ARKAYLI BIOPHARMA

Infantile Hemangioma Opportunity

Changing the Approach to Treatment for Infantile Hemangiomas

Improving the Treatment of Infantile Hemangioma (IH)

- **Vision**

  Provide a safe, efficacious option that allows early treatment of IH

- **Technology**

  Novel formulation of esmolol that allows once daily application without systemic beta blockade

- **Regulatory Path**

  505(b)(2) NDA, seeking orphan drug designation; cost- and time-efficient

- **Patent/IP**

  IP protection to 2037; 7.5 years exclusivity with orphan designation and pediatric data

- **Key Milestones**

  In 24 months—IND filed, orphan designation, and Phase 1b clinical trial results

- **Team**

  Expertise in infantile hemangioma, drug formulation, development, and M&A

Infantile Hemangioma is an Undertreated Disease

Last year ~170,000 infants were born with Infantile Hemangiomas[1,2]

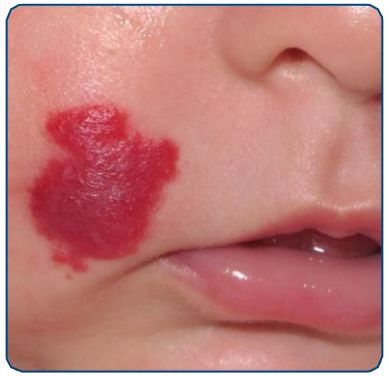
- Lesions grow rapidly in the first weeks of life
- Early treatment is critical - ***Optimal treatment begins at 4–8 weeks of age***
- Referral to ***a dermatologist typically occurs at 5 months -*** by then most growth has occurred[3]
- Currently, one **oral beta-blocker** is the only FDA approved therapy
  - However, generic propranolol is often used due to low price and easy access
- Many Hemangiomas are ***not being treated or treated only after they are very advanced***
  - Treatment is delayed because;
  - Disease variability and difficulty in risk assessment by primary care physicians
  - The perceived and real risk of side effects of oral beta blockers in young infants

1. U.S. Census Bureau, Population Division, 2020 Census preliminary data
2. Munden A, et al. Prospective study of infantile hemangiomas: incidence, clinical characteristics and association with placental anomalies. Br J Dermatology 2014;170:907-913
3. Hemangioma Investigator Group, Haggstrom A, et al. Prospective Study of Infantile hemangiomas: demographic, prenatal, and perinatal characteristics. 2007: 150:291-294,2007

About Infantile Hemangioma (IH)

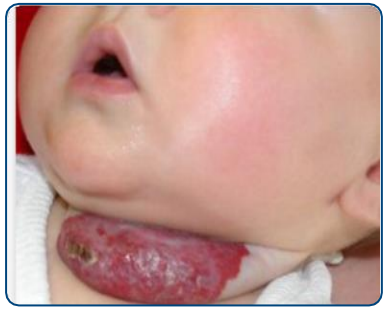
- A type of benign vascular tumor
  - ***Abnormal growth of blood vessels***
  - Risk factors include low birth weight and prematurity
- If left untreated, growth may lead to:
  - ***Damage to surrounding tissues***
    - IH on the eye lid can lead to permanent vision impairment
  - ***Tissue necrosis*** which can lead to:
    - Skin and soft tissue ulceration
    - Bleeding
    - Scarring
  - Risk of ***permanent disfigurement***

Female, 1 month

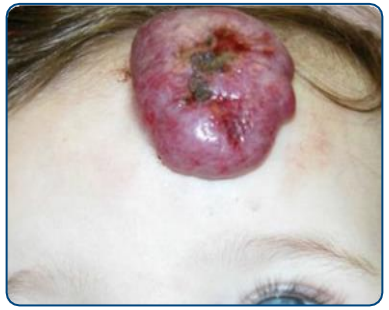


Female, 1 month

IH become evident in the first few weeks to months of life



Female, 4 months



Female, 9 months

If untreated, IH can grow quickly, resulting in ulceration and permanent scarring

**Photos on file from Arkayli*

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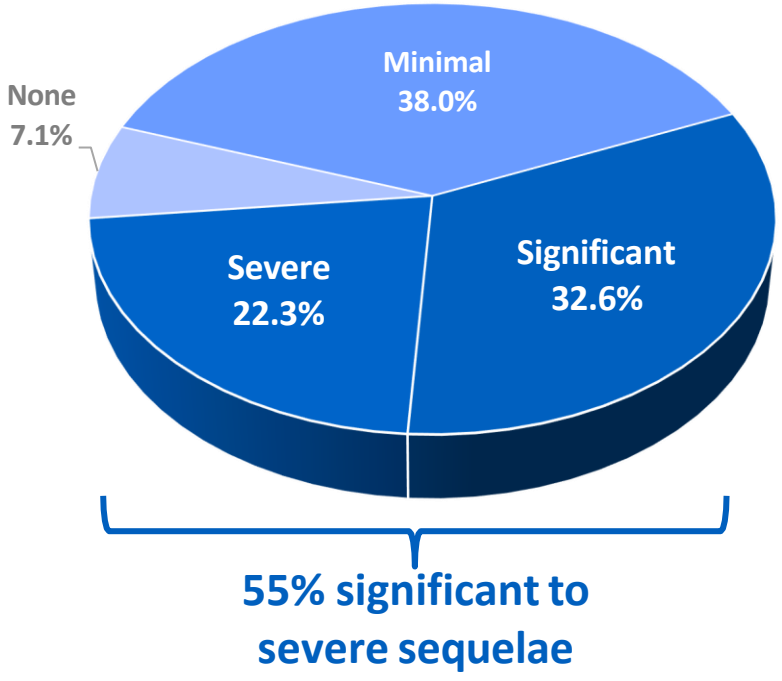
The Majority of IH Cause Permanent Residual Effects

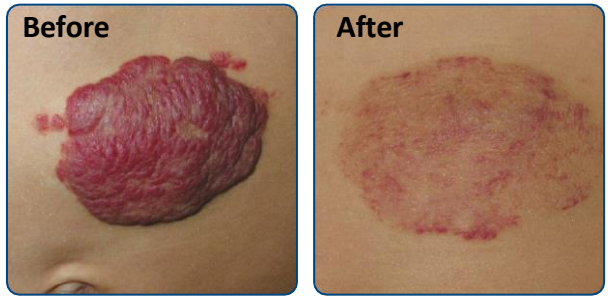
IH undergo slow involution that can take several months to years

Proportion of IH with sequelae following involution[1]

