Pediatric Trials Network

Efficacy, Safety and Pharmacokinetics of Topical Timolol in Infants with Infantile Hemangioma (IH)

NICHD-2015-TIM01

Phase 2 Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding Mechanism: Task Order

Protocol Date:	19 NOV 2021
Protocol Version:	8.0
IND Number:	129154
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NCT02913612

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Council for Harmonisation (ICH) E6(R2) guideline on Good Clinical Practice (GCP), and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (Human Subjects Protection), 21 CFR 312 (Investigational New Drug), 21 CFR part 50 (Informed consent), and 21 CFR part 56 (Institutional Review Boards [IRB]) as well as international regulatory requirements if applicable.

All individuals responsible for the design and/or conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the investigator brochure or product label, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the effectiveness and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all participants with informed consent forms, as required by government and International Council for Harmonisation regulations. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, part 312.64 as well as international regulatory requirements if applicable.

_____
Principal Investigator Name (Print)

_____ _____
Signature Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

The signature below documents the review and approval of this protocol and the attachments (e.g., package inserts), and provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

Pediatric Trials Network

Study Principal Investigator Name

Signature

Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AUC_{0-24}	Area Under the Concentration Time Curve 0-24 hours
AUC_{ss}	Area Under the Concentration Time Curve at Steady State
BP	Blood Pressure
BPD	Bronchopulmonary Dysplasia
BPCA	Best Pharmaceuticals for Children Act
BW	Birth Weight
CA	Calcium
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	Maximum Concentration
CRF	Case Report Form
DCC	Data Coordinating Center
DCF	Data Collection Form
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FiO_2	Fraction of Inspired Oxygen
FDA	US Food and Drug Administration
GA	Gestational Age
GAS	Global Assessment Scale
GCP	Good Clinical Practice
GFS	Gel-forming solution
HIG	Hemangioma Investigator Group
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDES	Internet Data Entry System
IEC	Independent or Institutional Ethics Committee
IH	Infantile Hemangioma

Abbreviation	Definition
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
K	Potassium
kg	Kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mcg	Microgram
MOP	Manual of Procedures
N	Number (typically refers to participants)
Na	Sodium
ng/mL	Nanogram per milliliter
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRN	Neonatal Research Network
PI	Principal Investigator
PICU	Pediatric Intensive Care Unit
PNA	Postnatal age
PMA	Postmenstrual age (gestational age plus postnatal age)
PK	Pharmacokinetic
PTN	Pediatric Trials Network
PTN POP01	Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care
QOL	Quality of Life
RAD	Reactive airway disease
SAE	Serious Adverse Event
TOF	Tetralogy of Fallot
TORO	Transfer of Regulatory Obligations
$t_{1/2}$	Half-life
VAS	Visual Analog Scale
Vss	Volume of distribution at steady state
WHO	World Health Organization

PROTOCOL SYNOPSIS

Protocol Title:	**Efficacy, Safety and Pharmacokinetics of Topical Timolol in Infants with Infantile Hemangioma (IH)**
Phase:	2
Product:	0.25% and 0.5% Timolol Maleate Gel Forming Solution (GFS) for topical application to IH
Objectives:	Primary: Describe the efficacy of 0.25% and 0.5% topical timolol maleate GFS as assessed through IH changes in volume Secondary: Describe the safety of topical timolol maleate GFS for treatment of IH Exploratory: Describe the pharmacokinetics (PK) of topical timolol maleate GFS for treatment of IH
Study Design:	Multi-center, double-masked randomized, efficacy, safety, and PK study
Study Population:	**Inclusion Criteria** 1. Documented informed consent from legal guardian 2. 0-84 days postnatal age at time of first study dose or when enrolled into the non-intervention cohort. 3. Clinical diagnosis of superficial cutaneous or mucosal infantile hemangioma (must include all of the following): a. Superficial lesion in the dermis b. Thin <2 mm in thickness c. ≥0.5 cm at its longest dimension and ≤10 cm^2 d. Involves skin or keratinized mucosa **Exclusion Criteria** 1. History of previous treatment with any pharmacologic or laser therapy for IH 2. Ongoing therapy with an oral beta blocker or oral corticosteroid (e.g., cardiac arrhythmia, adrenal insufficiency, upper airway obstruction, tetralogy of fallot (TOF), hypertension, reactive airways disease) 3. IH that requires systemic therapy (defined by dynamic complication scale >3) 4. IH of the non-keratinized mucosa 5. Infants with more than one hemangioma that requires therapy 6. Hemodynamically significant cardiovascular disease, as determined by the investigator 7. Known allergy to beta blockers or vehicle 8. Heart rate <100 beats per minute at screening visit 9. Known prenatal or postnatal diagnosis of $2^{nd}/3^{rd}$ degree atrioventricular block 10. History of Reactive Airways Disease (RAD) 11. Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study
Number of Participants:	Approximately 110
Number of Sites:	Approximately 10 sites

Duration of Participation:	Treatment arms: Up to 270 days (180 days of study drug plus 7 days of safety monitoring after last study dose for all adverse events and 90 days of safety monitoring after last study dose for adverse events of special interest). Non-Intervention cohort: Up to 180 days
Estimated Duration of study	Up to 2 years
Dose Schedule:	1:1 randomization to 0.25% versus 0.50% timolol GFS

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The Best Pharmaceuticals for Children Act (BPCA) mandates the National Institutes of Health (NIH) prioritize therapeutic areas in critical need for pediatric labeling, sponsor pediatric clinical trials, and submit these data to the United States Food and Drug Administration (FDA) for consideration for labeling changes. This study will be conducted in accordance with Section 409I of the Public Health Service Act; as such, the results from this research may be submitted to the FDA for review and use in negotiated labeling changes. This research study is contractually supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The NICHD awarded a contract to Duke University to establish the Pediatric Trials Network (PTN) through its Duke Clinical Research Institute (DCRI). The purpose of this contract is to facilitate trial design for studies supported by NIH. A separate contract was awarded to The Emmes Company to serve as the BPCA Data Coordinating Center (DCC).

Infantile hemangiomas (IH) are the most common tumor of childhood. In the United States, approximately 80,000 children per year are diagnosed with the tumor, 12-20% of which are significantly complex and require referral to specialists for consideration of treatment.
Complications of hemangiomas include permanent disfigurement, ulceration, bleeding, visual impairment, and airway obstruction. Hemangiomas occur exclusively in infants; therefore, efficacy, pharmacokinetic (PK), and toxicity data from older children and adults are not available. Furthermore, hemangiomas preferentially affect premature and low birth weight infants (<2500 g). According to a previous study, every 500 g reduction in birth weight below 2500 g results in a 25% increased risk of developing a hemangioma.[1]

Efficacy of systemic beta-blockers for the treatment of IH has been reported. Historically, agents with reported activity in treating IH include corticosteroids, interferon alpha, and vinca alkaloids. In 2008, the initial report of oral propranolol use for the treatment of IH was published.[2] This was followed by a number of case series describing its efficacy for IH.[3-9] Given propranolol's efficacy and immediate availability in a US suspension, it has rapidly been adopted as first-line therapy for IH.[2,10] Furthermore, a multicenter, randomized, double-mask placebo-controlled, industry-sponsored trial of a new formulation of oral propranolol has been performed and this formulation was approved by the FDA for treatment of IH.[10] In this study, 460 infants 1 to 5 months of age were randomized to either placebo or one of four dosing regimens. A rapid response to treatment was observed in 88% of infants receiving 3mg/kg/day by week 5.[10]

Despite its adoption as first-line systemic therapy for IH, the mechanism of action of oral propranolol for IH remains poorly understood. Investigators have proposed multiple mechanisms, including pericyte-mediated vasoconstriction, inhibition of vasculogenesis and catecholamine-induced angiogenesis, the disruption of hemodynamic force-induced cell survival, and the inactivation of the renin-angiotensin system.[11]

Pediatric dermatologists are using topical timolol despite limited efficacy, safety, or pharmacokinetic data. The success of oral propranolol for IH treatment has led many practitioners to use topical beta blockers off-label for the treatment of IH.[12] There are currently no commercially available forms of propranolol designed for application to the skin; however, intraocular preparations of timolol are commercially available. Similar to the initial reports on oral beta blockers, publications on the use of 0.25% or 0.5% timolol maleate gel-forming intraocular solutions applied directly to hemangiomas on the skin or mucosa for off-label use in IH are rapidly emerging.

Efficacy of topical application of timolol for IH: Numerous case reports and small studies, including those of premature infants, have reported growth arrest and reduction in thickness and redness of IH within 2 weeks to 4 months topical application timolol maleate, particularly in superficial lesions.[13-18] As a result, existing prospective studies of topical timolol for IH have focused on application to superficial IH rather than deeper lesions. In the largest available prospective study of 124 Chinese infants with IH, administration of timolol therapy directly to the IH for 4 months resulted in controlled growth of IH in 36/101 (36%) infants, and regression of IH in 56/101 (56%) infants. Only 3/23 (13%) infants in the control group had regression of IH.[18] In a retrospective study, investigators treated 73 infants (median age 4.3 months, 25th, 75th percentiles: 2.6, 7.2 months) for a mean of 3.4 months, and the mean visual analogue scale improvement at the last follow-up visit was 45%.[19] Previous investigators also conducted a prospective, placebo-controlled analysis of topical timolol efficacy in 41 infants, ages 5 to 24 weeks. Among those who received treatment, a higher proportion of IH decreased in size as assessed by the visual analog scale by >5% at week 20 compared to those who did not receive treatment, $p<0.02$.[20] In a study of 25 infants treated for 6 months, timolol was more effective when applied to thinner, plaque-type morphology than nodular superficial lesions.[17]

Outcome scales used to assess efficacy of treatment for IH:

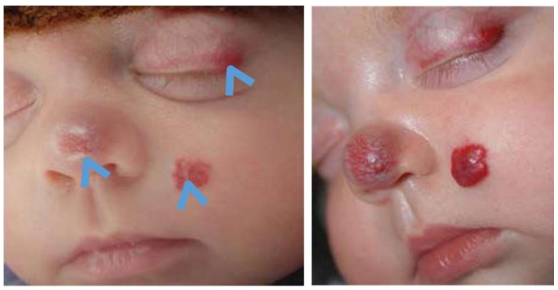


Figure 1. IH on tip of nose, cheek and eyelid demonstrating 3 dimensional growth over 3 week period.

