RELAY®
THERAPEUTICS

Webinar:
Vascular Anomalies

March 2026

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Vascular Anomalies Overview

~170k US patients with PIK3CA-driven Vascular Anomalies

Somatic PIK3CA mutation → **drives malformed vasculature** → **leading to vascular anomalies**

Current treatment options are limited

Local Treatments: temporary, only treat symptoms → **Systemic Treatments: non-selective, limited toxicity/efficacy** → **Large unmet medical need**

Zovegalisib is uniquely positioned to address driver of disease

First mutant-selective PI3Kα inhibitor

Initial clinical data showing:

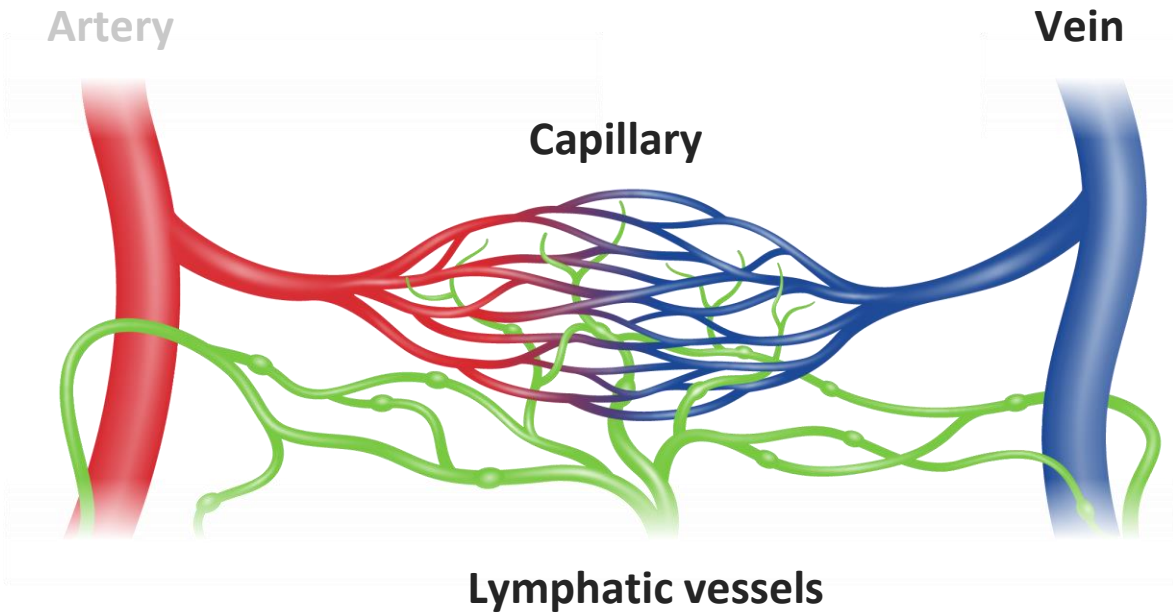
- Selectivity
- Tolerability
- Efficacy

Potential for chronic systemic treatment option

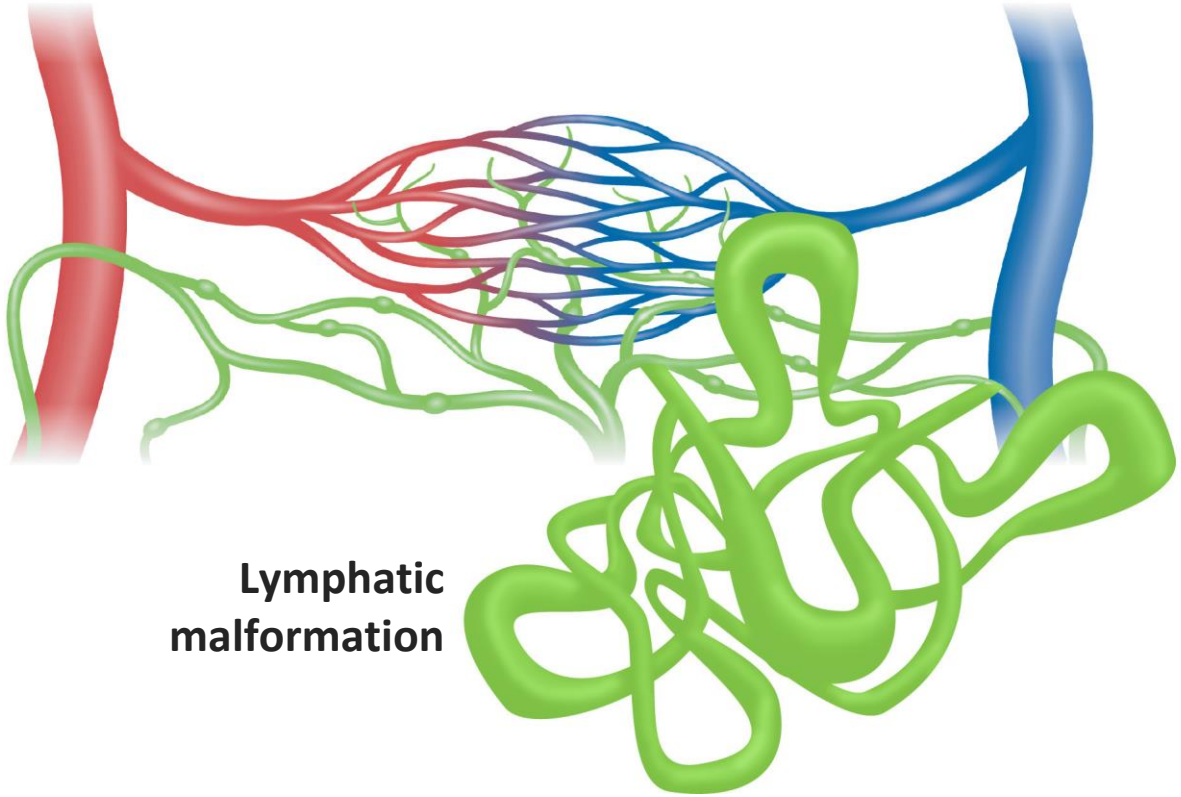
Sources: ISSVA classification, NORD, Mayo Clinic, Novartis, Penington et al 2023, Gallagher et al 2022, Luks et al 2015, Limaye et al 2015, Peyre et al 2021, Hong et al 2021, and company primary market research

