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# A Crossover Trial for Acetylsalicylic Acid in the Management of Head and Neck Lymphatic Malformations: The CASAL Trial

Group 3

Biostatistics 524

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# Background

# Introduction

LM result from abnormal lymphangiogenesis

LM can result in

- Asymptomatic mass
- Facial disfigurement
- Affect vital functions
- Affect psychosocial development and daily life

Treatment is challenging

- No evidence-based guidelines
- Limited outcome measures





# DeSerres Classification



I  
Unilateral  
Infrathyroid



II  
Unilateral  
Suprahyoid



III  
Unilateral  
Supra and Infrathyroid



IV  
Bilateral  
Suprahyoid



V  
Bilateral  
Supra and Infrathyroid



## Treatment Modalities for Lymphatic Malformations

Active Observation

Medical Therapies

Sclerotherapy

Surgery

Non-Invasive Modalities

Invasive Modalities



# Active Observation: Spontaneous Regression

200 patients with HNLM

↳ 65 (34%) offered observation

↳ 55% spontaneous regression  
~ 20%





# Surgery

## For MLM HNLM

- Complete response: 90.5%
- Recurrence-free survival: 86%
- Complications: 1 phrenic nerve paralysis, asymptomatic. Minor complications

## Benefits:

- Single vs. multiple procedures
- Histologic confirmation of the disease
- No radiation burden
- Potentially curative





# Sclerotherapy

For MLM HNLM

- Any size reduction: 83% (CI 0.76-0.89)
- >50% size reduction: 68% (CI 0.59-0.75)
- Complications: 1 phrenic nerve paralysis, asymptomatic. Minor complications

Advantages:

- Percutaneous treatment
- Usually outpatient

Disadvantages:

- On average had twice as many treatments
- Quality of the data is limited. No long-term follow up.

# Medical Therapies in LM

## Sirolimus

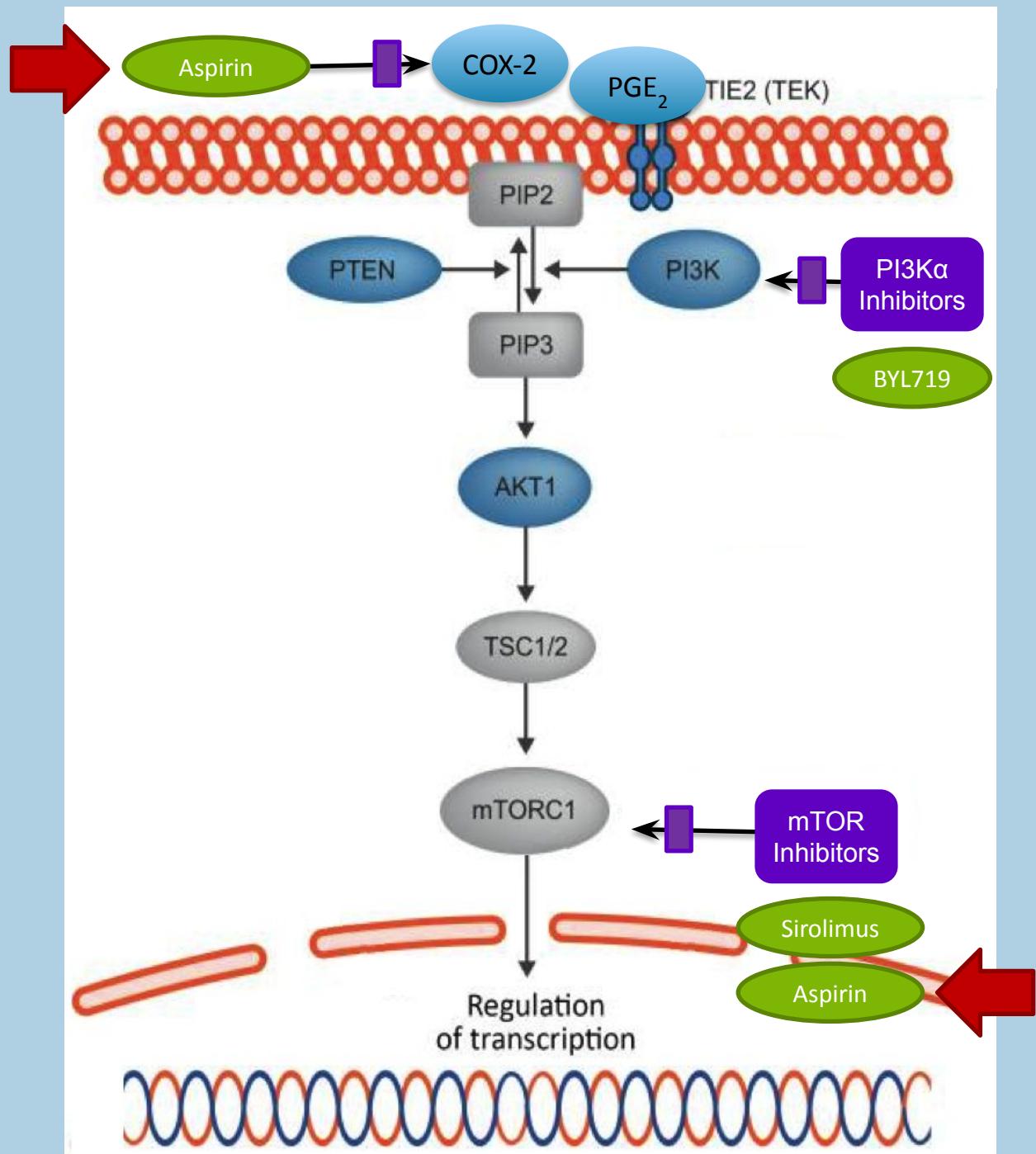
- Off label use
- Modest/unpredictable change in size
- Adverse effects: 90% of patients. Eczema, emesis, mouth sores, nausea, neutropenia, rash, transaminitis, acne, fatigue