Because most of the growth observed in IH is in tumor thickness not width, assessment of IH progression or regression has proven difficult with standard methods of measurement. Therefore, investigators have developed several scales to assess IH growth and efficacy of treatment for IH. All available scales are based on a shared concept of visual changes (progression or regression) at the determined endpoint compared to baseline or time zero, and aim to convert subjective improvement or worsening to quantitative measures. The visual analog scale (VAS) methodology is a widely accepted and frequently used measurement instrument for assessment of IH growth. When responding to a VAS item, raters specify the level of change from time zero to the endpoint (growth or regression) by indicating a position along a continuous line between two end-points. The best results are observed when lesional photographs are taken and a centralized assessment is made by unbiased, masked, and well-trained investigators. Although not formally validated, the VAS methodology has been used in several IH studies to evaluate response of IH to treatment with both topical and oral therapies. Most recently, a centralized VAS methodology was used in a study to gain FDA approval for an oral propranolol formulation for treatment of IH. Further, the VAS has demonstrated good agreement between masked observers, based on the intraclass correlation coefficient.[19,21,22] Studies have demonstrated the best interreader and intrareader reliability when primary efficacy is assessed by trained and validated raters using standardized digital photographs.[23]

Safety of topical application of timolol for IH: In contrast to oral propranolol for which safety data from a completed industry-sponsored trial exists, publications reporting the efficacy of topical timolol have not been subjected to the usual stringency of Phase 1/2/3 clinical trials. In addition, these studies have been relatively small in size and short in duration, with no pharmacokinetic data and little to no prospective safety monitoring; therefore, rare adverse events (AEs) may have been missed.

In a prospective study of 124 infants, parents reported no AEs related to study drug administration,

although investigators did not formally monitor bradycardia or hypotension.[18] In the retrospective analysis of 73 infants, parents reported sleep disturbance in one subject, but investigators reported no other AEs in the cohort.[19] In the prospective trial of 41 young infants, only 19 of whom were treated, investigators monitored heart rate and blood pressure at specified intervals until the end of the study. [20] There were no significant differences in heart rate or blood pressure between the treatment and observation groups.[20]

In contrast to the few documented AEs in the above studies, investigators documented episodic bradycardia in 4 of 22 infants who received Holter monitoring concomitant with timolol therapy for IH.[24] Two of these infants with clinically significant bradycardia had weights <2500 g at the initiation of therapy, both were <40 weeks postmenstrual age (PMA) at drug initiation, and both were receiving a timolol dose higher than most of the cohort.[24] In a case report of an infant treated with ophthalmic timolol and anti-glaucoma medications, the infant developed altered mental status, hypotonia, hypothermia, bradycardia, apnea, hypotension, and bronch- obstruction, and required intensive care.[25] A second case report documented apneic spells in a 2-week-old premature infant who was receiving timolol therapy for glaucoma.[26] Apneic spells ceased after discontinuation of timolol.[26] In the randomized trial that supported use of intraocular timolol maleate gel-forming solution (GFS) in children with glaucoma, 3 of 72 subjects (4%) developed bradycardia or hypotension.[27]

Pharmacokinetics of topical application of timolol for IH: Information regarding the PK of topical timolol in children is limited. Studies in adults with intraocular application have indicated systemic absorption of up to 80% of each drop of 0.5% timolol solution.[28] In a limited PK study (5 pediatric subjects) of intraocular application of 0.5% timolol solution, plasma timolol concentrations ranged from 3.5 ng/mL in a 5-year-old to 34 ng/mL in a 3-week-old.[29] Although the GFS form of timolol is thought to have lower systemic absorption compared to the solution, the likelihood of transcutaneous absorption is potentially increased when timolol is applied to the highly vascularized or ulcerated tissue of IH, or in the presence of occlusion (e.g., diaper hemangiomas).[12] Moreover, compromised barrier function of preterm infant skin and smaller volume of distribution relative to adults may lead to increased systemic absorption when compared to adults.[12] Previous investigators measured plasma concentrations of timolol 30 minutes after applying timolol solution to occluded skin over IH after treatment with fractionated CO_2 laser.[30] Timolol concentrations were below the limit of detection (20 pg/mL) in all 9 infants. An additional small study demonstrated absorption in all patients sampled (average of 0.18 ng/dL), but the biologic significance of this is unknown.[31]

Preliminary data on safety and outcomes of infants treated with topical timolol: The Hemangioma Investigator Group (HIG) conducted a retrospective, multicenter cohort study of topical timolol (applied directly to the hemangioma) solution for IH.[32] This study included 738 infants from 9 pediatric dermatology and vascular anomalies centers, thereby demonstrating the wide off-label use of topical timolol for IH. The majority of infants were prescribed timolol in the outpatient setting and none of these received prolonged monitoring. During the active growth phase (0-3 months of age) 51% of infants showed improvement after 3 months of therapy and 82% after 6-9 months of therapy. AEs were rare, occurring in 3.4% of infants and there were no serious adverse events (SAEs).[32] There were no serious cardiovascular adverse events.

Univariate and multivariate mixed-effects models showed that only initial IH thickness significantly predicted early improvement in size ($p = 0.0003$) and color ($p = 0.0001$ with IH <1 mm responding more quickly than IH 1-3 mm or >3 mm. The difference in response lost significance with longer duration of treatment, which may reflect natural involution of thicker lesions. While rebound growth with discontinuation of propranolol is well-recognized, optimal treatment duration for topical therapy to prevent rebound upon discontinuation has not been determined

Preliminary data collection on pharmacokinetics of topical timolol: Through the PTN study entitled "Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care (NICHD-2011-POP01)," PK evaluation of topical timolol in premature infants with IH is ongoing. Preliminary serum levels in our PTN sponsored study range from 0.03-66.4 ng/ml with a median of 1 (standard deviation 13.0) ng/ml. None of the infants in this cohort had signs or symptoms of beta blockade or adverse events from timolol.

Timolol clinical pharmacology and product label: Timolol maleate is a nonselective β-adrenergic receptor inhibitor formulated as a 0.25% and 0.5% solution, or GFS for ophthalmic administration. Timolol maleate was approved in 2007 for ophthalmic use for children <6 years of age with glaucoma. Safety and intraocular pressure-lowering effect of timolol maleate GFS 0.25% and 0.5% have been demonstrated in children in a 3-month, multicenter, double-masked, active-controlled trial. This trial included 107 subjects 1 week to <6 years of age who received 1 intraocular drop of either timolol GFS 0.25% or 0.5% once daily.[27] PK of timolol GFS was not assessed in this trial.[27]

According to the product label, contraindications for intraocular inoculation of timolol include: bronchial asthma (or history of), severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, and hypersensitivity to any component of the product.[33] These contraindications mimic those of other oral beta blockers in children and adults.

2.2 Scientific Rationale

Given the perceived safety of topical application of beta blockers for IH, continued off-label use is expected. Specifically, we predict a precipitous and wide-spread adoption of topical timolol (applied directly to the IH) for treatment of IH by primary care providers over the next 2-5 years. This phenomenon will expose many more infants to this drug. For example, when comparing the incidence of IH (1-4/100) to that of infantile glaucoma for which timolol is FDA approved (1/50,000), 80 times more infants will receive timolol for IH compared to glaucoma, even if only 10% of infants with IH receive beta blocker therapy. Given the likelihood for increased population exposure to topical timolol, and limited existing data about the efficacy, safety, and PK of different timolol formulations, the study of 0.25% and 0.5% topical timolol in a randomized, masked fashion represents an urgent public health need.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

2.3.1.1 Risks of Blood Drawing

There are small risks to blood sampling, usually some pain/discomfort with the blood stick and blood loss. Every effort will be made to avoid additional (to standard of care) sticks for this study and will time clinical blood draws to coincide with timed samples, using existing intravenous lines when possible.

2.3.1.2 Risks of topical timolol therapy

Transcutaneous absorption of topical timolol solution has not been extensively studied in adults or children. Application of topical timolol to highly vascularized or ulcerated tissue of infantile hemangiomas or under occlusion (e.g. diaper hemangiomas) may increase transcutaneous absorption, and pose a greater risk of adverse events associated with systemic beta-blockers. Effects of systemic beta blockade include bronchial hyperreactivity, hypotension, bradycardia, hypoglycemia, sleep disturbance, hypothermia, and changes in extremity color or temperature e.g., coldness. Infants with known baseline risk factors for bradycardia, hypoglycemia, or bronchial hyperreactivity will be excluded from enrollment according to the protocol's predefined

criteria. More specific to the topical application of timolol, irritation or dermatitis may occur.

2.3.2 Potential Benefits

Initial studies suggest efficacy of topical application of timolol in the treatment of IH, improving both the color and the volumetric size of the lesion. Treatment may also prevent functional complications. Topical treatment of IH with beta blockers will likely have an improved safety profile when compared to oral therapy although transcutaneous absorption has not been fully characterized. Conclusions drawn from this study will benefit infants receiving timolol in the future through better understanding of the efficacy and the characterization of the safety and PK profile of two different formulation strengths of this drug.

3 OBJECTIVES

Primary: Describe the efficacy of 0.25% and 0.5% topical timolol maleate GFS as assessed through IH changes in volume.

Secondary: Describe the safety of topical timolol maleate GFS for treatment of IH.