Vascular Anomalies – Driven By Vascular Overgrowth

Normal Blood and Lymphatic System



Vascular Malformation



The type and location of vasculature that overgrows drives clinical presentation

Vascular Anomalies – Disparate Disorders Classified by Phenotype

Long history of Vascular Anomaly disorders being described and named by highly heterogenous clinical presentations

2010s
Genetic testing of these diseases identified associated mutations

PIK3CA Tie2/TEK RASA1 MAP2K1 Etc.

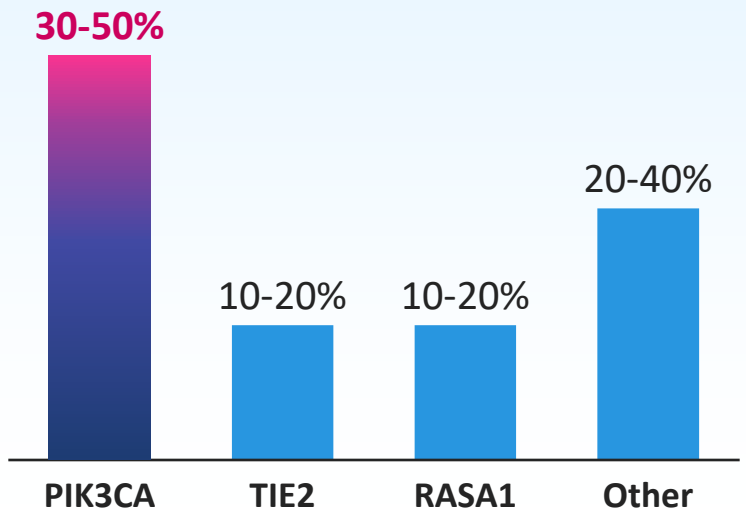
CLAPO = capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry of face and limbs and Partial/generalized overgrowth; CLOVES = congenital lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies; FAVA = fibro-adipose vascular anomaly; GLA = generalized lymphatic anomaly;; KTS = Klippel-Trenaunay syndrome; LMs = lymphatic malformations; MCAP = megalencephaly-capillary malformation-polymicrogyria syndrome; PROS = PIK3CA-related overgrowth spectrum