## Aspirin

- SCH HNLM: 78% Symptomatic improvement, reduction in size
- Adverse effects: Oral mucosal bleeding, subsided with discontinuation

## PI3K Pathway Inhibitors

- Promising on compassionate use in PROS patients
- Clinical trials underway



# Aspirin Suppression of PIK3CA Pathway as a Novel Medical Therapy for Head and Neck Lymphatic Malformations

Determine efficacy and safety of ASA for treatment of HNLM

Pilot retrospective study on off-label use of ASA for HNLM (2009-2018).

Treatment indications: oral pain or blebs, and sudden or persistent swelling.

Outcomes:

- Improvement in symptoms
- Treatment response: complete, partial or none.

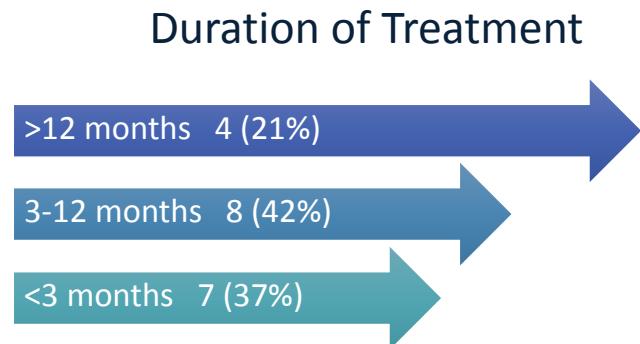
## Results:

23/53 patients accepted ASA treatment; they were more likely:

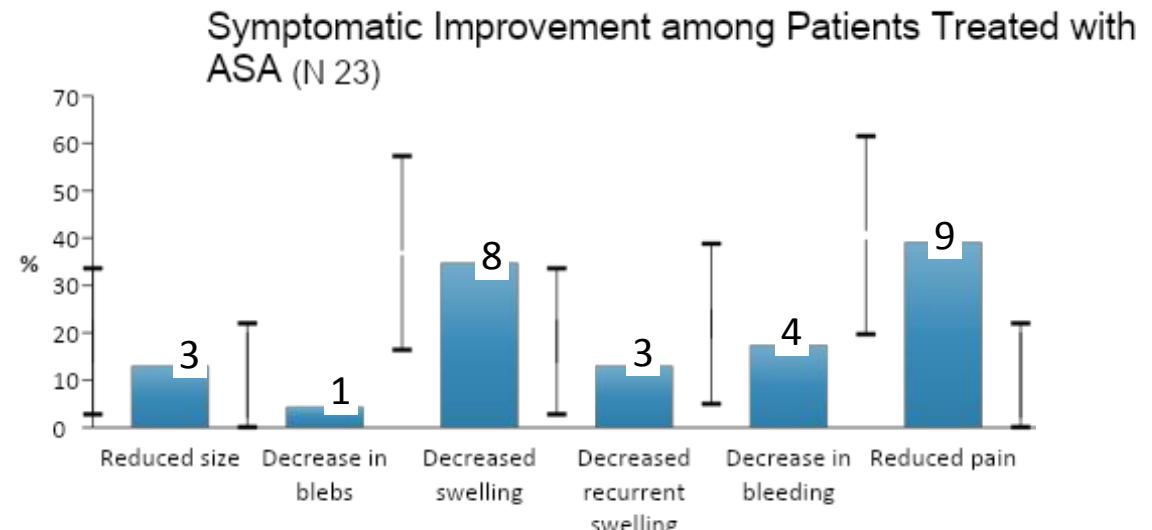
	ASA vs. Refused	p
EXIT	17% vs. 0%	p=0.0327
Stage IV/V	26% vs. 0%	p=0.036
Oral cavity	30% vs. 7%	p=0.039
Not in the neck	48% vs. 80%	p=0.039
Bilateral	39% vs. 0%	p=0.000
Staged surgery	35% vs. 10%	p=0.054
Not observed or primary surgery	26% vs. 43%	p=0.054
>2 invasive treatments	57% vs. 17%	p=0.0145
Tracheotomy	26% vs. 0%	p=0.004