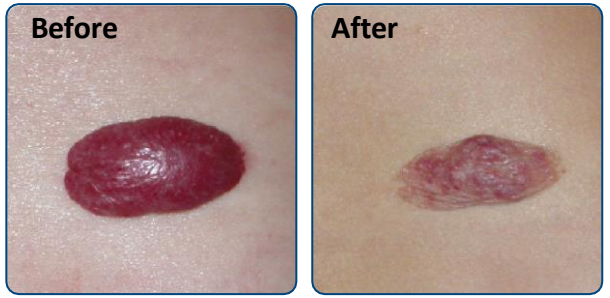


Type of IH Sequelae after Involution[1,2]

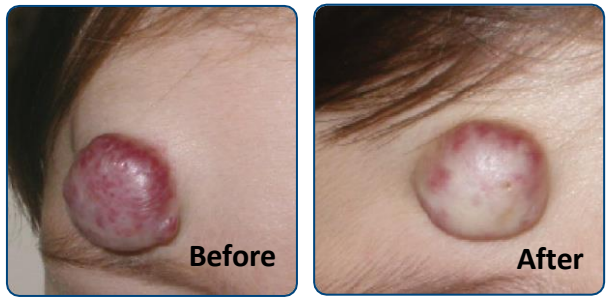
Permanent Scarring



Anetodermic Skin
(loss of skin elasticity)



Redundant Skin
(excess skin)



Fibro Fatty Tissue

1. Baselga E, et al. Dermatol *JAMA Dermatol*. 2016;152(11):1239-1243. Bauland CG. Untreated hemangiomas: growth pattern and residual lesions. *Plast Reconstr Surg*. 2011;127(4):1643–164

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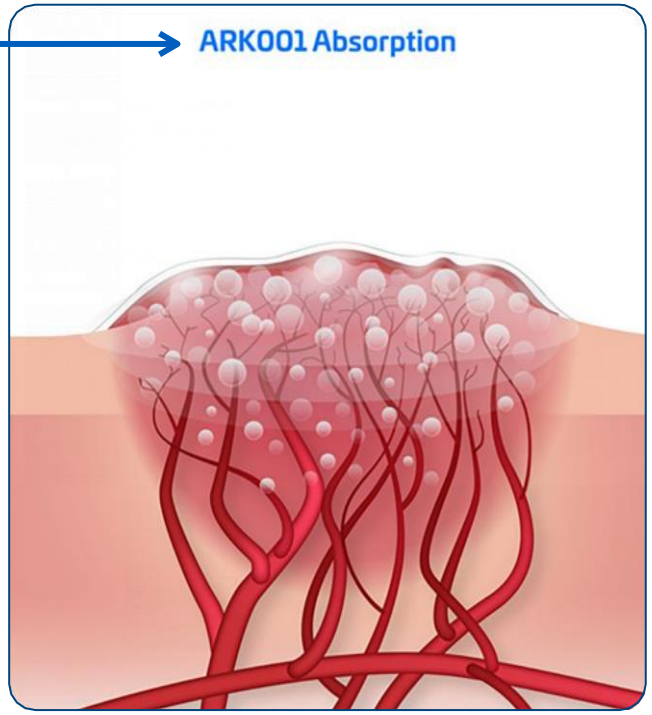
ARK001: A Novel Esmolol Product to Treat IH

- **Pediatric-specific formulation**— Clear topical esmolol gel designed for sensitive skin
- **Topical delivery**— Applied directly to the IH where it is absorbed to act locally
- **Ultra-short half-life**— Esmolol is rapidly metabolized locally by red blood cells; no systemic beta blockade
  - Less risk of hypoglycemia – can be administered without food/no need to wake a baby for feeding
- **Low risk of side effects seen with other beta blockers**
  - Esmolol is beta-1 selective, and does not cross the blood brain barrier
    - Low risk of bradycardia or wheezing
    - Low risk of CNS side effects such as sleep disturbance or negative cognitive impact

ARK001 is applied directly to the IH

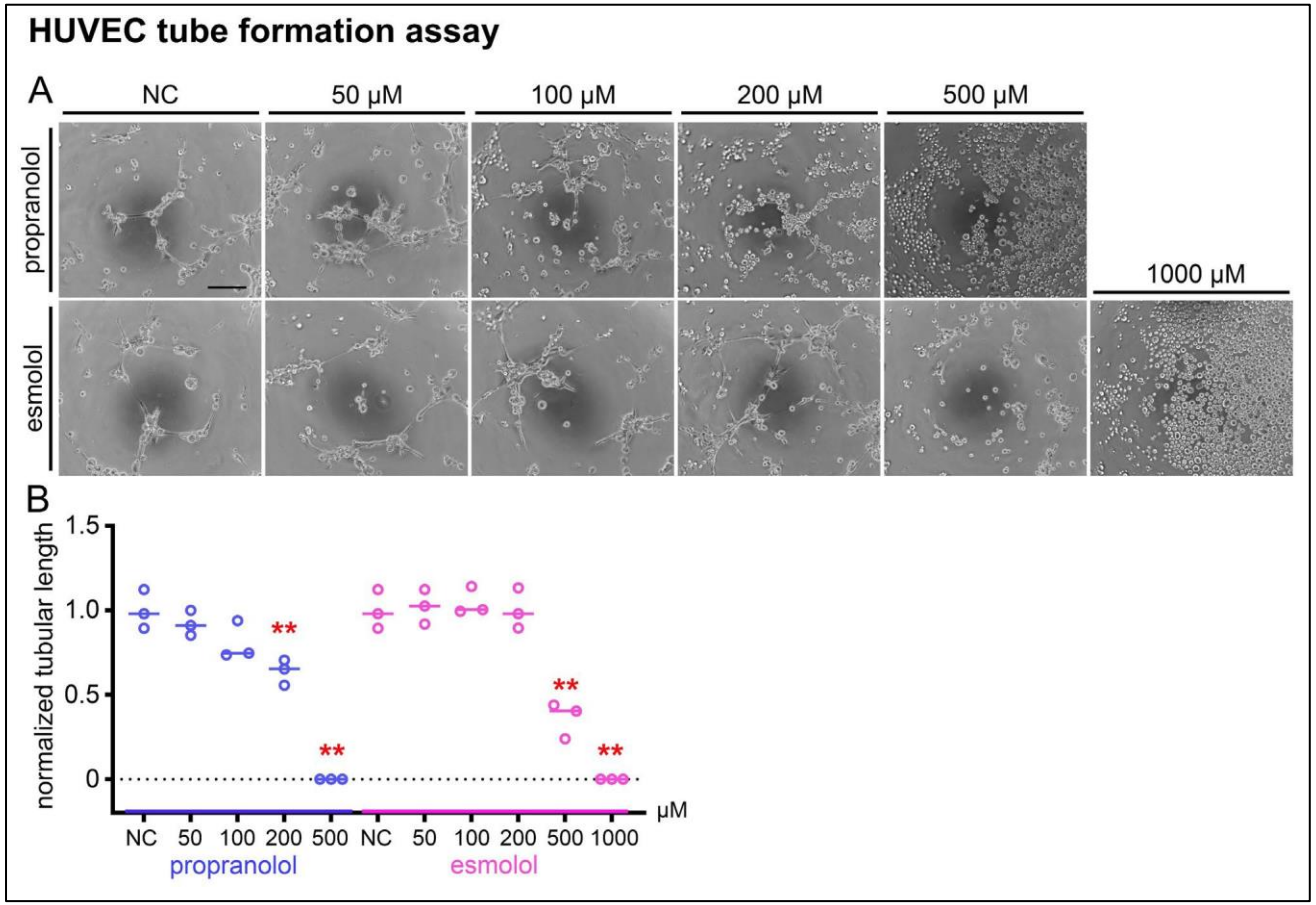


ARK001 is absorbed into IH, where it acts and then is rapidly deactivated by red blood cells