Vascular Anomalies – Disparate Disorders Driven by Common Somatic Mutations

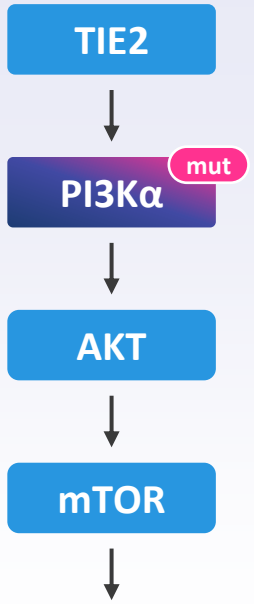
PIK3CA mutations are among the most common driver of Vascular Anomalies[1]

Mutation Frequency by Gene[2]

Unlike cancer, these are often single-driver events occurring in an otherwise quiet genome with intact cell regulation



Somatic mutations to the PI3K pathway drive abnormal development in Vascular Anomalies



Abnormal proliferation, growth, differentiation, angiogenesis

- Cell/tissue overgrowth
- Disorganized vasculature
- Weak vessel walls

Vascular Anomalies

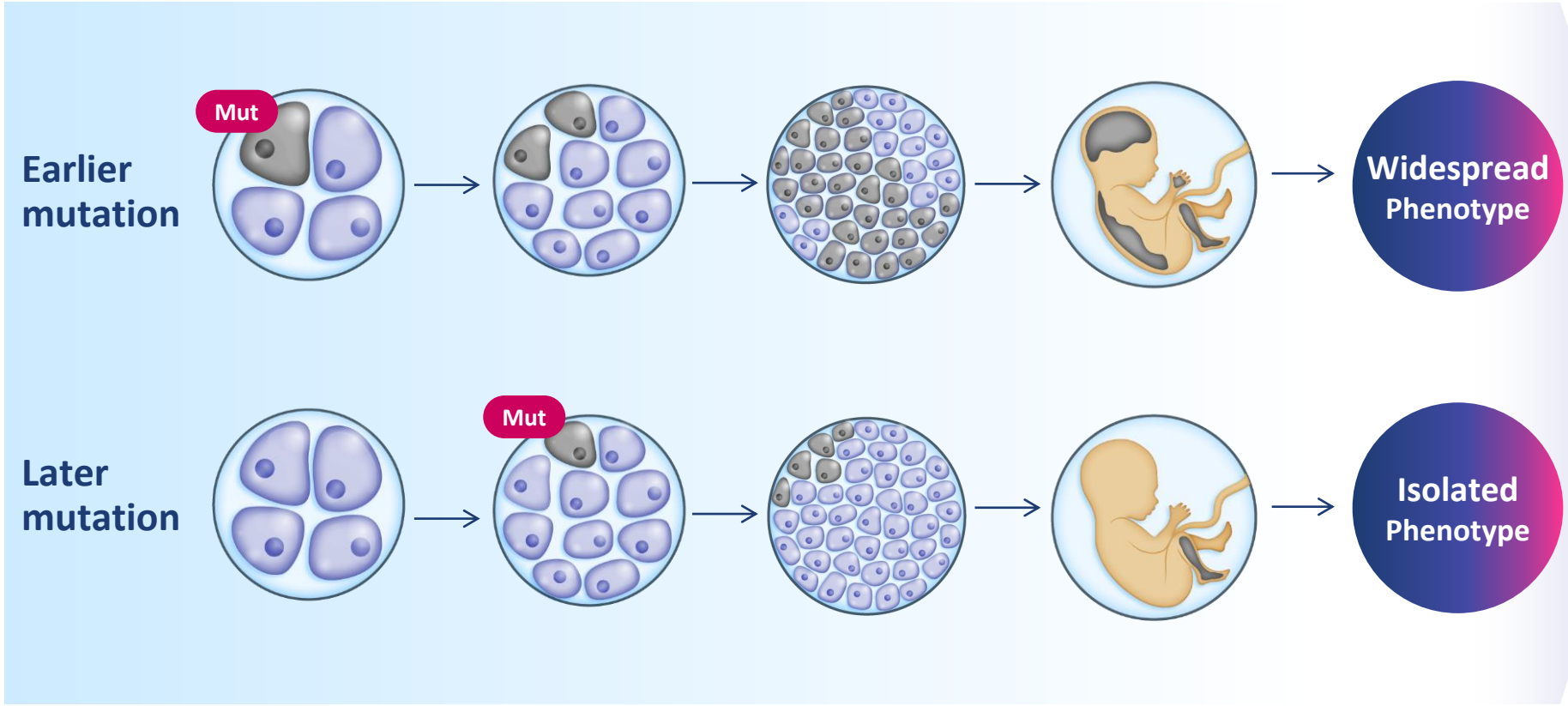
Other tissue types may also be implicated in overgrowth

