B. FPIN's Clinical Inquiries. Aspirin use in children for fever or viral syndromes. *Am Fam Physician.* 2009;80(12):1472.

48. Schror K. Aspirin and Reye syndrome: a review of the evidence. *Paediatr Drugs.* 2007;9(3):195-204.

49. Food, Drug Administration HHS. Labeling for oral and rectal over-the-counter drug products containing aspirin and nonaspirin salicylates; Reye's Syndrome warning. Final rule. *Fed Regist.* 2003;68(74):18861-18869.

50. Bonilla-Velez J, Whitlock K, Ganti S, et al. Acetylsalicylic Acid Suppression of PIK3CA Pathway as a Novel Medical Therapy for Head and Neck Lymphatic Malformations. Abstract. Annual Meeting American Society for Pediatric Otolaryngology (ASPO). https://cdn.ymaws.com/aspo.us/resource/resmgr/files/aspo_2019_annual_meeting_pro.pdf2019.

12.0 APPENDICIES

12. 1 Appendix A – Study Visit Procedures

Table 1. Visit Schedule for the Phase II Trial to Test the Efficacy and Safety of ASA to treat pediatric patients with head and neck lymphatic malformations						
	Screening Period	Double-Blind Treatment Period		Crossover Period		
Milestones		Baseline		End of Double-Blind Phase	Last Treatment Dispense	EOT EOS
Visit Number	V1	V2	V3	V4	V5	V6
Day	D-28	D1	D91	D182	D273	D364
Week	wk-4	wk0	Wk13	Wk26	Wk39	wk52
Screening / Baseline						
Study Informed Consent	X					
Inclusion / Exclusion	X					
Medical History	X	X				

Demographics	X	X				
Comorbidities		X	X	X	X	X
Randomization		X				
Treatment						
Administration Training		X				
Study Drug Dispensation		X	X	X	X	X
Concomitant Medications		X		X		X
Safety Assessments						
Blood Pressure and Pulse		X	X	X	X	X
Body Weight		X	X	X	X	X
Physical Exam		X	X	X	X	X

Diary Check		X				X
Lab Testing						
CBC		X		X		X
PT/aPTT		X		X		X
d-dimer		X		X		X
Blood Smear		X				X
Primary Outcome Assessment						
MRI		X		X		X
Lymphatic malformation function assessment		X	X	X	X	X
iCOO		X	X	X	X	X
PedsQL		X	X	X	X	X
Secondary Outcomes Assessment						

Clinical Photos		X		X		X

12.2 Appendix B: Sample Informed Consent Form(s)

Parental Permission Form
Study Title: CASAL TRIAL: A CROSSOVER TRIAL FOR ACETYLSALICYLIC ACID IN THE MANAGEMENT OF HEAD AND NECK LYMPHATIC MALFORMATIONS:

Principal Investigator: Juliana Bonilla-Velez, MD

The Research Team:

Name/Degree	Title	Phone Number	E-mail
Juliana Bonilla-Velez, MD	Principal Investigator	(XXX) XXX-XXXX	-
Alex Lois, MD	Co-Investigator	(XXX) XXX-XXXX	-
Hantong Hu	Co-Investigator	(XXX) XXX-XXXX	-
Yunhan Wu	Co-Investigator	(XXX) XXX-XXXX	-

If you have any problems regarding this study, you can contact any of the members above.
If you have any questions about your rights as a research participant, you can call the Institutional Review Board at (XXX) XXX-XXXX.
In the case of a life-threatening emergency, call 911. We also have a 24-hour emergency contact number at (XXX) XXX-XXXX.

1. Researcher's Statement:

You have the option to have your child take part in a research study that can potentially benefit the head and neck lymphatic malformation (LM) of your child. This form is a parental permission form that provides you information about what would happen in the study and help you decide if you want your child to be in the study.
Feel free to take notes, write questions, or highlight any part of this form. If you have any questions during or after finishing this form, feel free to ask any member of the research team or the study staff who handed you this form.
If you decide to let your child take part in this study, you would sign this form to confirm your decision. A copy of this form would be sent to you for your records.
The word "**you**" in the rest of this form refers to your child.

2. What you should know about this study:

- This form explains what would happen if you join this study.
- Take time to read this form carefully and explain it to your child if necessary.

- You can ask questions about the study any time by reaching out to the research team.
- Your participation in this study is voluntary, and would not affect your care in any case.
- You can change your mind any time during the study.
- The benefit you receive from participating in this study will only be stopped but not retrieved after you quit the study.

3. What is the goal of this study?

The goal of this study is to answer the questions:

- Does aspirin improve the existing condition of head and neck lymphatic malformations?
- If it does, to what extent can it improve (such as decrease in size or improve daily function)?
- Does aspirin have any side effects particularly in treating head and neck lymphatic malformations?

4. How many children will take part in this study?

96

5. What would happen to my child if I decided to join the study?

If you join the study, you would expect to take pills **daily** and have some tests and exams **every 12 weeks during the study period**. Both the pills and the tests are completely free of cost. The tests are to help us understand how well aspirin functions and if it causes any side effects. For your safety and the success of this study, we strongly encourage you to participate in every test on time.

All the tests and procedures are listed in the chart below. Some of the items require the parent or guardian to fill in the forms.