ARK001 Mechanism of Action:
Comparable Effect of Esmolol to Propranolol on Vessel Formation

- IH are derived from endothelial progenitor cells driven by local hypoxia in the skin[1]
- The primary antiproliferative mechanisms of beta blockers on IH have been attributed to inhibition of angiogenesis due to:
  - Decreased endothelial cell migration
  - Decreased endothelial cell proliferation
  - Increased endothelial cell apoptosis
- Arkayli in-vitro experiments demonstrate inhibition of angiogenesis with esmolol comparable to propranolol[2]

Comparable Effect of Esmolol to Propranolol on Vessel Formation



1. Krowchuk D, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. *Pediatrics* 2019;143;1-28.
2. In-vitro experiments conducted at the University of Wisconsin. Data on File, Arkayli Biopharma

HUVEC = Human umbilical vascular endothelial cells

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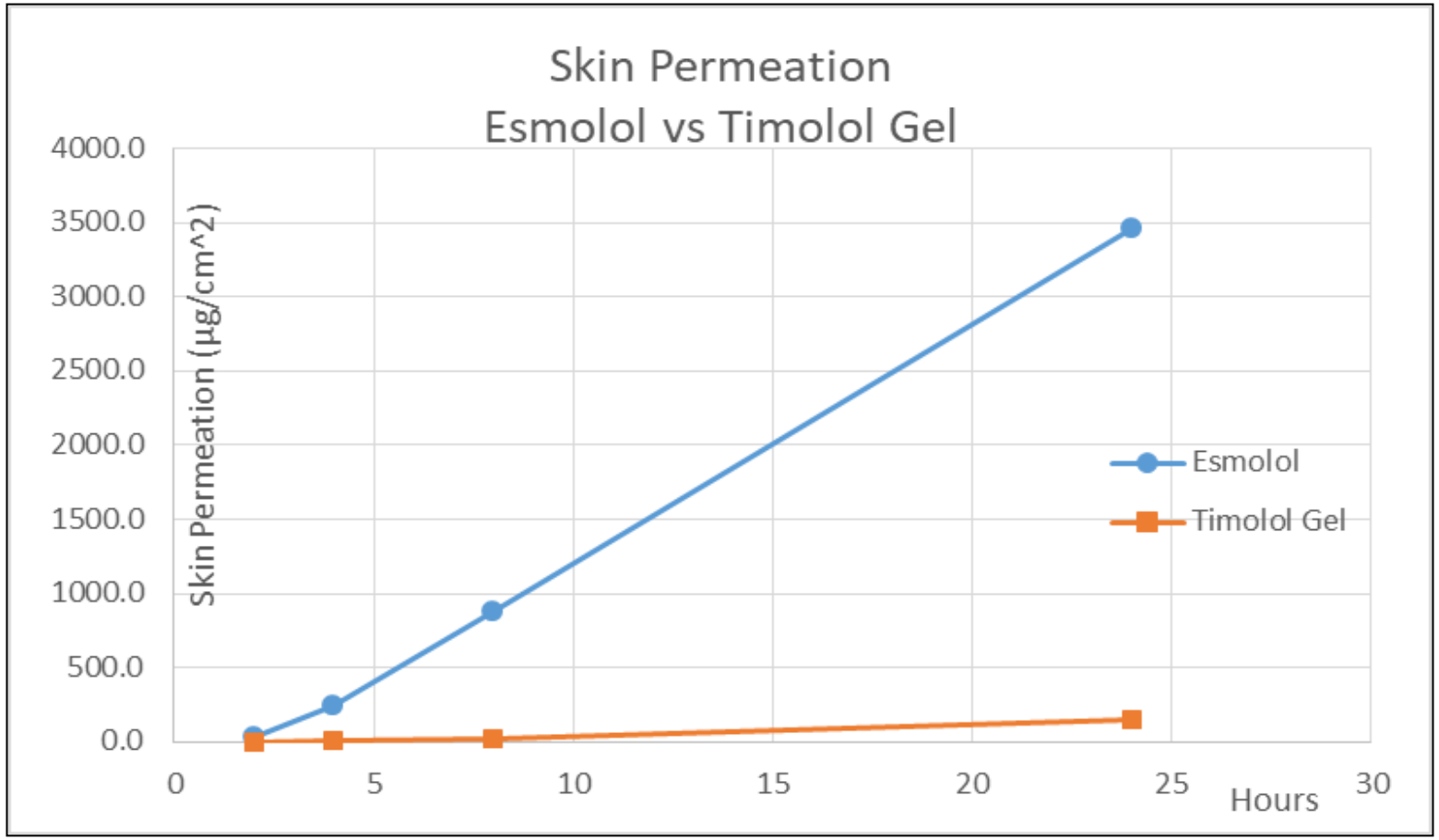
ARK001 Target Product Profile (TPP)

Comparison to Profile of Current Therapies used for IH

	ARK001 TPP (esmolol)	Hemangeol® (propranolol 4.28 mg/ml)	Propranolol oral soln. (4.0, 8.0 mg/ml)	Timolol ophthalmic (0.25%, 0.5%)
FDA approved for IH	**Investigational**	✓	✗	✗
Topical delivery	✓	✗	✗	✓
Once-daily dosing	✓	✗	✗	✗
Ultra-short half life	✓ 4.5-7.0 minutes	✗ 3.0-6.0 hours	✗ 3.0-6.0 hours	✗ 2.6-4.8 hours
Does not achieve blood levels consistent with beta blockade	✓	✗	✗	✗
Low risk of hypoglycemia (administer regardless of feeding)	✓	✗	✗	✗
Does not cross the blood brain barrier	✓	✗	✗	✗
Low Risk of CNS side effects (sleep disturbance, memory impairment)	✓	✗	✗	✗
Beta-1 receptor selective (low risk of wheezing, bradycardia)	✓	✗	✗	✗

ARK001 can be Delivered at a Higher Rate into IH Lesion than Timolol Ophthalmic Gel



ARK001—Esmolol gel is designed to increase delivery of beta blocker to the lesion, without systemic beta blockade

Timolol ophthalmic gel is not approved for IH but is included in the American Academy of Pediatrics Clinical Practice Guideline as a therapy for thin/superficial IH. Timolol gel has been widely adopted in the treatment of IH.