# Aspirin as a Novel Treatment for Lymphatic Malformations

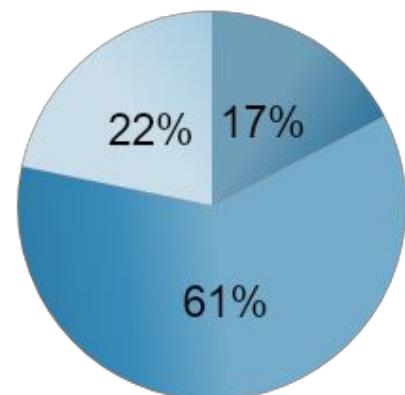
**78%**  
of patients reported  
improvement in symptoms  
(18/23, 95% CI 56-93)



Compliance  
18 (78%)  
Complications from  
ASA: 3 (13%)



## Treatment Outcomes



- Complete response (N=4)
- Partial response (N=14)
- No response (N=5)

# Aspirin as a Novel Treatment for Lymphatic Malformations

- Patients interested in ASA had more advanced disease and prior treatments.
- ASA **improved symptoms** and achieved a **partial response** in most patients
- ASA was **well tolerated** and had a **low-risk of complications**.





- Response to Treatment may Vary by Stage and Degree of Functional Compromise



I  
Unilateral  
Infrathyroid



II  
Unilateral  
Suprathyroid



III  
Unilateral  
Supra and Infrathyroid



IV  
Bilateral  
Suprathyroid



V  
Bilateral  
Supra and Infrathyroid

### Symptoms, Signs and Concerns

Mass  
No functional  
compromise

Mass, pain and  
bleeding from tongue  
when feeding

Mass, breathing,  
feeding, neck  
deformity,

### Successful Treatment?

Resolution of the mass  
Attend  
daycare/kindergarten  
without calling attention

Resolution of pain and  
bleeding

Avoidance or removal of  
tracheostomy and  
gastrostomy

# Anticipated Benefits of ASA over other Pharmacologic Alternatives

- Inhibition upstream and downstream of PI3K pathway may be more beneficial than other therapies
- Anti-inflammatory properties may contribute to the treatment effect
- Medication in use for many years with known safety profile
- Low-cost medication
- No need for surveillance laboratory tests, which is particularly important in the pediatric population
- Widely available, particularly in developing countries where access to novel targeted therapies is prohibitive



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# Research Plan



# Primary Objective

- Assess the efficacy of acetylsalicylic acid or aspirin (ASA) in producing a clinical improvement in pediatric patients (age 2-18 years) with lymphatic malformations (LM) of the head and neck.



# Primary Endpoint

- Composite outcome:
  - Biomarker:
    - LM size reduction on magnetic resonance imaging (MRI)
  - Caregiver-reported outcome measures 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 ASA in treating LM in a pediatric population.
- Assess patient ability to adhere to ASA therapy.
- Examine the impact of drug treatment on healthcare utilization and time in healthcare.
- Assess the effect of ASA on size and external appearance of LM
- Assess the effect of ASA on radiographic appearance of LM
- Assess the effect of ASA on how patients feel and function using the individual caregiver-reported outcomes measures.