Mutant PI3Kα is a validated driver of the majority of vascular anomalies

1. For vascular anomalies that may require chronic systemic treatment; 2. Stor et al. 2023

Vascular Anomalies – Timing & Location of Somatic Mutation Determines Phenotype

Timing and Location of Somatic Mutation During Embryogenesis



Observed Symptoms with a Range of Severity

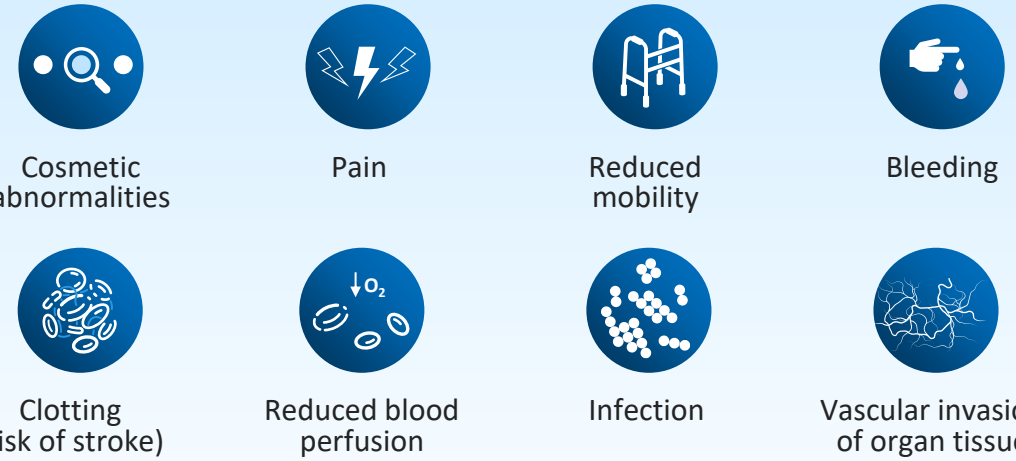
Key factors include

- **Location of lesion**
  Internal vs. cutaneous
- **Type of vasculature**
  & other tissue involved

Vascular Anomalies – Phenotype & Symptoms

Variety of Observed Symptoms are Part of Subtypes of the Same Disease

Symptoms



Symptoms occur with a range of severity

PIK3CA-driven Vascular Anomalies

PROS
(PIK3CA-Related Overgrowth Spectrum)

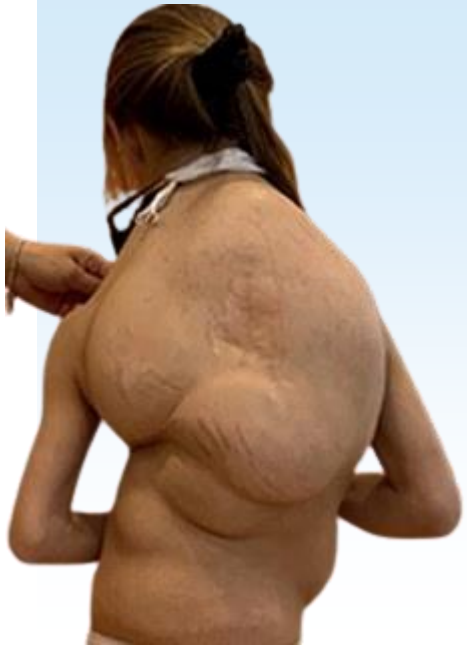
PIK3CA-driven Lymphatic Malformations
(LM)