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Arkayli Intellectual Property

Patents Filed:

- WO 2020/242962, PCT 2020/034270
- Covers two molecules and innovative formulations: Esmolol and Landiolol
- Provisional patent application for next generation formulation

IP Protection:

- US: Potential for 7.5 years exclusivity with orphan drug designation (ODD), plus an additional 6-month pediatric extension
- EU: Potential for 10 years exclusivity with orphan medicinal product designation (OMPD), plus an additional 2 years pediatric extension
- Method of claims for IH to 2037

ARK001 Progress to Date - Accomplishments

De-risking ARK001 development program

- Agreement from FDA to proceed directly into 28-day Phase 1b trial in infants with IH
- 5-day minipig study for PK and dermal irritation completed
  - Demonstrated negligible esmolol systemic exposure, well below systemic beta blockade levels
- HUVEC cell experiment completed - Demonstrated esmolol effect on angiogenesis comparable to propranolol
- Canfield 3D photography Study (n=75): Validate clinical efficacy endpoint measure is completed
  - Determined optimal endpoint for Phase 1b is change in color of IH
- AMES, Dermal Sensitization and Phototoxicity studies all Completed – Reported exceptionally clean results
- Dose Ranging Finding Study Completed in mini pigs (BID and SQ dosing) – Positive results
- 28-Day Mini Pig study on track to finish December 21st, 2024.

Additional milestones achieved

- Formulation design and enclosure delivery device complete; skin permeation experiments completed
- ODD application submitted, FDA provided feedback, extension granted until August of 2025
- Preliminary market research conducted with physicians and payer supports unmet market need and commercial viability

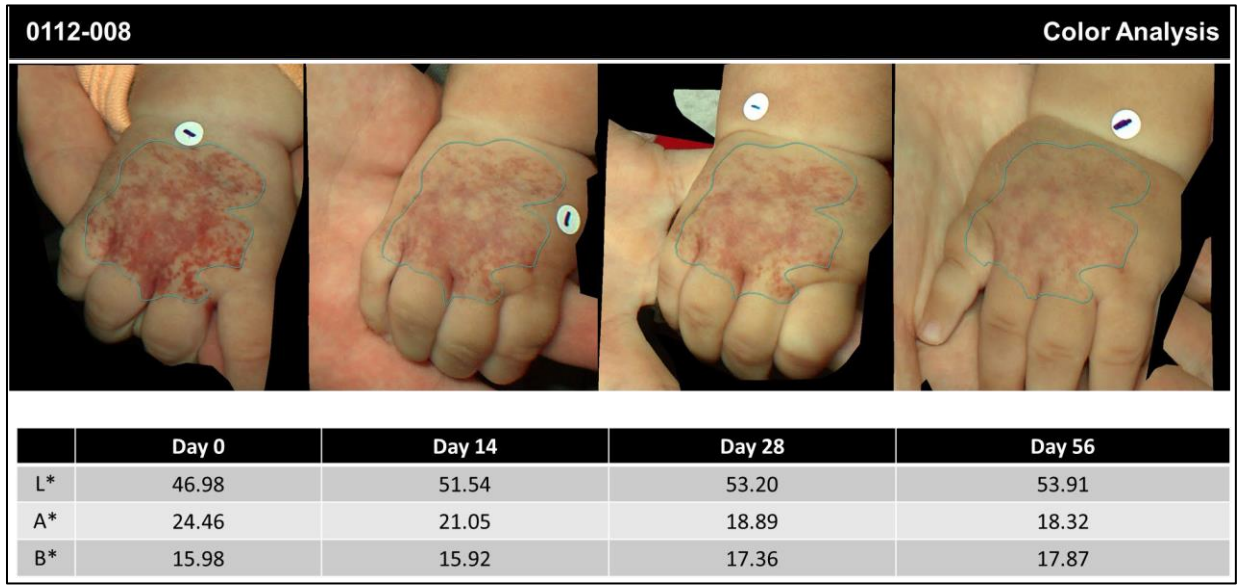
ARK001 Phase 1b Trial Plan

- **Design:**
  - Open-label, dose-escalation study (sentinel dosing in first cohort)
  - Population size: n=20 infants with IH
  - Dose escalation: 3-5 patients per treatment cohort
  - Length of treatment: 28 days
  - Outcome measures: PK, safety and tolerability, IH color change
  - Single U.S. site
- **Inclusion:**
  - Infants with hemangioma: Age > 28 days
  - IH Location: Non-facial/diaper location, not complicated
- **Endpoints/Evaluation:**
  - Safety: Cardiovascular and metabolic safety, local tolerability, PK
  - Efficacy (exploratory): Change in IH color assessed by Canfield 3D Photography and the hemangioma dynamic severity scale (HSS)

Study to Validate Efficacy Measure for IH

Arkayli validation study of Canfield 3D digital imaging for use in IH studies*

- N=75 infants completed to date; 271 images analyzed
- Non-invasive 3D photography at baseline (Day 0) and Days 14, 28, and 56
- Measurement of change in volume and color intensity
- Result: Determined that change in color is more sensitive efficacy measure for 28-day Phase 1b study than change in volume



	Day 0	Day 14	Day 28	Day 56
L*	46.98	51.54	53.20	53.91
A*	24.46	21.05	18.89	18.32
B*	15.98	15.92	17.36	17.87

Example of propranolol treated infant

*Historically, in studies of IH, restrospective expert rater reviews were used to measure efficacy and found to be unreliable