Exploratory: Describe the PK of topical timolol maleate GFS for treatment of IH.

3.1 Study Outcome Measures

3.1.1 Primary Efficacy Outcome

Partial response of hemangioma volume from baseline to 180 days within each treatment arm and compared with untreated controls.

3.1.2 Secondary Outcome Measures

1. Efficacy
    - Partial response of hemangioma color from baseline to 180 days within each treatment arm and compared with untreated controls
    - Comparison of partial response of hemangioma volume from baseline to 180 days between the two treatment arms
    - Comparison of partial response of hemangioma color from baseline to 180 days between the two treatment arms
    - Improvement of hemangioma complication in infants within each treatment arm
    - Assess time to partial response by comparing baseline to day 30, day 60, day 120 and day 180 in both treatment arms
    - Hemangioma Quality of Life assessment for infants within each treatment arm
2. Serious adverse events and adverse events of special interest in infants treated with topical timolol maleate (0.25% and 0.5%) GFS for the treatment of infantile hemangioma

3.1.3 Exploratory Outcome Measures

- Pharmacokinetics: Clearance (CL), Volume of distribution (V), Area under the curve (AUC), Maximum concentration (Cmax)
- Relationship between hemangioma characteristics and plasma concentrations

4 STUDY DESIGN

4.1 Study Design

This is a prospective, multi-center, double-masked, randomized, efficacy, safety, and PK study. Infants who satisfy all eligibility criteria will be randomized (1:1) to 0.25% or 0.5% timolol GFS and will be treated for a period of 180 days (Figure 1).

Randomization will be stratified using two age groups: <4 weeks postnatal age and ≥4 weeks postnatal age. Infantile hemangiomas are more common in preterm and low birth weight infants, therefore, it is expected that 10% of enrolled subjects will be preterm infants. Infants who are eligible for the study based on inclusion and exclusion criteria but whose parents decline treatment of the hemangioma will constitute the non-intervention arm of the study and will serve as a control group.

Infants who have progressive disease and require additional therapy as determined by the treating physician will be unmasked: if on the 0.25% timolol maleate GFS they will receive open label 0.5% timolol GFS two times a day and continue to be followed per the schedule of study procedures (Table 6-1). If they are on 0.5% the investigator may choose to continue the 0.5% open label or withdraw the participants from the Treatment Phase and proceed into the safety follow-up period and receive alternate therapies.

This study will be conducted in accordance with current U.S. Food and Drug Administration regulations and guidelines, (or, as applicable, international regulations and associated guidelines), the International Council for Harmonisation Guidelines on Good Clinical Practice (which incorporate the principles of the Declaration of Helsinki), as well as all other applicable national and local laws and regulations.

4.1.1 Study design for Control Cohort

Previous experience with clinical trials designed for IH treatment and performed in the US have demonstrated that parents are unlikely to enroll in double-masked, randomized, placebo- controlled studies. Therefore, two different strategies will be implemented to obtain age- matched control data. One strategy will include sharing of data and clinical photographs from two other completed randomized, placebo controlled studies in infants with IH. The patients in these studies are of similar age to our study and present similar IH characteristics. For the purpose of this study, the control group and the placebo groups from the two similar studies will serve as the untreated control cohort in our study.

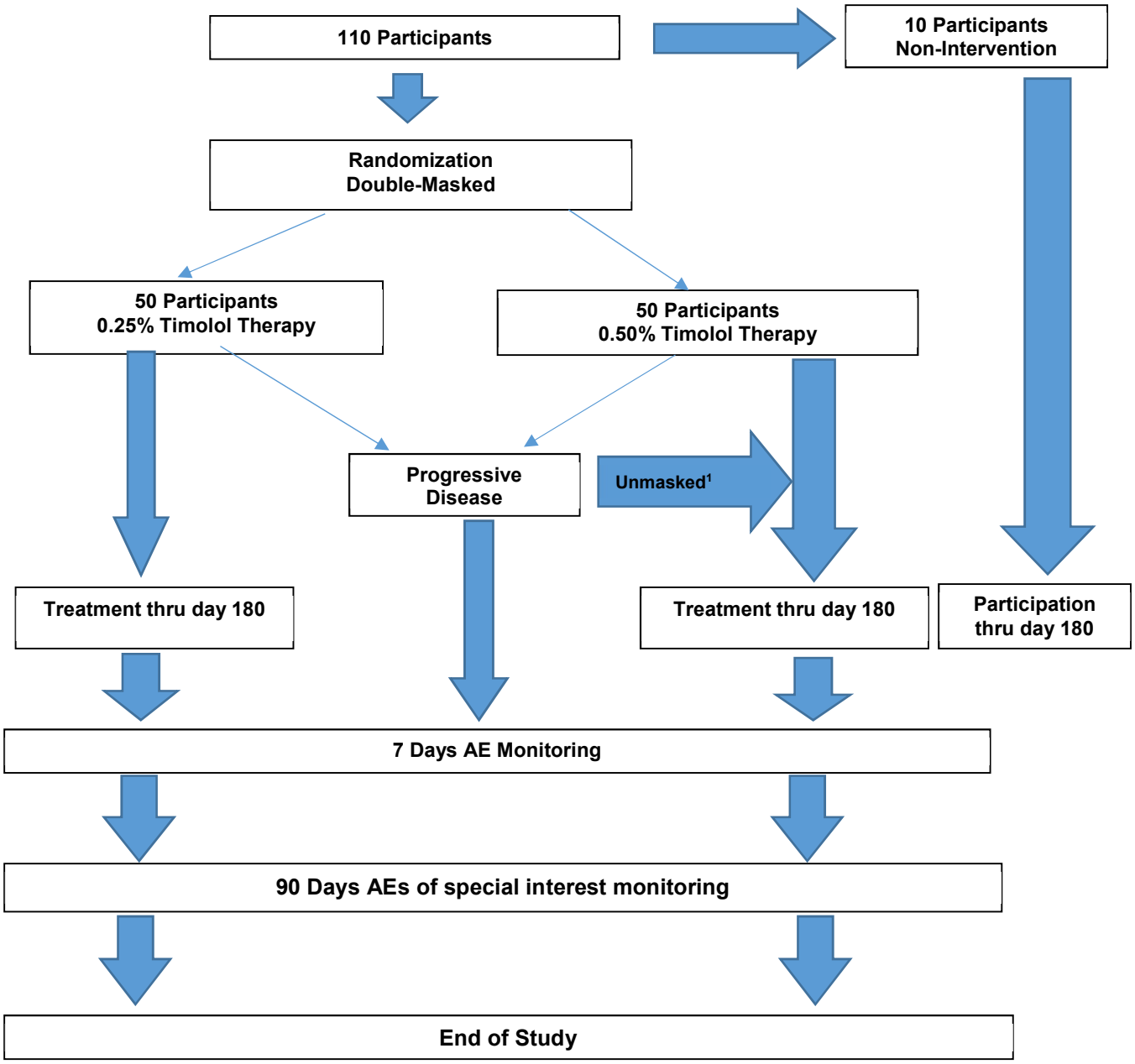
The first study identified is a recently completed prospective, single-center, double-masked, randomized, placebo-controlled efficacy study in Barcelona, Spain (Efficacy and safety of topical administration of timolol maleate 0.5% solution in the treatment of Child Proliferative Hemangioma Early Stage Surface. Randomized Controlled Study). This study has enrolled a total of 70 patients, 35 randomized to 0.5% timolol BID and 35 to placebo BID for 6 months. (EudraCT Number: 2013-005199-17). In addition, photographs from a second previously published double-masked, randomized, placebo-controlled trial (Australian and New Zealand Clinical Trials Registry Number: ACTRN12610001069044) are anticipated to be provided for analysis.[20] These studies are anticipated to provide paired clinical photographs of approximately 35 placebo-treated patients through up to 180 days following baseline.

As a secondary strategy, approximately 10 infants who are eligible for this study based on inclusion and exclusion criteria, but whose parents decide not to treat the IH, will be enrolled and also serve as a part of the untreated control cohort.

4.2 Duration of Study Participation

Duration of infant participation in the study is up to 270 days for infants in the treatment arms (180 days of study drug, 7 days of safety monitoring after last study dose for all adverse events and 90 days of safety monitoring after last study dose for adverse events of special interest) or 180 days for infants in the non-intervention arm.

Figure 1.



[1]Infants that cross from randomized, masked timolol maleate GFS to open label 0.5% timolol maleate GFS will continue to be followed per the schedule of study procedures (Table 6-1).

5 STUDY POPULATION

5.1 Selection of the Study Population

Young infants with superficial small hemangiomas in the proliferative phase and who have been identified by their treating physician as needing topical treatment with timolol maleate GFS will be considered for the study. For infants with more than one lesion, a target lesion (a lesion that will require treatment with study drug) will be identified. The infants will be administered study drug only on that lesion. Infants who are eligible for the study based on inclusion and exclusion criteria but whose parents decline treatment with timolol will be included in the non-intervention (control group) in the study.

The majority of recruitment is anticipated to be from outpatient pediatric dermatology clinics, but additional recruitment may occur from inpatient units including the newborn nursery and neonatal intensive care units.