PIK3CA-driven Venous Malformations
(VeM)

PIK3CA-driven Cerebral Cavernous Malformations
(CCM)

Deep Dive – PIK3CA-Related Overgrowth Spectrum (PROS)

PIK3CA-Related Overgrowth Spectrum (PROS)



Includes many conditions:

- CLOVES
- M-CAP
- KTS
- FIL
- FAVA
- *& others*

Multifocal, syndromic disease presentation:

- Malformation of multiple types of vasculature (LM and/or VeM)
- May also include many different tissues: fat, muscle, bone, nerve, brain
- May feature fluid-filled or lipomatous (fatty) overgrowth
- Typically more severe disease

Symptoms include:

- Often severe manifestations of lymphatic and/or venous symptoms
  - Bleeding, infection, pain, limited mobility
- Overgrowth may impinge on critical organs & alter skeletal structure

100% PIK3CA-driven
share of prevalence driving disease

~5,000-10,000 patients
in the US (PIK3CAmut)

Vijoice (alpelisib) is only US approved
systemic therapy for PROS

Sources: ISSVA classification, NORD, Mayo Clinic, Novartis, Penington et al 2023, Gallagher et al 2022, Luks et al 2015, Limaye et al 2015, Peyre et al 2021, Hong et al 2021

Deep Dive – PIK3CA-Driven Lymphatic Malformations (LM)

Lymphatic Malformations (LM)

Simple/Isolated (Cystic)

- Micro
- Macro
- **Mixed**

~60K US patients

Complex anomalies:

- GLA
- KLA
- GSD
- Etc.

~1-2K US patients

Disease presents with malformed lymphatic vessels/channels:

- Often occur in lymph-rich regions like head and neck, though may infiltrate other soft tissues anywhere on the body
- Cystic LMs are most common, characterized by size: Macro, Micro, Mixed
    - Most cystic LMs are mixed

Symptoms include:

- Buildup of lymph fluid & blood into cystic pockets causing pain, swelling, leakage, and functional/mobility impairment
- Dysfunctional lymphatic system can lead to infection, cellulitis

80% PIK3CA-driven
share of prevalence driving disease

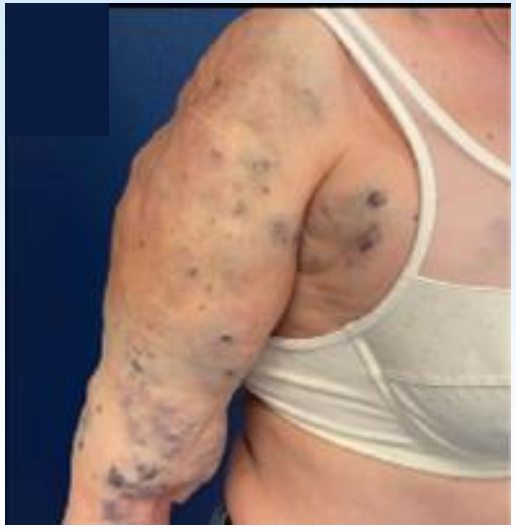
~60,000-65,000 patients
in the US (PIK3CAmut)

No approved systemic therapy
for LMs population

Sources: ISSVA classification, NORD, Mayo Clinic, Novartis, Penington et al 2023, Gallagher et al 2022, Luks et al 2015, Limaye et al 2015, Peyre et al 2021, Hong et al 2021

Deep Dive – PIK3CA-Driven Venous Malformations

Venous Malformations (VeM)



Disease presents with abnormal, dilated veins containing blood

- Soft, compressible lesions with blueish color, often sub-cutaneous
- Veins consist of enlarged or distorted endothelial cells surrounded by disorganized extracellular matrix
- May be localized/superficial, but can also infiltrate muscles/joints

Symptoms include:

- Pain and functional impairment due to localized or diffuse swelling
- Vein leakage leads to bleeding and reduced blood perfusion of organs
- Risk of blood clots, which can lead to pulmonary embolism & stroke