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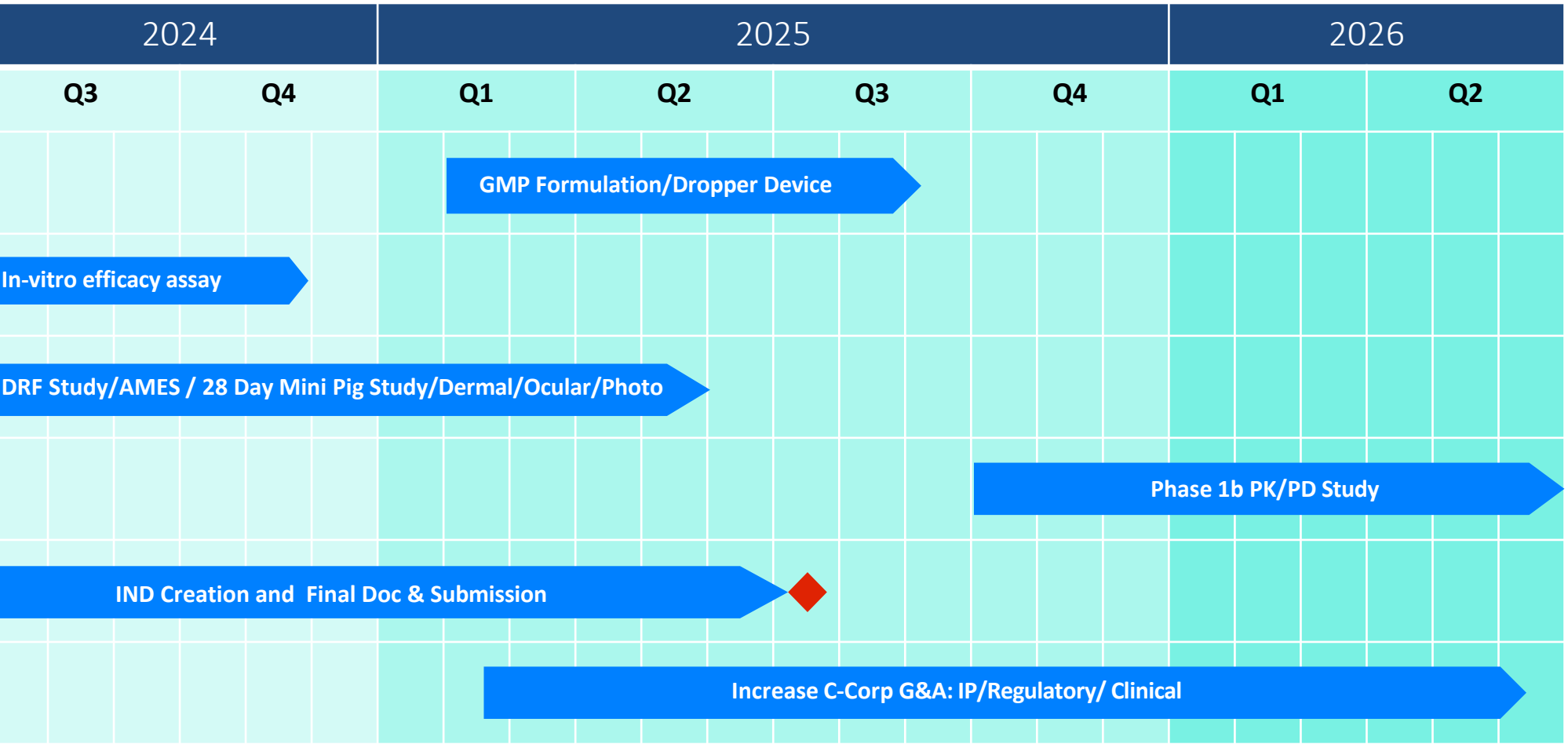
Development Timeline



◆ = Open IND

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Arkayli Funding Plan and Use of Proceeds

$2M
(Seed Raised)

$9.5M
(Series A)

$15-25M
(Phase 2/3)

$27-37M Total

Preclinical → Proof of Concept → Full Development to NDA

IND Filing 2Q2025

PH 1b PoC IH Data: $3.5M

- Complete PH 1 POC clinical trial ($2.7M)
  - 28-day safety, dose, efficacy
- Phase 1 Formulation ($70K)
- IP, G&A, market research, regulatory ($740K)
  - Obtain Orphan Drug Designation (ODD)

Tox enabled for PH2/3 adaptive trial: $6M

- 9-month toxicology to enable Ph 2/3 ($3.4M)
- CMC for Phase 2 ($500K)
- Phase 2/3 regulatory and other prep ($2.1M)
  - Negotiate registration trial(s)
  - Determine approvable clinical endpoint(s)
  - G&A

ODD 2026

FDA Meeting Ph 2/3 Ready 2H2026

Strategic Transaction -or- Series B

- 2-3 years
- Phase 2/3 trial (130-250 patients)
- $15-25M

NDA Approval 2029

◆ = Key Milestones

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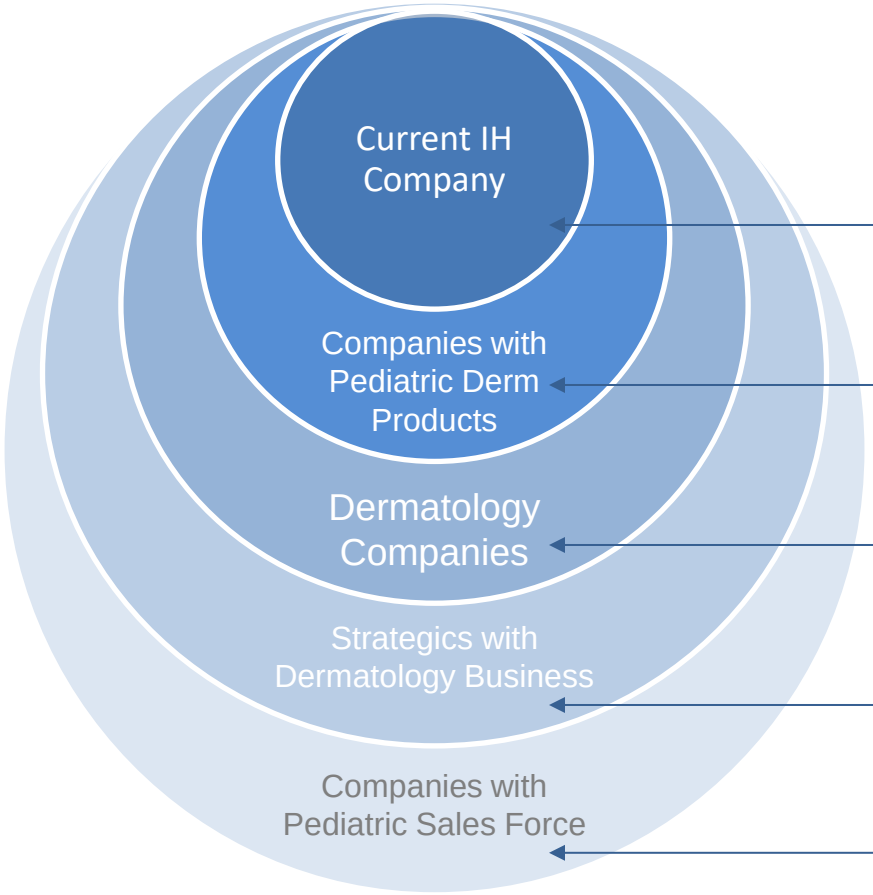
Landscape of Potential ARK001 Acquirers or Partners