5.2 Inclusion/Exclusion Criteria

5.2.1 Inclusion Criteria

1. Documented informed consent from legal guardian
2. 0-84 days postnatal age at time of first study dose or when enrolled into the non-intervention cohort.
3. Clinical diagnosis of superficial cutaneous or mucosal infantile hemangioma: (must include all of the following):
   a. superficial lesion in the dermis of the skin
   b. thin (<2 mm in thickness)
   c. ≥0.5cm at its longest dimension and ≤10 cm^2
   d. Involves skin or keratinized mucosa

5.2.2 Exclusion Criteria

1. History of previous treatment with any pharmacologic or laser therapy for IH
2. Ongoing therapy with an oral beta blocker or oral corticosteroid (e.g., cardiac arrhythmia, adrenal insufficiency, upper airway obstruction, tetralogy of fallot, hypertension, reactive airways disease)
3. IH that requires systemic therapy (defined by dynamic complication scale >3)
4. Infants with more than one hemangioma that requires therapy
5. IH of the non-keratinized mucosa
6. Hemodynamically significant cardiovascular disease, as determined by the investigator
7. Known allergy to beta blockers or vehicle
8. Heart rate <100 beats per minute at screening visit
9. Known prenatal or postnatal diagnosis of $2^{nd}/3^{rd}$ degree atrioventricular block
10. History of reactive airway disease (RAD)
11. Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study

5.3 Treatment Assignment Procedures

5.3.1 Additional Participants

If more than 10 total treated infants are withdrawn on or before the Day 30 visit or 20 total treated

infants are withdrawn at any time in the study for reasons other than lack of efficacy after randomization, additional infants may be enrolled. All infants receiving ≥1 dose of study drug will have safety follow up for at least 7 days after the last dose.

5.3.2 Randomization Procedures

Patients meeting eligibility criteria whose parents agree to treatment with timolol will be randomized in a 1:1 ratio to 0.25% or 0.50% timolol GFS. Randomization will be stratified by study site and age group: <4 weeks postnatal age vs ≥4 weeks postnatal age at time of randomization.

The infant's randomized treatment assignment will be obtained through the Advantage eClinical[SM] enrollment module. In the event that Advantage eClinical[SM] is not available at the time of randomization, a back-up system specified in the MOP will be used.

5.3.3 Reasons for Participant Withdrawal

5.3.4 Withdrawal from Treatment Phase (study drug dosing)

The clinician or family may choose to suspend study drug dosing for any reason during the study period, and the infant will remain in the study.

If at any time during the study, the treating physician determines that the target hemangioma failed therapy and the IH requires more aggressive surgical or alternate pharmacologic therapy (e.g., oral beta blockers, or oral or topical corticosteroids), the infant may be withdrawn from the Treatment Phase and move into the 7 day safety follow-up period. If the participant continues to participate in the study, they will be followed for safety for 7 days after last study dose, and should continue to return for planned study visit activities including photography of the IH.

If a treating physician chooses to withdraw the participant from the Treatment Phase (i.e. discontinue timolol maleate GFS dosing), the treating physician must immediately report this to the DCRI study PI and Protocol Chairs.

The investigator will withdraw a participant from receiving further study drug if:

1. Any clinically significant adverse event (AE) is deemed by the principal investigator to require discontinuation of study drug.
2. The treating physician determines that the target hemangioma failed therapy and requires alternate pharmacologic, laser or surgical intervention.
3. Participant develops ulceration of the target hemangioma after therapy is initiated.
4. Participant receives oral or intravenous corticosteroids or additional oral, intraocular, or topical beta blockers for treatment of any other conditions.
5. Requested by the NIH, FDA, DMC, or PTN.

5.3.5 Withdrawal of Consent for Study Participation

The infant's parents or legal guardians may withdraw consent voluntarily from participation in the study at any time. The infant's parent or legal guardian is not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/withdrawal section of the electronic case report form (eCRF).

Following withdrawal of consent, no study procedures or collection of data may occur.

5.3.6 Disease Progression Unmasking

Infants enrolled in the treated arms who are determined by the treating physician to have progressive disease will be unmasked and:

- If on 0.25% timolol maleate GFS they will receive open label 0.5% timolol GFS two times a day.
- If on 0.5% timolol maleate GFS the investigator may choose to continue study treatment with 0.5% open label, or withdraw the infant from the Treatment Phase and proceed directly into the 7 day safety follow-up period. Participants may receive alternate therapies during the safety follow-up period.

Infants that are unmasked and receive open label 0.5% timolol maleate GFS will continue to be photographed and followed per the schedule of study procedures (Table 6-1).

5.3.7 Randomization of Participants in the Non-intervention Arm

If at any time during the study the parents of an infant in the non-intervention arm change their mind and want timolol maleate GFS therapy, the infant will be randomized for participation in the study if there is a need for additional enrolled subjects and the infant meets the inclusion criteria and none of the exclusion criteria at the time of first dose.

5.3.8 Termination of Study

This study may be terminated at any time by FDA, NIH, the Investigational New Drug (IND) application sponsor, or upon recommendation by the Data Monitoring Committee (DMC).

6 STUDY PROCEDURES

6.1 Summary of Procedures

Table 6-1: Schedule of Study Procedures

	Screen/ Baseline	Treatment phase							
Time (Day)*	0[1] Visit #00/ Visit #01[8]	30 (±5 days) Visit #02	60 (±- 5 days) Visit #03	90 (± 5 days) Phone contact Visit #04	120 (± 5 days) Visit #05	150 (± 5 days) **Phone** contact Visit #06	180 (± 5 days) Visit #07	Day 7 (+ 5 days) Phone contact post 180 day study period or early withdrawal Visit #08	Day 270 (± 5 days) Phone contact Confirm ongoing therapy Visit #09
Informed consent	X								
Demographics	X								
Randomization	X								
Vitals: HR, BP[10]	X[8]	X	X		X		X		
Physical Exam of lesion[2]	X	X	X		X		X		
Photograph of lesion	X	X	X		X		X		
Medical History	X								
Physical Exam (systems assessment)[9]	X	X	X		X		X		
Actual Weight	X	X	X		X		X		
Study Drug Dispensation	X	X	X		X				
Review of Participant Diary (Treatment Administration Info)	X	X	X		X		X		
SOC Timolol Dosing Info (from Phone Script/Follow-up Diary)								X	X
Concomitant Medications	X	X	X	X	X	X	X	X	
Adverse Events	X[4,8]	X	X	X	X	X	X	X	X[3]
Blood sampling[5]	X	X	X		X		X		
Parent reported QOL Survey[7]	X		X				X		
Hemangioma Dynamic Complication Scale[6]	X	X	X		X		X		
Assessment for treatment failure		X	X		X		X		

[1] Refers to time point prior to start of study drug and may be the same calendar date as day 1.

[2] This includes treating physician's assessment by Visual Analog Scale (VAS) and measure of width and

thickness. Note: VAS should only be performed at visits 02, 03, 05, 07 and unmasking.

[3]AEs of special interest will include bradycardia, hypotension, new alteration in mental status, new local skin irritation, new sleep disturbance, apnea, bronchospasm, hypoglycemia, and diarrhea.

[4]AEs will be collected following initial study-specific procedure (e.g., screening, blood draws, dosing)

[5]For infants who are enrolled into the PK portion of the study; up to 3 samples will be obtained throughout the study period and at least one sample should be collected within 2 hours of dosing. Clinic visits for infants in the PK portion of the study will be scheduled to fall within the appropriate time period. Blood pressure and heart rate must be collected within 15 minutes before or after sample collection.

[6]The Hemangioma Dynamic Complication Scale must be collected for all participants.

[7]The parent-reported QOL survey is not required for non-English speaking parents.

[8]OUTPATIENT: When possible the participant should remain in clinic for 2 hours after the first application of timolol in order to monitor for heart rate and BP at 1 hour (+/-15 mins) and 2 hours (+/- 15 mins) after first application. The site PI must also monitor for signs of bradycardia, bronchospasm and hypoglycemia.
INPATIENT: All inpatients will be monitored for the first 24 hours for any signs of bradycardia or any other SAEs of special interest. Hospital staff must also
monitor BP and HR 1 and 2 hours after the first administration of timolol.

[9]If performed per local standard of care (SOC)

10 Blood Pressure Measurement should include systolic and diastolic measurements

*All visits (except for Day 7 post 180 days study period or early withdrawal) can occur within a 5 day window (±5 days). Day 7 post 180 day study period or early withdrawal must occur within a +5 day window (+5 days).

6.2 Screening/Rescreening

Infants 0-84 days postnatal age with IH will be screened for eligibility.

A participant may be rescreened if there is a transient disease status (e.g., parent/guardian reports a “cold or fever” and met a temporary delaying enrollment criterion of acute illness or fever). No participant may be screened more than twice due to a screening failure result.

6.3 Enrollment/Baseline

Research staff will obtain informed consent from the parent/guardian for all participants who satisfy eligibility criteria.

Once the informed consent has been obtained the following information will be recorded in the CRF:

1. Infant demographics, including birth weight and gestational age at birth and postnatal age.
2. Medical history (birth history and cardiac or pulmonary diagnoses)
3. Physical examination, including weight, height/length, baseline blood pressure, heart rate. Note, at the Baseline Visit, blood pressure* and heart rate must be at 1 hour and 2 hours after the first application of timolol.
4. Photographs and measurements of the IH. Collection of data on the clinical characteristics and measurement of width and thickness of the target hemangioma.
5. Adverse events following initial study-specific procedure (see Table 6-1)
6. Hemangioma Dynamic Complication Scale
7. Parental Hemangioma Quality of Life (QoL) screen
8. Concomitant Medications

* The preferred method of blood pressure collection is auscultation (i.e. manual), however, blood pressure may be collected via machine. Whichever method is used at visit #01 (baseline) should be used at all subsequent visits. Blood pressure measurements should include systolic and diastolic pressure measurements.

6.4 Treatment Period

6.4.1 Randomized Cohort

For those randomized to one of the two treatment arms the study drug Treatment period will include days 1 to 180 days for all infants.

Hospitalized infants who are enrolled in the study will be monitored for the first 24 hours for any signs of bradycardia or any other AEs or AEs of special interest. Hospital staff must also monitor heart rate and blood pressure at 1 and 2 hours (+/- 15 minutes) after the first application of timolol.