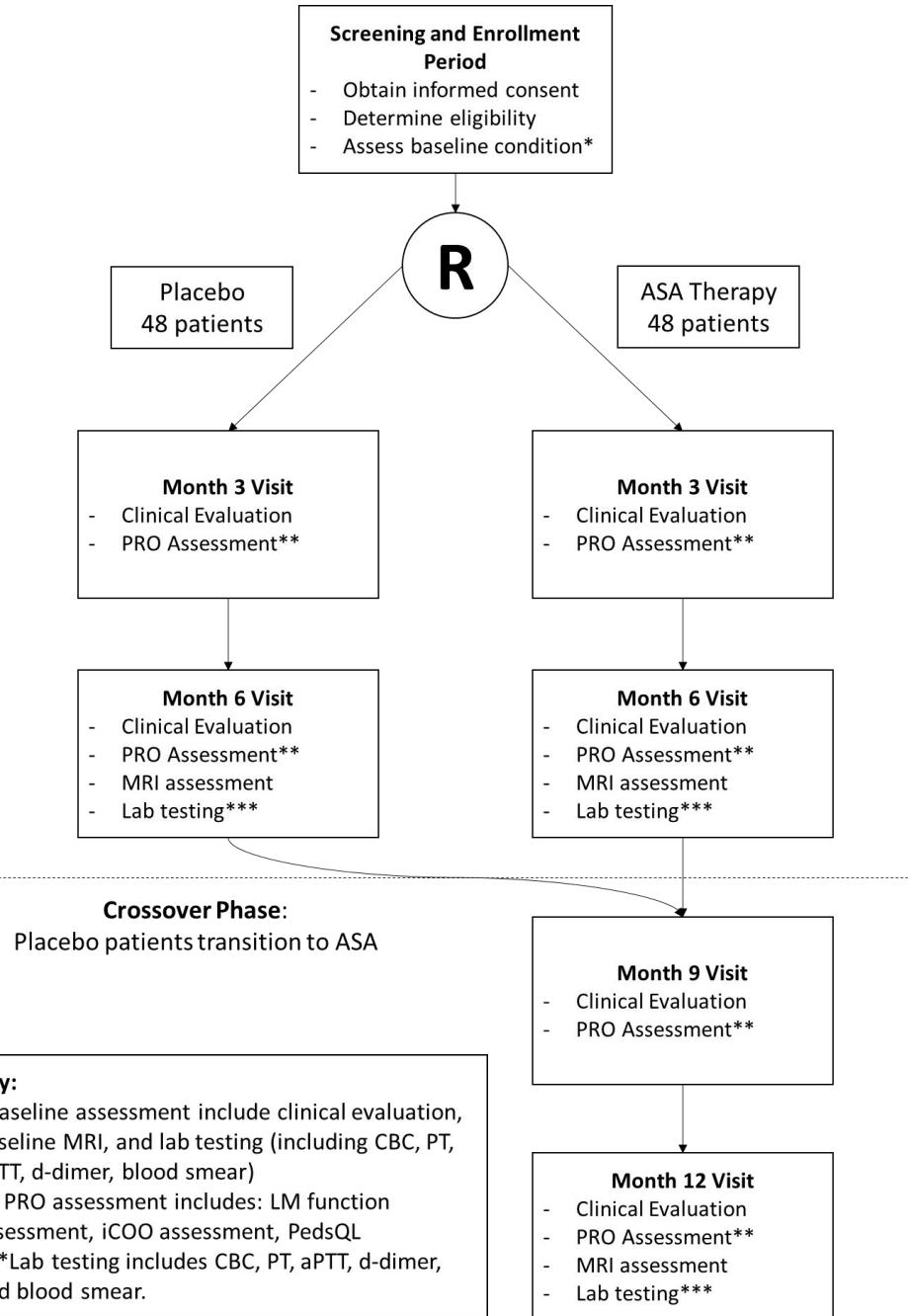
## Secondary Endpoints

- AE and SAEs between ASA and placebo
- Medication adherence using medication counts and weights
- Frequency of healthcare visits between ASA and placebo
- External appearance of LM using clinical photography
- Radiographic appearance of LM using MRI
- Individual caregiver-reported outcomes measures