Pierre Fabre (Hemangeol®)

Pfizer (Cibinqo®, Eucrisa®, Staquis®), Sanofi (Dupixent®), Abbvie (Rinvoq®), Botanix (Sofdra®), Krystal (Vyjuvek®)

Incyte dermatology, Galderma, Leo Pharma, Bausch Health, Arcutis, Dermavant, Tarsus

Novartis (Cosentyx®), Amgen (Otezla®), Bristol Myers Squibb (Sotyktu®), Lilly (Olumiant®), Janssen (Tremfya®)

Pfizer, Incyte, Merck, Moderna, Gilead, Glaxo Smith Kline, Jazz, Horizon, Sumitomo

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Dermatology Phase 2 Deal Comparables

Over 25 development phase dermatology deals (licensing and M&A) identified by Arkayli*

Arkayli Phase 2 Deal Comparables		
Company	**Acquirer or Licensee**	**Deal Information**
Aristea	Arena	Phase 2b: CXCR2 inhibitor for palmoplantar pustulosis (orphan) **$60M upfront**; $10M equity option staged for buyout
AFT	Timber	Phase 2: Rapamycin for facial angiofibromas in TSC All development costs plus $20M in milestones
Pellepharm	Leo Pharma	Phase 2b: Patidegib topical gel for Gorlin syndrome **$70M upfront** equity; $690M milestones
Elastagen	Allergan	Phase 1/2: Tropoelastin for acne scars and stretch marks **$95M upfront** plus milestones
Topokine Therapeutics	Allergan	Phase 2b: XAF5 topical for steatoblepharon (undereye bags) **$85M upfront** plus milestones
SPARC	Sun Pharma	Phase 2: Oral S1P1 agonist for AD and psoriasis **$20M upfront**; $125M milestones

*database available upon request

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U.S. IH Market Size and Value

Market Size

All Incident IH Patients in the U.S. (170,000)

55% of patients at risk of significant or severe sequelae

IH Patients at risk for complications/ permanent deformity (93,500)

10% of patients require systemic treatment[2]

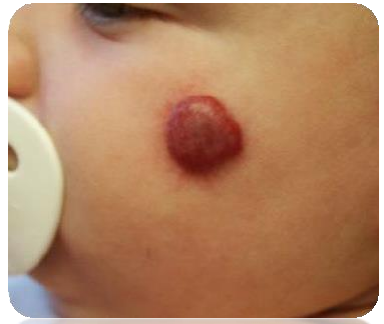
IH patients eligible for topical therapy (84,000)

Market Value[3]

$2.1 Billion

$1.2 Billion

$1.05 Billion



1. Baselga E, et al. Risk factors for degree and type of sequelae after involution of untreated hemangiomas of infancy. JAMA Dermatology 2016;152:1239-1243
2. Haggstrom AN, et al. Prospective study of infantile hemangiomas: Clinical characteristics predicting complications and treatment. Pediatrics 2006;118(3):882-887
3. Market value calculated based upon price parity to current Hemangeol price if used in infants of median weight treated for 12 months (=$1034/mo)

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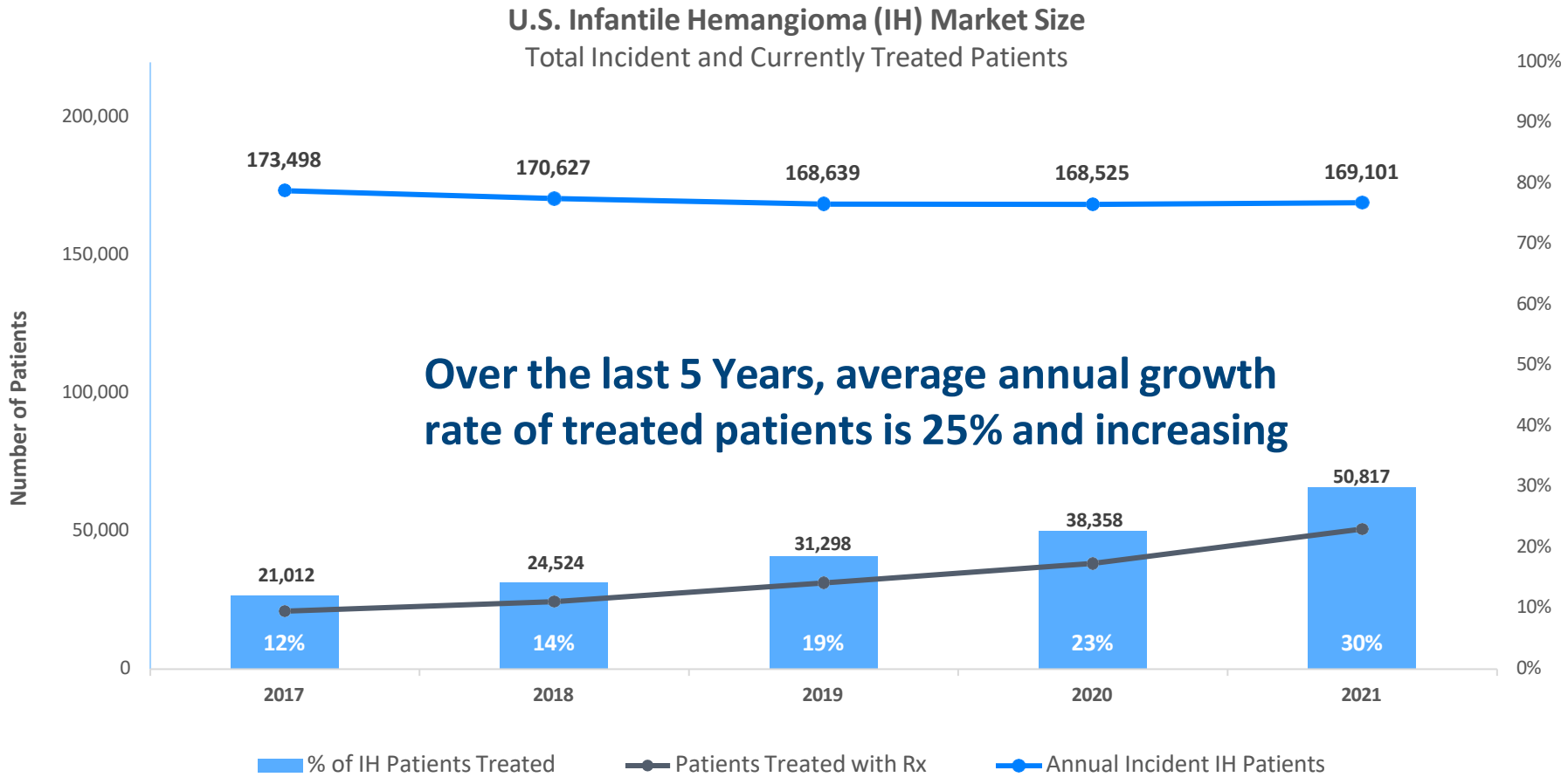
Only 30% of Infants with IH are Treated