Data from a minimum of 25 outpatient infants remaining in clinic after initial application must be collected. Parents of all outpatient infants enrolled in one of the treatment arms will be requested to remain in or close to the clinic for a period of 2 hours after the initial application of timolol. Vital signs (heart rate and blood pressure) will be collected at 1(+/-15 mins) and 2 hours (+/-15 mins) after the first application of timolol. The infant will be monitored for signs and symptoms of an AE or AE of special interest during this period, particularly bronchospasm, arrhythmias, and hypoglycemia .

Thereafter, all infants enrolled in one of the treatment arms will have follow-up office visits at day 30±5 days, 60±5 days, 120±5 days, and 180±5 days and follow-up phone calls at day 90±5 days,150±5 days. Participants will be monitored by their parent/caregiver as instructed in the patient diary. For parents who have agreed to the PK portion of the study, at least one visit should be scheduled to occur within 2 hours of study drug administration when possible.

Parents will be instructed to administer the study medication immediately after or soon after feeding to avoid hypoglycemia. For each participant, the first application of topical timolol will be applied by the site study team (Site PI or designee).

During the office visits, the following procedures will be performed as specified in Table 6-1:

1. Physical examination, including weight, blood pressure, heart rate.
2. Photographs and measurements of the IH. Collection of data on the clinical characteristics, measurement of width and thickness of the target hemangioma, and color and volumetric size VAS assessments.
3. Hemangioma Dynamic Complication Scale
4. Adverse events/ solicitation of AEs of special interest
5. Parent Hemangioma QoL screen
6. PK sampling (see 6.8) for infants whose parents have consented to this portion of the study (optional). PK sampling will not be collected during the unmasking visit.
7. Concomitant medications
8. Timolol dosing log (to record dose, timing)
9. Weighing of the timolol bottle to verify compliance

During the phone calls, solicitation of concomitant medications and assessment of adverse events will be conducted and documented.

6.4.2 Non-intervention Cohort

Infants whose parents decline treatment with timolol will have follow-up office visits at day 30±5 days, 60±5 days, 120±5 days, and 180±5 days.

During the office visits, the following procedures will be performed as specified in Table 6-1:

1. Physical examination, including weight, blood pressure, heart rate.
2. Photographs and measurements of the IH. The treating physician will collect data

on the clinical characteristics and measure width and thickness of the target hemangioma and perform color and volumetric size VAS assessments.
3. Hemangioma dynamic complication scale for IH that are ulcerated or threaten function
4. Adverse events/ solicitation of AEs of special interest
5. Parent Hemangioma QoL screen
6. Concomitant medications

6.5 Follow-up Period

For treated participants, a follow-up period through day 7 (+5 days) after completing study drug or last study procedure, as applicable, will include solicitation of concomitant medications and assessment of adverse events/AEs of special interest.

For all treated participants that complete 180 days of treatment on study drug, the follow-up period through day 90 (±5 days) after study drug has been completed, will include solicitation of timolol dosing information and adverse events of special interest.

If a participant's last day of treatment phase ends after day 180 (+5 days) (e.g., out-of-window visit), site staff should continue the follow-up period for the full 90 days post last dose.

Infants who participate in the non-intervention cohort, will have no further follow up beyond 180 days.

6.6 Efficacy Assessment Using Centralized VAS

Efficacy will be determined at the end of the study by centralized evaluation of five standardized digital photographs (taken by investigators at each visit). All collected images from both arms of the study and the untreated control group will be evaluated in a masked fashion by expert pediatric dermatology Raters. Each study site will be given photographic equipment and a minimum of two individuals at each site will be trained to capture standardized photographs. Detailed information will be in the MOP and the photography vendor's User's Manual on how to take the pictures of the infant's hemangioma in order to obtain a systematic and consistent approach. All study and control photographs will undergo a centralized/standardized color calibration by the photography vendor before they are sent for assessment by the Raters. Two expert Raters and one Adjudicator will be trained on the Visual Analog Scale (VAS), how to recognize change in volume and color, and in the comparison of the hemangioma from baseline to study endpoint. However, assessment will initially be completed by 2 of the Raters. Adjudication by the Adjudicator will occur in a case of disagreement between the two Raters (see Rater's User's Manual). For the purpose of this study, a disagreement will be defined as a difference in both Raters' assessment concerning the treatment response categories on the VAS scale. Raters will use the VAS (see Section 10.1) to rate changes in volume and changes in color separately. Raters will be masked to both treatment assignment and timing of the digital photograph. Interreader and intrareader reliability of the Raters will be assessed prior to evaluation of study infants. The scores of the centralized Raters will be used to determine the success or failure of timolol therapy to obtain partial or complete regression of hemangioma in each study infant.

6.7 Laboratory Evaluations

When clinically indicated, investigators will evaluate infants for the presence of hypoglycemia (serum glucose < 60 mg/dL).

6.8 PK Sampling

Parents/guardians of infants in the treated groups will have the option to consent for PK blood draws, heel sticks, or finger sticks. **Refusal to provide consent for the PK portion of the study**

does not preclude involvement in the main study. Infants who have parental/guardian consent for the PK portion of the study will have up to 3 blood samples obtained during the study period and at least one sample should be collected within 2 hours of any dosing. Table 6-2 below outlines optimal sampling periods. Efforts should be made to obtain samples according to the sampling schedule; however, samples obtained outside of the sampling windows will not be considered protocol deviations. Blood pressure and heart rate must be collected within 15 minutes before or after sample collection.

Table 6-2: Optional sampling collection windows (relative to drug application)

Sample option*	Sampling Window
1	Within 2 hours
2	2-4 hours
3	5-7 hours
4	8-10 hours
5	11-12 hours (prior to repeat dose)

*** At least one sample should be collected within 2 hours of dosing.**

6.8.1 Minimizing Blood Loss

Blood samples will be collected in 250 µL aliquots. To minimize the amount of blood sampling, no more than 3 PK samples (750 µL in total) will be obtained from each infant for analysis.

6.8.2 Specimen Preparation, Handling, and Shipping

Detailed information will be in the MOP.

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

Dosing scheme

Parents/guardians or hospital providers will topically apply 1 drop [approx. 0.05 ml of timolol maleate 0.5% GFS, which is 0.25 mg, or approximately 0.05 ml of timolol maleate 0.25% GFS, which is 0.125 mg] twice daily soon after feeding, to the surface of the hemangioma. The site will remain uncovered unless ulcerated or under the diaper, in which case a bandage will be applied when possible. Parents will record daily dosing in a log. Written instructions on how to apply study drug on the hemangioma will be provided to the parents at time of randomization and/or first study drug dispensing; the study site team (PI or designee) will show the parents how to apply the correct dose (i.e., drop) by applying the first treatment. Detailed instructions will be provided in the MOP. At each visit study drug bottles will be weighed to verify compliance. A discrepancy of >0.75g (+/-) between the expected bottle weight and the actual bottle weight at Visits 02 and 03 will be recorded as a protocol deviation. A bottle weight discrepancy of >1.5g (+/-) at Visits 05 and 07 will be recorded as a protocol deviation. Participants will not be early terminated because of a bottle weight discrepancy or participant non-compliance.

A deviation for participant non-compliance will be recorded if:

A participant has 12 or more missed doses per visit (previous 30 days of the treatment period)

A participant has 72 or more missed doses over the 6-month treatment period

A participant has 4 consecutive missed doses.

7.2 Formulation, Packaging, and Labeling

Any requisite clinical trial materials will be provided with labeling in accordance with all applicable regulatory requirements. Detailed information will be part of the MOP.

7.3 Product Storage and Stability

All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements provided by the Sponsor. Detailed information will be part of the MOP.

7.4 Other Medications/Treatments

The following concomitant medications are not permitted during the study:

1. Topical corticosteroids applied to the IH (topical corticosteroids used on areas unaffected by IH are permitted)
2. Oral or intravenous beta blockers
3. Oral or intravenous corticosteroids

All other drugs are permitted while on study.

8 ASSESSMENT OF SAFETY

8.1 Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Safety will be assessed in all infants following initial study-specific procedure through 7 days (+5 days) post last study dose or last study procedure, as applicable, and will be assessed by frequency and incidence of AEs and SAEs. Those outpatient infants whose parents are willing and able to remain in clinic for a period of 2 hours after the initial application of timolol will also have vital signs (heart rate and blood pressure) collected at 1 hour and 2 hours (+/- 15 mins). The infant will be monitored for signs and symptoms of an AE or AE of special interest during this period, particularly bronchospasm, arrhythmias, and hypoglycemia.

Inpatient infants will be monitored by hospital staff. Hospital staff will collect vital signs (heart rate and blood pressure) 1 and 2 hours after the initial application of timolol and monitor for signs of an AE or AE of special interest during this period.

For all treated participants that complete 180 days of treatment on study drug, the follow-up period through day 90 (±5 days) after study-specific drug has been completed will include solicitation of adverse events of special interest only. Infants whose parents decline treatment with timolol will have no further follow up beyond 180 days. Refer to Figure 1 and Table 6-1. A safety monitoring committee (DMC) will be convened by NIH to review data and safety information from study infants throughout the study.

8.1.1 Adverse Event

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. (Any change in clinical status, routine labs, x-rays, physical examinations, etc.), that is considered clinically significant by the study investigator is considered an AE.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A reasonable possibility implies that there is evidence that the drug caused the event.

Adverse reaction is any adverse event caused by the drug.

Serious adverse event or **serious suspected adverse reaction** or **serious adverse reaction** as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

1. Death
2. Life-threatening AE (“life-threatening” means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.1.2 Adverse Events of Special Interest

In addition, we will specifically evaluate infants for the following adverse events of special interest:

1. Bradycardia (need for pharmacologic intervention, or a persistent heart rate below 100 while awake and alert after drug administration) (per study clinician or per parent report if informed by another clinician)
2. Hypotension (need for pharmacologic intervention, or blood pressure < 80% standard values for age) (per study clinician or per parent report if informed by another clinician)
3. New alteration in mental status (e.g., drowsiness, lethargy) (per study clinician or parent report)
4. New local skin irritation (per study clinician or parent report)
5. New sleep disturbance (per study clinician or parent report)
6. Apnea (per study clinician or parent report)
7. Bronchospasm (evaluated by study clinician when clinically indicated or per parent report if informed by another clinician)
8. Hypoglycemia (serum glucose < 60 mg/dL) (evaluated by study clinician when clinically indicated or per parent report if informed by another clinician)
9. Diarrhea (per parent report)
10. Arrhythmias

8.1.3 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert or investigational plan.