# Study Design

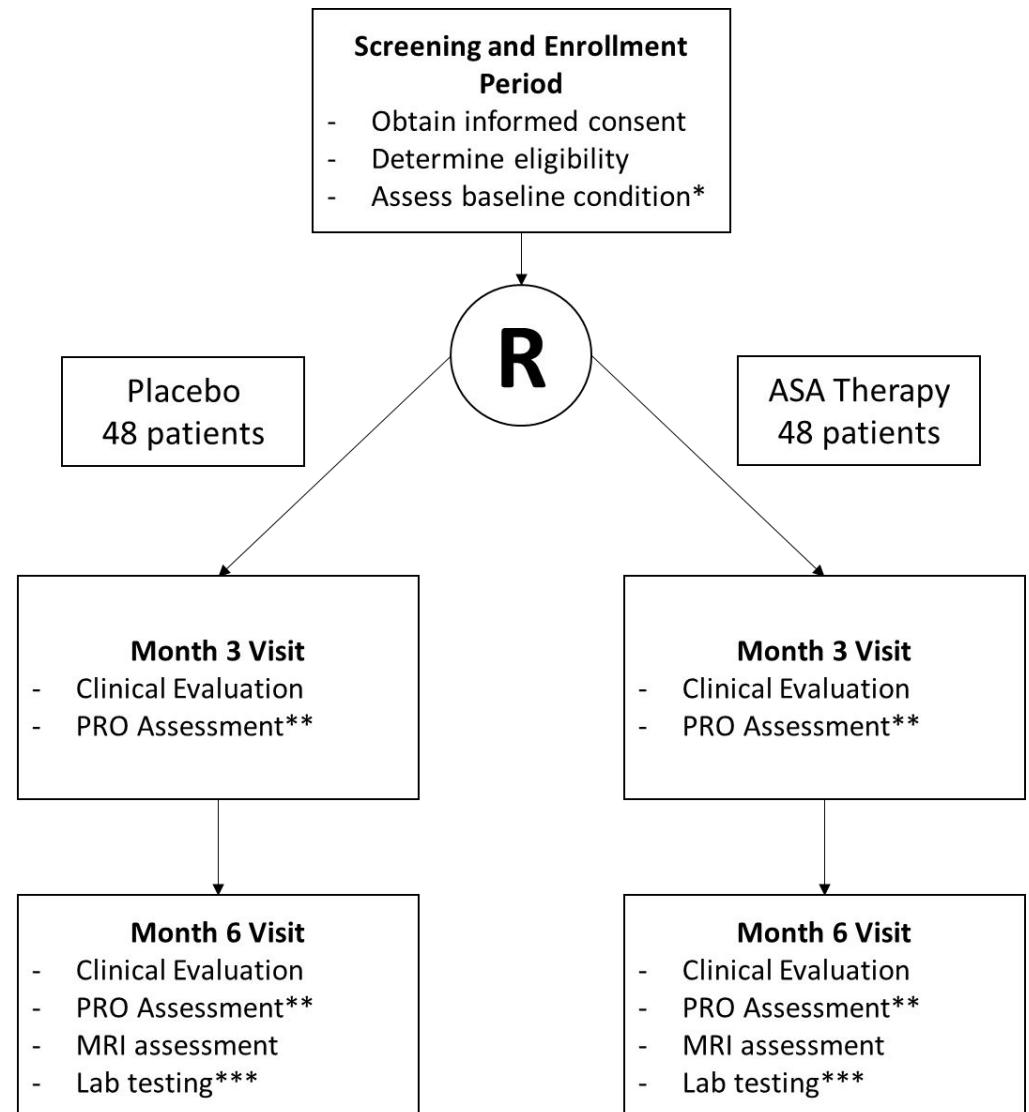
- Double-blinded, placebo-controlled randomized trial with crossover.
- Patients with symptomatic lymphatic malformation of the head and neck, ages 2-17.
- 96 patients: 48 assigned to treatment, 48 assigned to control
- Oral aspirin 30-50mg/kg/day rounded to the nearest half tablet (81mg) or equivalently-dosed rectal suppository
- 6 years - 5 year accrual period followed by 12 month follow-up period