Symphony Health Metys™ patient count for use of propranolol solution and timolol ophthalmic by dermatologists and pediatricians

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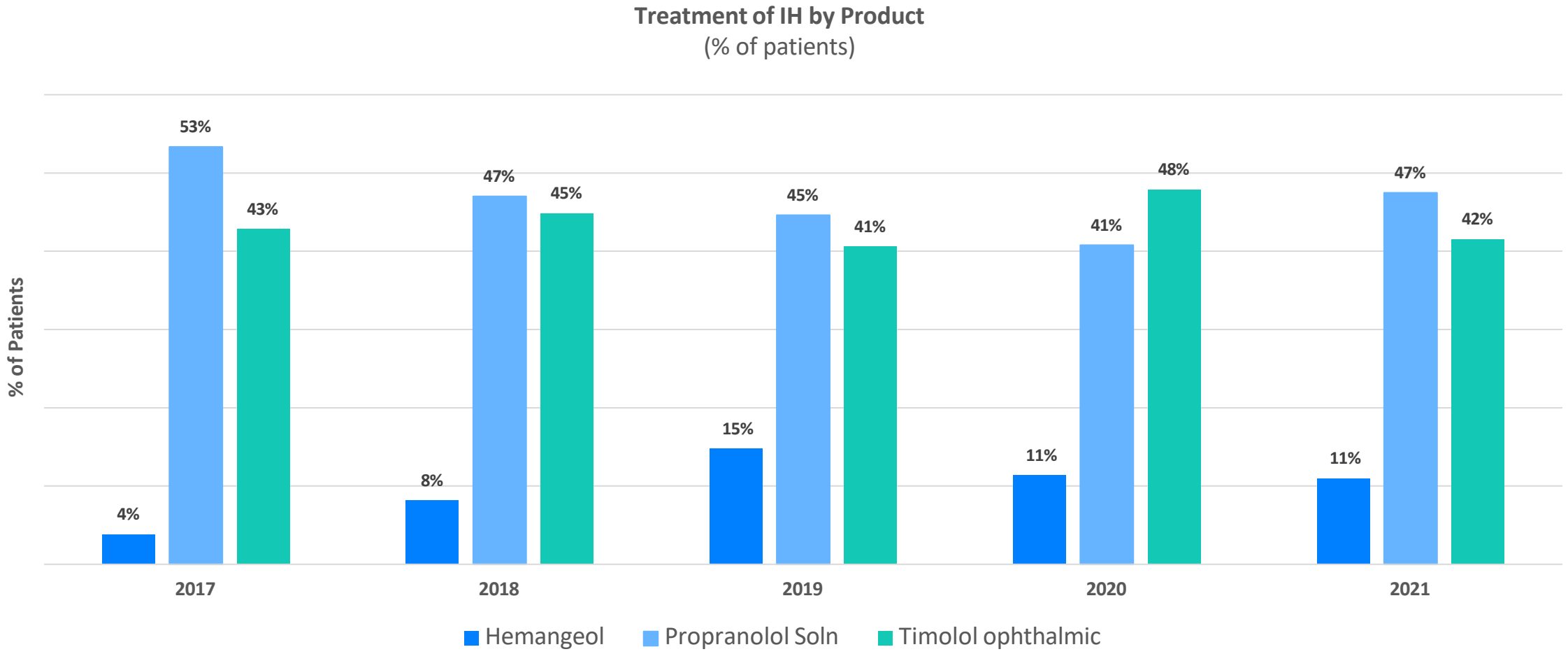
Most Infants are Treated with an Off-Label, Generic Beta-Blocker



Source: Symphony Health, Metys prescription data for oral propranolol solution and timolol ophthalmic solution factored by use by pediatricians and dermatologists

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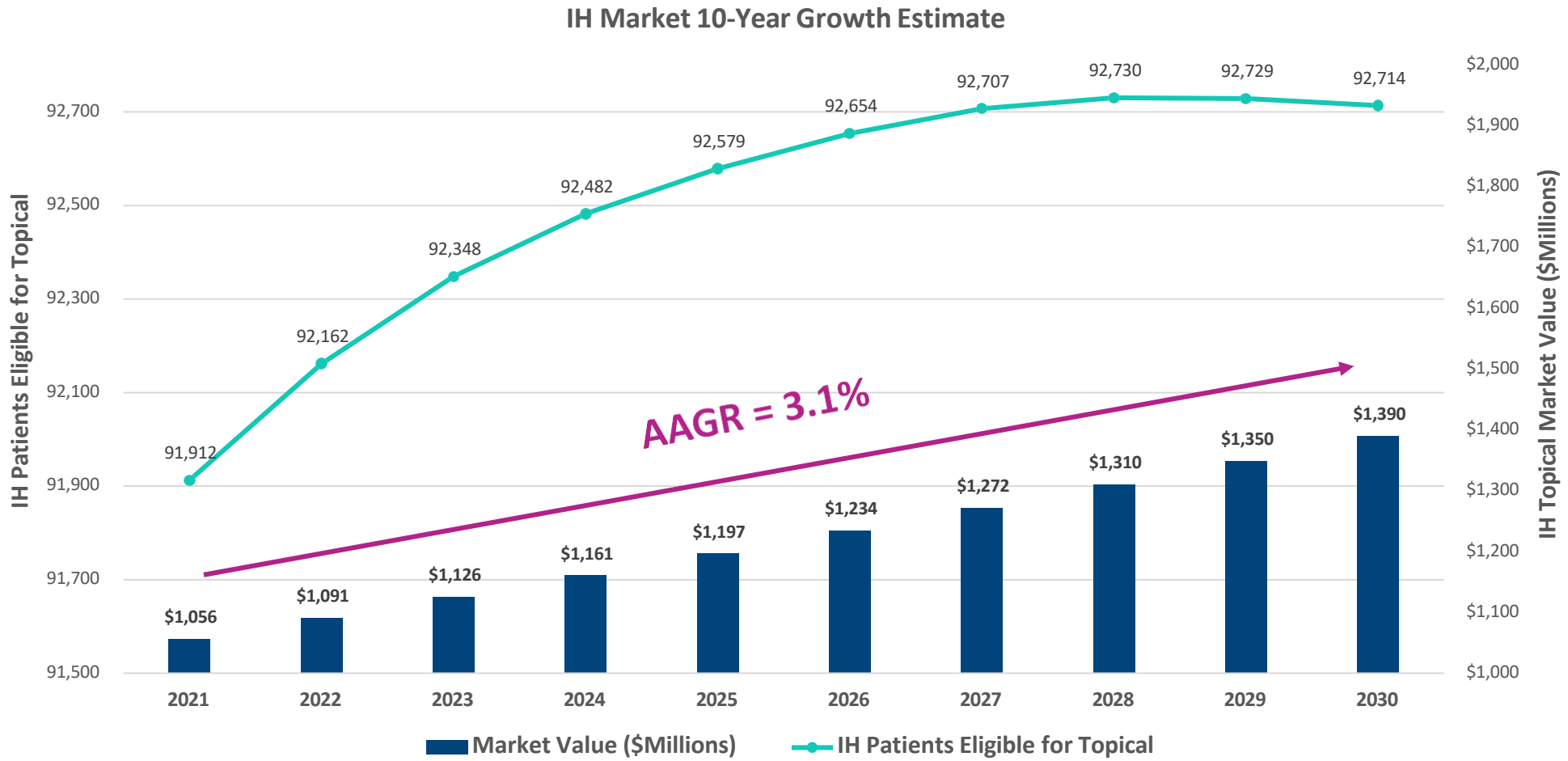
Forecast Growth in Topical IH Market Size and Value in the Next 10 Years