8.1.4 Identification of Events and Timeframe for Reporting

Pre-existing conditions will not be considered as adverse events. New events that occur or pre- existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be reported in the electronic case report form (e-CRF). The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome.

Any event excluding adverse events of special interest beginning more than 7 days after the last dose of study drug or last study procedure will not be reported. For participants in the treatment arm adverse events of special interest only will be reviewed and reported at 90 days after the last dose of study drug.

8.1.5 Follow-up of Adverse Events

All events (study-related or not) must be followed to adequately evaluate the infant's safety or until the event stabilizes/resolves. Any safety event that is identified at the last assessment (or an early termination) must be recorded on the appropriate eCRF with the status of the safety event noted. All serious suspected adverse reactions and serious adverse reactions will be followed until resolution or until the infant is medically stable. All other events that cannot be resolved by 37 days after the last study dose or last study procedure, as applicable, will have the status of the ongoing event entered in the electronic data capture (EDC) system at that time.

8.1.6 Guidelines for Assessing Grade of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required.
2. **MODERATE**: Participant experiences enough symptoms or findings to require

intervention.
3. **SEVERE**: Participant experiences symptoms or findings that require significant intervention.

8.1.7 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug, where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the drug caused the event? ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.1.8 Discontinuation of a Participant Due to Adverse Events

Infants may be withdrawn from the study at any time. Infants withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator until the clinical outcome from the AE is determined. Any infant who experiences an AE may be withdrawn at any time from the study at the discretion of the investigator. The AE(s) should be noted on the appropriate CRFs, and the infant’s progress should be followed until the AE is resolved or considered stable. The Medical Monitor and the Protocol Chair/PI must be notified.

8.1.9 Reporting Procedures

Information about AEs will be solicited by investigators and study coordinators.

All adverse events will be entered into the safety data system within 7 days of study staff identification. Serious events will be entered into the data system within 24 hours of study staff identification. If there are any technical difficulties, the SAE will be reported by direct communication with the Medical Monitor.

8.2 Serious Adverse Events

Any serious adverse event entered in the safety database will generate an automatic email notification to the DCC, IND sponsor and funding sponsor. The DCC medical monitor will review all SAEs at the time that they are reported but no later than one business day. Investigators must also submit safety reports locally as required by their IRB.

8.3 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The IND sponsor will submit expedited safety reports (e.g. IND safety reports) to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB. Documentation of the submission and receipt by the IRB must be retained for each expedited safety report.

All serious events irrespective of their designation as “related” or “not related” to study product(s) will be reported to the FDA at least annually in a summary format.

8.4 Safety Oversight

The DMC will review serious adverse events at regularly scheduled meetings. In addition, a qualified and experienced clinician not otherwise associated with this protocol will serve as the medical monitor. The medical monitor will review all SAEs at the time they are reported. If safety concerns are identified, the medical monitor may request a meeting of the DMC to review safety data. At a minimum, the medical monitor will comment on the outcomes of the SAE and causal relationship of the SAE to the study product. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator. If no SAEs prompt review at an earlier time point, the DMC will review AEs and SAEs at the regularly scheduled meeting. The DMC will convene and make recommendations on termination of the study based on review

of safety reports and halting rules. The safety data will be compiled by DCC. Based on the recommendations of the DMC, NIH and IND sponsor will make a decision to terminate or continue the study.

8.5 Halting Criteria: Safety Concerns

The trial will be halted (paused) for a safety review by the DMC if there are 2 or more Serious Adverse Reactions.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCRI sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations (TORO), NIH, FDA, or its designee will conduct site-monitoring visits as detailed in the monitoring plan or in the manual of procedures.

Site visits will be made at standard intervals as defined by the site monitoring plans and may be made more frequently as directed by the IND sponsor. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

10 STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

Efficacy Categories for IH volume:

Progressive disease: >20% *increase* in hemangioma volumetric size

Partial response: >20% and up to 80% *reduction* in volumetric size of hemangioma

Complete/near complete response: >80-100% *reduction* in volumetric size of hemangioma

Stable disease: none of the above or between 20% *increase* in hemangioma volumetric size and 20% *reduction* in volumetric size

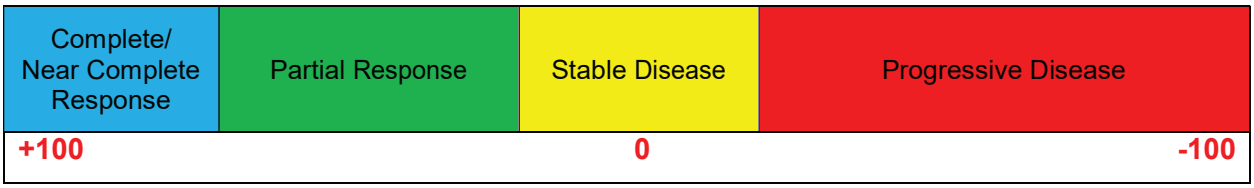
Efficacy Categories for IH Color:

Progressive disease: >30% *increase* in hemangioma color

Partial response: >30% and up to 80% *reduction* in color of hemangioma

Complete/near complete response: >80-100% *reduction* in color of hemangioma

Stable disease: none of the above or between 30% *increase* in hemangioma color and 30% *reduction* in color



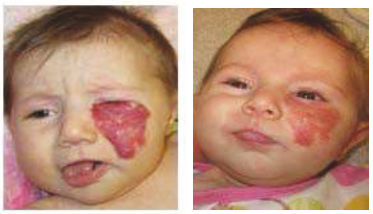
Visual Analog Scale (VAS)[21]: 100 mm scale used to independently grade volume and color

-100 indicates hemangioma has doubled in volumetric size/color: twice as intense

0 indicates no change

+100 indicates complete shrinkage or complete resolution of volumetric size/color

The **partial response** or greater of hemangioma will be based on centralized VAS-volume and VAS-color scores from baseline to Day 180 in both treatment arms assessed by three independent, expert and masked pediatric dermatologists (Section 6.6).



Example of partial response in VAS- volume after 32 days of timolol treatment.

Primary Efficacy Endpoints:

Estimation of the proportion of infants with partial response in hemangioma volume (partial response or greater as assessed by VAS-volume) from baseline to day 180 within each randomized treatment arm and compared with the untreated controls.

Secondary Endpoints:

Secondary **efficacy** endpoints will include the following:

1. Estimation of the proportion of infants with partial response in hemangioma color (partial response or greater as assessed by VAS-color) from baseline to day 180 within each randomized treatment arm and compared with the untreated controls.
2. Comparison of partial response of hemangioma volume (partial response or greater as assessed by VAS-volume) between the two treatment arms.
3. Comparison of partial response of hemangioma color (partial response or greater as assessed by VAS-color) between the two treatment arms.
4. Absolute change in hemangioma dynamic complication scale from Day 0 to end of study within each treatment arm.
5. Assess time to partial response by comparing baseline to day 30, day 60, day 120 and day 180 in both treatment arms.
6. Absolute change in IH-QoL score scale from Day 0 to end of study within each treatment arm.

Secondary **safety** endpoints are the rate of serious adverse events and adverse events of special interest (Section 8.1.2) from randomization to Day 180 in infants treated with topical timolol maleate (0.25% and 0.5%) GFS for the treatment of infantile hemangioma.

Exploratory Endpoints:

Exploratory PK endpoints include estimation of PK parameters such as clearance (CL), volume of distribution (V), area under the curve (AUC), and maximum concentration (Cmax), as possible.

The relationship between different hemangioma characteristics and plasma concentrations may also be described as an exploratory endpoint.

Treatment Failure for Partial Response in Hemangioma Color or Volume

The infant will be considered a treatment failure for the primary endpoint of partial response of VAS-volume or the secondary endpoint of partial response of VAS-color from baseline to Day 180 if any of the following conditions are met:

1. Partial response not achieved at the Day 180 visit in infants who complete the 180-day treatment period.
2. Infant withdrawn from masked treatment due to progressive disease. This will include participants randomized to the 0.25% treatment arm and switched to the 0.5% treatment arm.
3. Ulceration of the target hemangioma after initiation of masked treatment.
4. Infant withdrawn from study treatment due to safety concerns.
5. Study drop-out or loss to follow-up after the 30-day visit and before the 180-day visit for reasons other than progressive disease, ulceration, or safety concerns without having achieved partial response at the last study visit before drop-out.

Partial response will not be evaluated in participants who drop-out from the study for reasons other than progressive disease, ulceration, or safety concerns or are lost to follow-up before the 30-day visit. Sensitivity analyses will be performed to assess the impact of assumptions made to account for drop-out on the primary analysis. This will include summaries of partial response that exclude participants who withdrew for reasons other than lack of efficacy. Other methods, such as multiple imputation, may be considered based on drop-out rates and cause of missingness.

In addition to the assessments of partial response through the 180-day visit, the proportion of participants who achieve partial response through each study visit will be summarized. The number of participants with partial response before but not at the 180-day visit will be summarized.

10.2 Study Hypotheses Tested

For the primary analyses of treatment efficacy, let p_{RC} be the proportion with partial or greater response in hemangioma volume for the control cohort, p_{R25} the proportion with partial or greater response in hemangioma volume for the 0.25% arm, and p_{R50} the proportion with partial or greater response in hemangioma volume for the 0.5% arm. The following set of hypotheses will be assessed:

Hypothesis 1 (H_1): The partial response proportion in the 0.5% arm is greater than the partial response proportion in the control cohort.