Visit	**Procedures**	**Location and Duration**
Visit 1 / Screening	Signing the informed consent form Questions about your medical history Finishing a paper of questions about your basic information such as gender, race, stage of LM, etc.	Specific to each site
Visit 2 / Day 1	An examination by the research doctor	

	Questions about your medical history if different from last time Confirmation of your basic information if different from last time Measurement of your heart rate, blood pressure, temperature, respiratory rate, weight Taking sample of your blood for lab test A paper questionnaire about how you are feeling Taking photographs of your LM A special scan of your LM (MRI) Drug dispensation and dosing instructions Instructions and training in regards to the home Drug Administration Diary	
Visit 3 / Day 91 / Month 3	An examination by the research doctor Measurement of your heart rate, blood pressure, temperature, respiratory rate, weight A paper questionnaire about how you are feeling Drug dispensation and dosing instructions	
Visit 4 / Day 183 / Month 6	An examination by the research doctor Measurement of your heart rate, blood pressure, temperature, respiratory rate, weight Taking sample of your blood for	

	lab test A paper questionnaire about how you are feeling Taking photographs of your LM A special scan of your LM (MRI) Drug dispensation and dosing instructions	
Visit 5 / Day 273 / Month 9	An examination by the research doctor Measurement of your heart rate, blood pressure, temperature, respiratory rate, weight A paper questionnaire about how you are feeling Drug dispensation and dosing instructions	
Visit 6 / Day 364 / Month 12	An examination by the research doctor Measurement of your heart rate, blood pressure, temperature, respiratory rate, weight Taking sample of your blood for lab test A paper questionnaire about how you are feeling Taking photographs of your LM A special scan of your LM (MRI) Checking of the previous home Drug Administration Diary	

6. How long will the study last?

If you choose to participate in all the study visits, you would be in the study for **one year**.

You can decide to stop at any time for any reason. If you decided to stop, you would need to talk with the research team in order for you to leave in the safest way possible.
You might be taken out of this study if the research study doctors find out it is not safe for you to continue participating. If this is the case, we would give you a full explanation and compensate for your loss if possible.

7. What are the potential harms or risks if I join this study?

The only medication you would expect to be taking in this study is aspirin, which you can find all of its side effects on any bottle of aspirin in any store. We list some of the risks below for your inference.

- Common (<10%): dyspepsia, increased bleeding tendencies, headache, abdominal pain, drowsiness, epigastric discomfort, heartburn, and nausea
- Rare (<0.1%): Aplastic anemia agranulocytosis, thrombocytopenia, anaphylactic reactions including shock, Steven-Johnson syndrome, Lyell's syndrome, erythema nodosum, erythema multiforme, hemorrhagic vasculitis, menorrhagia

There are some other risks caused by LM:

- Bleeding
- Difficulty in swallowing and/or breathing
- Gastric Ulcers
- Gastrointestinal Upset
- Rash
- Bruising

We do not know the possible harms or risks caused by aspirin specifically to LM patients, but we will ensure you are safe at each visit and contact you immediately if we find out other risks. We will also have a group of experts, called the Data Safety Monitoring Board, to review this study and ensure your safety in this study.

8. What if I were injured or harmed because I joined the study?

If you think that you were injured or harmed as the direct result of this research study, please reach out to us as soon as possible. Our contact information is provided at the top of this form. Once we get your contact, we will send one member of our research team or study staff doctor to check in with you and walk you through the possible options of treatment. You and your insurance would NOT need to pay for any treatment.

9. What can I benefit from joining this study?

Potential benefits from this study:

- You might have a reduced LM size.
- You might experience less pain caused by LM.
- The information you provided to this study can be used to benefit others who have LM.

Guaranteed benefits from this study:

- You will have completely free care and evaluation for LM size throughout the study.
- You will be compensated for your time and effort in this study.
- Each time you come to a study visit, we will provide complimentary items such as free snacks and free drinks.

10. Will you keep my information confidential?

If you decide to take part in this study, whether or not you quit at any point, we will make every effort to keep your information confidential.

Your personal information will be stored in a separate, locked file in an area with limited access to our staff only. We will assign a study number to your information prior to the study so we will not access your personal information in any ways during and after the study. If results of this study are published, we would not publish any information that identifies you or reveals your personal information.

We would only use your information for research purposes. Below are cases when we may need to share your information to guarantee the conduct of the study and your safety:

- If it's required by law.
- If we think you might be harmed
- Sponsors, government agencies (including the US Food and Administration), research staff, and the Data Safety Monitoring Board need to check if the research is done safely and legally. They are required to keep your information confidential as required by law.

If you join this study, we would ask you to complete a form before the study begins to allow us to notify your primary health care provider of your participation. We do this to ensure your primary care provider is aware of the medication you take during the study and ensure you are safe.

11. What would my signature on this form mean?

Your signature on this form would mean:

- The research study was explained to you.
- You had a chance to ask and have got answers to all questions you have at this time.
- You know who to look for if you decide to make any changes or ask for help during the study.
- By signing this consent form, you and your child do not give up any of your legal rights. The research team and/or sponsors are bound to protect your legal rights and your safety at any time after you sign this form and before the study ends.

If you have any questions about signing this form, feel free to ask any member of the research team or the study staff who handed you this form. You can find the contact list at the top of this form.

_____

Printed Name of Parent or Legal Guardian

_____ _____

Signature of Parent or Legal Guardian Date

12.3 Appendix C - Sample Budget