# Randomization Phase

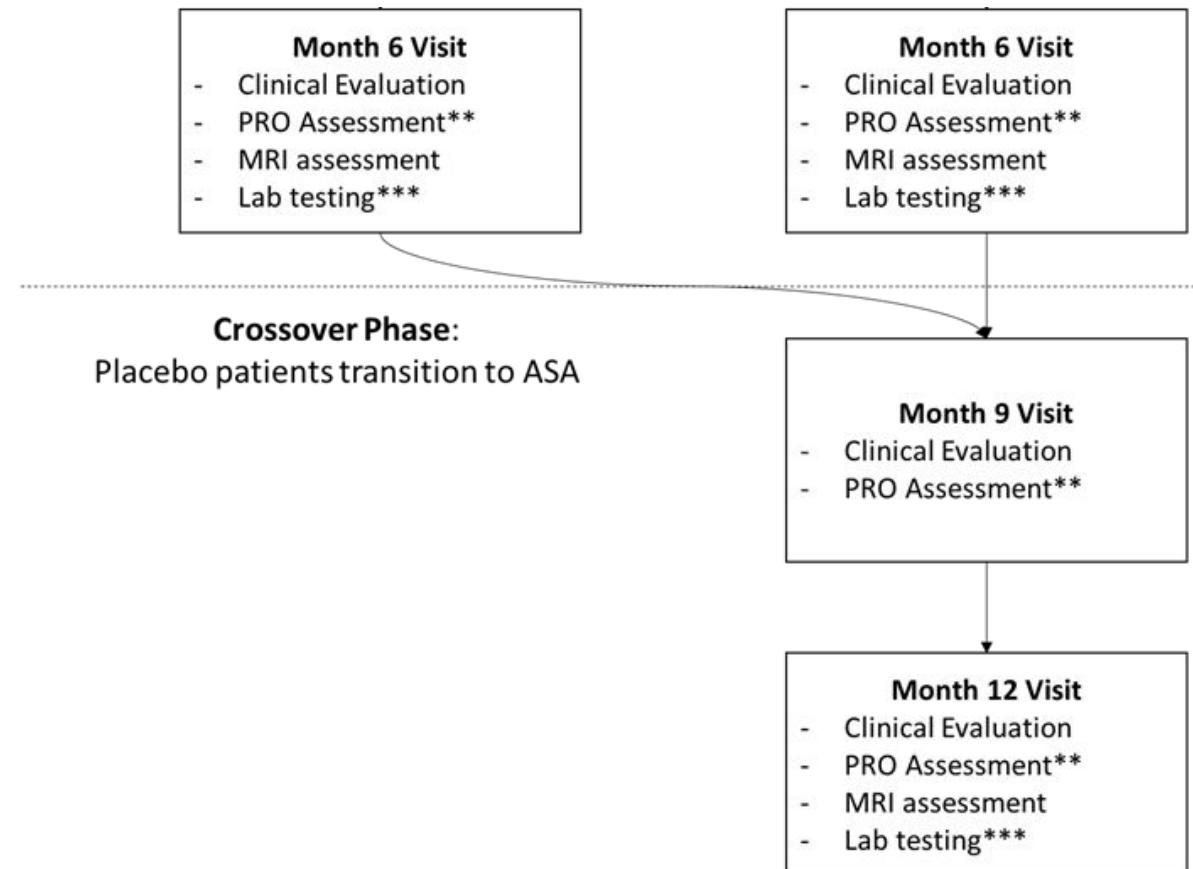
- Patients followed for 13 months
  - 1-month screening period
  - 6-month randomization period
  - 6-month crossover period





# Crossover Phase

- At 6 months:
  - Patients assigned to placebo crossover to ASA therapy
  - Patients assigned to ASA continue ASA therapy





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# Statistical Considerations



# Sample Size Calculation

- Our primary outcome is binary (patient clinical improvement: Yes/No)
- We expect the proportion of events for the ASA group to be 0.5, and the proportion of events for the placebo group to be 0.2. The effect size will be 0.3.
- Power = 0.9, type I error = 0.1, sample size for this trial N = 96



# 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.



# Primary Analyses

- Null Hypothesis: For pediatric patients with HNLM, 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.
- As we have a dichotomous primary outcome, we selected a Chi-squared test to examine the null and alternative hypotheses.



## Secondary Analyses

- We will examine whether the SAEs occurrence has different frequency between treatment and control group. We define a binary outcome for SAEs, and 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.
- We will report adherence based on self-report and weighing of pill bottles at clinical follow-up using frequency tables for both treatment and control arms; We assess patient healthcare utilization and time in healthcare by reporting summary statistics.



# Baseline Characteristics

- Summary statistics for baseline demographic
- 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.



**GRACIAS!**

Caño Cristales, Serranía de la Macarena, Meta, Colombia