Null hypothesis H_{10}: $p_{R50} \leq p_{RC}$

Alternative hypothesis H_{1A}: $p_{R50} > p_{RC}$

Hypothesis 2 (H_2): The partial response proportion in the 0.25% arm is greater than the partial response proportion in the control cohort.

Null hypothesis H_{20}: $p_{R25} \leq p_{RC}$

Alternative hypothesis H_{2A}: $p_{R25} > p_{RC}$

A secondary efficacy hypothesis comparing treatment arms will also be tested:

Secondary efficacy hypothesis (H_3): The partial response proportion in the 0.25% arm is not equal to the partial response proportion in the 0.5% arm.

Null hypothesis H_{30}: $p_{R25} = p_{R50}$

Alternative hypothesis H_{3A}: $p_{R25} \neq p_{R50}$

The α=0.05 level will be used for hypothesis testing. Hypotheses will be tested with chi-square or Fisher's exact tests. A Bonferroni multiplicity correction will be applied to the α level for the primary hypotheses. Response proportions will be further compared between groups using the odds ratio or estimated differences in proportions and corresponding confidence interval estimates.

10.3 Sample Size Considerations

Sample size calculations for primary efficacy hypotheses assume that 35 participants will have evaluable data in the untreated control cohort. The following success rates are assumed: 0.15 response proportion in the control cohort, 0.45 response proportion in the 0.25% arm, and 0.50 response proportion in the 0.5% arm. With 45 participants in each treatment arm and α = 0.05 as in Section 10.2, this gives the efficacy hypothesis comparing the 0.5% and control arms a power of 93% and the efficacy hypothesis comparing the 0.25% and control arms a power of 85% after applying the Bonferroni multiplicity correction to the alpha level. The study sample size of 100 randomized participants was determined by assuming that up to 10% of randomized infants will drop out with unevaluable partial response.

Sample size calculations for the secondary safety analyses assume that approximately 20% of participants will experience an AE of special interest and 5% will experience an SAE of special interest.[24,32] With 100 participants across the two treatment groups, 95% Wilson score confidence intervals are (0.02,0.11) (confidence interval width=0.09) for SAEs and (0.13,0.29) (confidence interval width=0.16) for AEs. These intervals are thought to be sufficiently precise for the estimation of key event rates. The probability is 0.63 and 0.99 that at least one event will be seen in the study population for rare events with probabilities 0.01 and 0.05, respectively, of occurring.

10.4 Analysis Plan

10.4.1 Population for Analysis

All randomized infants who received study dose and non-randomized participants enrolled in the untreated control cohort will be included in the intent-to-treat population. The primary analysis will use the intent-to-treat population with treatment group determined by randomization assignment.

All infants enrolled and receiving at least one dose of timolol therapy will be included in the safety population and the safety analysis. All infants who had at least one interpretable PK sample will be included in the PK analysis.

10.4.2 Descriptive Statistics

Descriptive statistics such as number of observations, mean, median, standard deviation, standard error, minimum and maximum will be presented by groups for continuous variables (such as age, weight, etc.). Other descriptive statistics such as counts, proportions, and/or percentages will be presented by group to summarize discrete variables (such as race, sex, etc.). Participant disposition will be summarized, including the number of infants completed and early terminated from the study and the reasons for termination.

10.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will also be summarized. Variables include race, postnatal age, gestational age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized in terms of number of days of dosing and reasons for final discontinuation of study drug.

10.4.4 Efficacy Analysis

Key efficacy endpoints are summarized in Section 10.1. Chi-square or Fisher's exact tests will be used to test response proportion hypotheses at study end. Response proportions will be further compared via odds ratio, difference in proportion, and confidence interval estimates.

Further adjusted analyses taking into account postnatal age, gestational age, and other baseline or demographic covariates of interest via logistic regression will be performed. Differences between studies used for the control data will be assessed.

As discussed in Section 10.1, randomized participants who switch to unmasked treatment with timolol maleate 0.5% GFS due to disease progression will be classified as treatment failures in the primary analysis. VAS scores following the switch to unmasked treatment will be analyzed as a secondary analysis. Both the VAS assessment of change from study baseline and change in VAS score from the time of treatment switching will be summarized in this secondary analysis. The duration of unmasked treatment will be summarized. Partial response of color or volume from the start of randomized treatment will be evaluated in participants who switch treatment using data collected after the treatment switch.

Additional secondary efficacy variables for analysis between randomized treatment arms include severity of the hemangioma, time to partial response, and quality of life measurement variables. Absolute change in overall severity will be measured via hemangioma dynamic complication scale from baseline to Day 180 within each treatment arm. Absolute change in quality of life will be measured via IH-QoL score scale from baseline to Day 180 within each treatment arm. Linear mixed effects modeling techniques will be used to analyze changes in the quantitative VAS scores, severity scale, or quality over time, and adjustments for demographic covariates of interest will be considered.

10.4.5 PK Analysis

If possible, PK parameters will be estimated by the population PK approach using non-linear mixed effects modeling in NONMEM. The relationship between hemangioma characteristics (e.g. hemangioma thickness, timolol formulation, sex, application site, hemangioma surface area, ulceration, or occlusion) and study drug concentration will be estimated. Timolol data from the Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care study (PTN POP01) will be combined with the data obtained from this study for the exploratory PK analysis.

10.4.6 Safety Analysis

The number and percent of AEs and SAEs will be summarized overall and by each Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Prior and concomitant medications will be summarized by World Health Organization (WHO) drug class. Summary statistics for proportion of infants with AEs of special interest will be presented. The equality of AE and SAE event rates will be tested between treatment arms as an exploratory analysis.

11 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Clinical study sites will permit access to such records.

The principal investigator will ensure that the use and disclosure of personal health information obtained during this research study complies with the Federal Privacy Regulation. In the U.S., the Health Insurance and Portability and Accountability (HIPAA) Privacy Rule applies. The rule provides U.S. federal protection for the privacy of protected health information sent to or collected in the U.S. for the purposes of this research by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. “Authorization” is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the applicable Federal Privacy Regulations. The relevant privacy authorization will be combined in the informed consent document (approved by the IRB).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. The CoC limits the ability of courts and other agencies from forcing the study team to share participant information or body fluids during a legal or legislative action without the participant’s permission. The CoC does not restrict the parents from sharing information voluntarily.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the infant's parent or legal guardian agreeing to participate in the study and continuing throughout the infant's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided with the infant's parent(s) and/or legal guardian (if applicable). Consent forms describing in detail the study procedures and risks will be given to the infant's parent(s)/legal guardian, and documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and local IRBs will determine whether one or two parent signatures are required based on the risk level of study or local regulatory requirements. The infant's parent(s)/legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the infant's parent(s)/legal guardian and answer any questions that may arise. The infant's parent(s)/legal guardian will provide informed consent prior to the conduct of any study procedures. The infant's parent(s)/legal guardian should have the opportunity to think about the study prior to allowing the infant to participate. The infant's parent(s)/legal guardian may withdraw consent at any time throughout the course of the study. A copy of the executed informed consent document will be given to the infant's parent(s)/legal guardian for their records. The rights and welfare of the infants will be protected by emphasizing to their parent(s)/legal guardian that the quality of their medical care will not be adversely affected if they decline to allow their infant to participate in this study. For non-English speakers, a fully translated consent or an oral presentation accompanied by a short form may be used to obtain informed consent. The fully translated consent and the short form must be approved by the IRB and executed according to local requirements.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the infants' risk to receive the investigational product. This new information will be communicated by the investigator to infants' parent(s)/legal guardian who have consented for their infant to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and infants' legal guardians will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to informed consent; however, before any protocol-specific procedures are performed to determine protocol eligibility, informed consent must be obtained and properly executed. The investigator will choose infants in accordance with the eligibility criteria detailed previously. To prevent bias, the investigator will not exercise selectivity.

By providing consent, the infant's parent/legal guardian agrees that the infant will complete all evaluations required by the trial, unless the infant's parent/legal guardian withdraws the infant voluntarily or the infant is withdrawn from the trial for any reason.

13 FUTURE USE OF STUDY DATA AND STORED SPECIMENS

After study-specific testing is complete, information about the study, including study data, will be de-identified and submitted to the NIH data repository (https://dash.nichd.nih.gov; referred to below as “DASH”) in compliance with NIH policies on data sharing. Other researchers may submit requests to DASH to use these data for future, unspecified research. The NICHD DASH Data Access Committee reviews all requests to determine whether the proposed use of the data is scientifically and ethically appropriate.

The de-identified photographs that were sent to the external raters and adjudicator will be destroyed after all study analyses and the FDA review of the study results are complete.

PK samples will be labeled at the site with a study-provided barcode label. The barcode will only contain a unique code number without protected health information (PHI) or any other information that could identify the study participant. These samples will be stored at the site and then shipped to a central lab for study-specific PK testing. After analysis, these PK samples will be stored until the FDA completes review of the final research study report and proposed drug label changes. Once FDA review of the study results is complete, the samples will be destroyed. No other biospecimens will be collected or stored in this study.

14 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

An electronic case report form (eCRF) will be used to record participation data. The eCRF will be used for the recording of all historical participant information and study data as specified by this protocol. The eCRF must be completed by designated and trained study personnel.

According to ICH E6(R2), source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, infant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x- rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico- technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the regulatory binder at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts, and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- Manual of Procedures
- Informed consent form (blank)
- Signed informed consent form
- Revised informed consent forms and/or all addenda (blank)
- IRB registration or other documentation of IRB compliance with FDA regulations
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2), Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Case report forms will be derived from the eCRFs and provided by the Data Coordinating Center (DCC).