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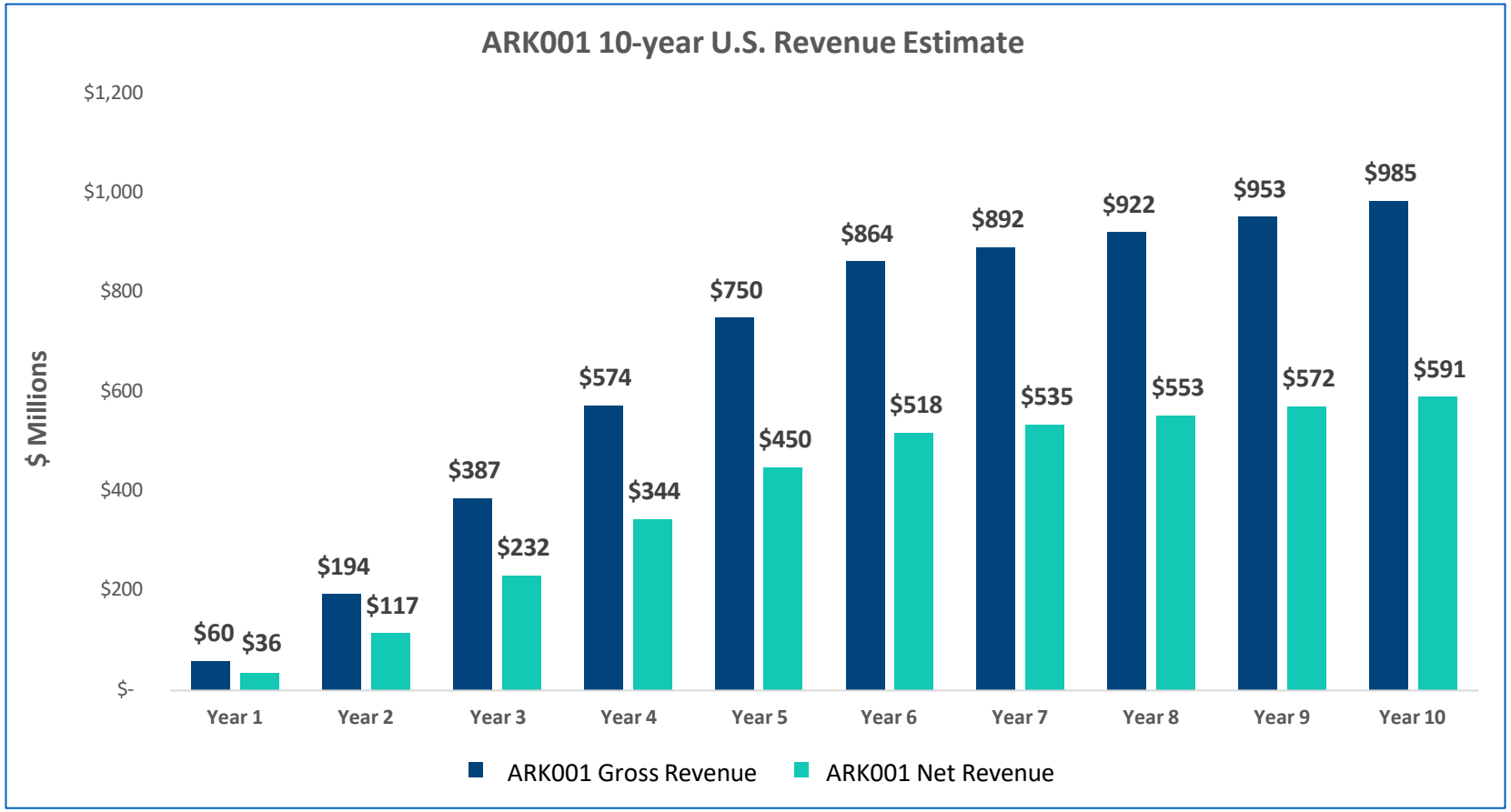
Sizable US Market and ROW Opportunities

Opportunity for Global Growth:

- First and only drug approval for treating IH was 8 years ago. Since then, US market growth has been significantly increasing.
- Significant growth opportunities projected in developing countries.



The assumptions used to create this revenue estimate are based upon secondary data. Projections are preliminary and primary research is necessary to validate certain forecast assumptions.

Symphony Health Metys™ patient count for use of propranolol solution and timolol ophthalmic by dermatologists and pediatricians

Proven Leadership Team

Thomas Rossi, PhD
Co-founder, Chairman

Seth Reno, MBA
CEO

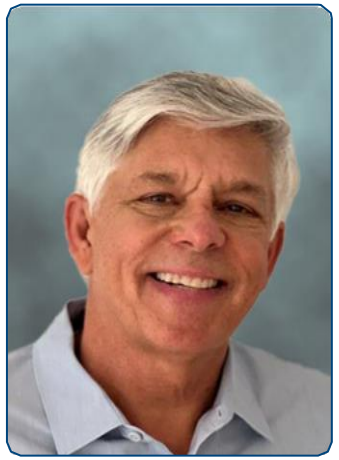
Beth Drolet, MD
Co-founder, Clinical Lead

Katie MacFarlane, PharmD, Commercial

Paul Manley, MSRB
Regulatory

Ric Stanulis, PhD, Toxicology, NonClinical Lead

Gil Price, MD, Board Member



Steve Gullans, PhD, Strategic Advisor

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Thank You

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