15 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, case report forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

Clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the PI, and NIH.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

16 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

16.1 Ethical Standard

The investigator will ensure that the study will be conducted in accordance with the protocol, the ethical principles of Good Clinical Practice [ICH E6(R2)] that have their origin in the Declaration of Helsinki, and all applicable national and local regulations. The investigator will ensure that the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs.

16.2 Institutional Review Board

Prior to enrollment of infants into this trial, the protocol, the informed consent form, and any materials or advertisements presented to infants' parent/legal guardian will be reviewed and approved by the appropriate IRB.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's federal-wide assurance number (if applicable) will be provided to the DCC.

If amendments to the protocol are required, the amendments will be written by the sponsor and provided to the investigator for submission and approval to the IRB.

16.3 Study Discontinuation

If the study is discontinued, enrolled infants will continue to be followed for safety assessments for 7(+5) days. All adverse events must be followed through resolution.

17 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable local laws, and the International Council for Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all expedited safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Case report forms will be derived from the eCRFs and provided by the DCC to the sites to record and maintain data for each participant enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF should be consistent with the case report form/source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the case report forms and eCRFs.

17.1 Data Management Responsibilities

All case report forms and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

The DCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

17.2 Data Capture Methods

Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant internet data entry system provided by the DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the case report forms/source documents/take home logs.

Timolol data from the PTN POP01 study will be combined with the data obtained from this study for the exploratory PK analysis.

17.3 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected periodically.

17.4 Study Records Retention

Records and source documents pertaining to the conduct of this study must be retained by the Investigator for a period of 2 years following the date the application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA

is notified. No records will be destroyed without the written consent of the Sponsor.

17.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1. Quality Assurance and Quality Control, section 5.1.1

5.2. Noncompliance, sections 5.20.1, and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor, via the DCC's Internet Data Entry System (IDES).

All deviations from the protocol must be addressed in study case report forms. A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

17.6 Participant Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

18 PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal under the oversight of the Publication Committee of the Protocol. The Publication Committee comprises representatives of the network cores, thought-leaders, DCC, and is responsible for generation and coordination of the publications that report scientific findings of the network. All public presentations (abstracts, manuscripts, slides and text of oral or other presentations, and text of any transmission through any electronic media) by participating investigators, participating institutions, DCC, and those that use data and are intended to represent the sponsor or the PTN will be reviewed by the Publication Committee per the Publication Committee charter.

The Publication Committee guarantees that the study results are presented by experts in the field that have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The committee goals are to ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included.

The Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journal. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase I trials), would be exempt from this policy.

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication. Refer to: http://publicaccess.nih.gov/ and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08- 033.html

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APPENDIX I

Hemangioma Quality of Life Assessment (prototype)

Table 1. Prototype IH-QoL 35-item

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1. My child has pain because of this hemangioma. (CPS)
2. My child seems sickly or prone to illness because of the hemangioma. (CPS)
3. My child is not growing or developing normally because of the hemangioma.[1]
4. My child has trouble sleeping because of the hemangioma. (CPS)
5. Because of the hemangioma my child has problems being soothed or comforted when crying. (CPS)
6. My child's hemangioma prevents him/her from participating in social events such as parties and play groups.[1]
7. Friend or relatives avoid touching and holding my child because of his/her hemangioma.[1]
8. Children seem to avoid touching or playing with my child because of his/her hemangioma. (CSI)
9. My child's hemangioma makes me feel sad or depressed. (PEF)
10. I am disappointed that my child has this hemangioma. (PEF)
11. I experience more headaches than usual as a result of my child's hemangioma. (PSF)
12. My child's hemangioma makes me feel anxious or nervous. (PEF)
13. I am bothered by how much time is needed to care for my child because of the hemangioma.[1]
14. I am bothered when strangers stare at my child. (CSI)
15. I worry about the amount of money I have to spend because of the hemangioma.[1]
16. I am embarrassed by the way my child looks because of his/her hemangioma. (PEF)
17. I am worried that in the future my child will not make friends as easily because of the hemangioma. (PEF)
18. I blame myself or my child's other parent that my child has this hemangioma. (PSF)
19. The hemangioma has affected how confident I feel about my child's medical care. (PEF)
20. I get worried when I see changes in my child's hemangioma. (PEF)
21. I have been frustrated with my child's medical care for the hemangioma. (PEF)
22. I am bothered that my child needs to be watched more closely at home because of the hemangioma. (PSF)
23. I feel physically weak as a result of my child's hemangioma. (PSF)
24. I am bothered when strangers offer opinions or ask questions about my child's hemangioma. (CSI)
25. My child's hemangioma affects our social life. (PSF)
26. My child's hemangioma has strained my relationship with my spouse or partner. (PSF)
27. I have been accused of child abuse because of my child's hemangioma. (CSI)
28. Our family is less likely to go to public places (e.g., grocery store) because of the hemangioma. (PSF)
29. My child's hemangioma affects my or my spouse/partner's work due to missed time. (PSF)
30. I am considering not having more children because of my child's hemangioma.[1]
31. I am bothered that children touch or comment on my child's hemangioma. (CSI)
32. I worry about my child based on information I read on the Internet. (PEF)
33. I worry about side effects of the medication(s) used to treat my child's hemangioma. (PEF)
34. I feel too tired to do the things I like to do because of my child's hemangioma. (PSF)
35. I have felt sick to my stomach as a result of my child's hemangioma. (PSF)

Abbreviations: CPS, child physical symptoms; CSI, child social interactions; IH-QoL, Infantile Hemangioma Quality-of-Life; PEF, parent emotional functioning; PSF, parent psychosocial functioning.

[1] Italicized items were excluded during analysis: 3, 6, 7, 13, 15, and 30.

APPENDIX II

Hemangioma Dynamic Complication Scale

Date Completed: _____ Dynamic Grading Scale for Hemangioma Complications

Please circle a single grade that best describes the patient's current clinical condition.

Investigator's Name:

Subject ID#:

Infection (Bacterial)	Grade
No infection	0
Infection present, topical antibiotics used or indicated	1
Infection present, oral antibiotics used or indicated	2
Infection present, intravenous (IV) antibiotics or operative intervention indicated	3
Life threatening infection (sepsis)	4
Ulceration	**Grade**
No ulceration	0
Superficial ulceration **that is not** interfering with daily living (diaper changes, bathing, feeding, sleeping)	1
Superficial or deep ulceration that is interfering with daily living	2
Deep of chronic ulceration requiring operative intervention (excluding pulsed dye laser)	3
Ulceration resulting in loss of vital structure	4
Feeding difficulties	**Grade**
No difficulties	0
Decreased oral intake with normal weight gain	1
Decreased oral intake with weight loss/lack or gain or nutritional supplements indicated	2
Significant weight loss/lack of gain or malnutrition (IV fluids, tube feeds, total parenteral nutrition needed)	3
Torticollis	**Grade**
No torticollis	0
Present intermittently; no physical therapy required	1
Persistent; abnormal head posture maintained most of the day; physical therapy required	2
Persistent; physical therapy and plagiocephaly therapy indicated	3
Cartilage distortion or destruction	**Grade**
No cartilage involvement	0
Distortion of cartilage (assume splaying of nasal cartilage at tip due to deep IH, change in pinna shape due to deep IH of ear)	1
Focal cartilage destruction (focal/small area of tissue loss or ulceration)	3
Major cartilage destruction to vital structure (i.e. collumella, pinna) requiring surgical intervention	4
Airway Involvement	**Grade**
No airway involvement	0
Asymptomatic, diagnosis based on exam, endoscopy, or radiograph, may be on medical management	1
Symptomatic (e.g., noisy airway breathing, hoarse cry, stridor), without respiratory distress; medical management indicated	2
Symptomatic causing respiratory distress; medical or surgical intervention required	3
Life-threatening airway compromise; tracheotomy or intubation indicated	4
Death	5
Visual compromise	**Grade**
No visual compromise	0
Eyelid distortion, no astigmatism or amblyopia	1
Astigmatism with or without partial visual axis occlusion	2
Proptosis, amblyopia, anisometropia	3
Complete visual axis occlusion	4
Permanent visual loss	5
Hypothyroidism	**Grade**
No hypothyroidism	0
Elevated thyrotropin, requires no intervention	1
Intervention required with standard thyroid replacement	2
Intervention required with increased from standard thyroid replacement	3
Severe and/or recalcitrant requiring IV therapy; signs of heart failure, central nervous system abnormalities	4
Death	5
Anemia (related to hemangioma)	**Grade**
No anemia	0
Asymptomatic anemia	1
Symptomatic anemia (tachycardia, pallor, lethargy) requiring oral medical management (iron)	2
Symptomatic requiring nonemergent transfusion	3
Symptomatic and severe requiring emergency care with emergent transfusion and/or resuscitation	4
Death	5
Congestive heart failure (related to high output failure related to hemangioma)	**Grade**
No CHF	0
Asymptomatic diagnostic finding; intervention not indicated	1
Asymptomatic and intervention indicated	2
Symptomatic and responsive to intervention	3
Symptomatic and refractory, poorly controlled; intervention such as mechanical ventilation indicated	4
Death	5
GI bleed	**Grade**
No bleeding	0
Bleeding without symptomatic anemia	1
Bleeding with symptomatic anemia (tachycardia, pallor, or lethargy); medical interention indicated	2
Bleeding with symptomatic anemia; intervention with transfusion or surgical intervention indicated	3
Life-threatening bleed; major urgent intervention indicated	4
Death	5
Hepatic dysfunction	**Grade**
No findings	0
Asymptomatic radiologic findings only	1
Hepatomegaly (defined as greater than normal span of liver) without hepatic dysfunction	2
Hepatomegaly with hepatic dysfunction (elevated bilirubin/liver enzymes, abnormal synthetic function, hypothyroidism requiring oral replacement)	3
Life-threatening liver failure, encephalopathy, compartment syndrome, requiring IV thyroid replacement	4
Death	5
Total Score:	