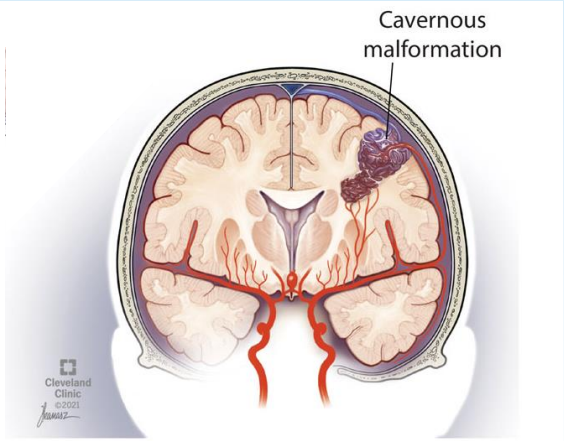
25% PIK3CA-driven
share of prevalence driving disease

~20,000-25,000 patients
in the US (PIK3CAmut)

No approved systemic therapy
for VeMs population

Deep Dive – PIK3CA-Driven Cerebral Cavernous Malformation

Cerebral Cavernous Malformation (CCM)



Defined by enlarged capillary cavities in the brain:

- Often asymptomatic for years, avg age of symptom onset is ~45 years
- “Popcorn” like presentation on MRI

Symptoms include:

- Lesions can cause headaches & neurological symptoms like numbness/ tingling
- In more severe cases, lesions are prone to rupture, leading to epileptic seizures, hemorrhaging, and functional neurological deficit

40-55% PIK3CA-driven
share of prevalence driving disease

~50,000-70,000 patients
in the US (PIK3CAmut)

No approved systemic therapy
for CCMs population

Vascular Anomalies – Patient Numbers

PIK3CA-driven Vascular Anomalies (VAs)

~170K US patients

Vascular Anomaly Subtypes

Initial clinical focus: ~25k US patients seeking systemic therapy

	PIK3CA-Related Overgrowth Spectrum (PROS)	PIK3CA-driven Lymphatic Malformations (LM)	PIK3CA-driven Venous Malformations (VeM)	PIK3CA-driven Cerebral Cavernous Malformations (CCM)
	~5-10k US patients	**~60-65k** US patients	**~20-25k** US patients	**~50-70k** US patients
	25-30% seek systemic tx	**20-25%** seek systemic tx	**15-20%** seek systemic tx	**25-30%** seek systemic tx

Sources: ISSVA classification, NORD, Mayo Clinic, Novartis, Penington et al 2023, Gallagher et al 2022, Luks et al 2015, Limaye et al 2015, Peyre et al 2021, Hong et al 2021, and company primary market research

Patient Referral Pathway

	Local Providers	Vascular Anomaly Centers
Details	**Generalized set of healthcare providers:** • Primary care • Dermatologist • ENT • Surgeon	**Coordinated care from vascular anomaly experts:** • Genetic testing, multidisciplinary care team, clinical trial & reimbursement support, etc. • Often associated with children's hospitals in US/Europe
Presentation	**Often present early (birth to 2 years old)** HCP involved depends on primary symptoms	**Usually referred from local providers**
Diagnosis	**Symptoms not usually diagnosed** as part of broader condition	**Experts will diagnose VAs clinically** (+/- genetic testing)
Treatment	**Symptomatic treatment,** watch-and-wait approach	**Multidisciplinary treatment approach:** Surgeon, interventional radiologist, dermatologist, hematologist-oncologist

Referral may take years:

- range of symptoms
- rarity of conditions
- misdiagnosis

Current Treatment Paradigm

Disease severity	Mild	Moderate	Severe
Current Treatment Paradigm	Watch & wait; Supportive treatment	Local intervention when necessary/possible	Attempt systemic therapy (limited duration)

Available Tx Options	• Compression garments
	• Anticoagulants
	• Pain medication
		• Surgery
		• Laser therapy
		• Sclerotherapy (TARA-002)
		• Topical (QTORIN®)
			• Non-selective targeting:
			  • Alpelisib
			  • Sirolimus
			  • Serabelisib (KP-001)

Limitations	Temporary; insufficient for majority of patients	Invasive, painful, likely to recur; Limited to cutaneous or well-defined lesions	Incomplete responses, side effects & toxicities limit widespread use

Potential Future Treatment Paradigm

Disease severity	Mild	Moderate	Severe
Future Treatment Paradigm	Watch & wait; Supportive treatment	**Evaluate chronic systemic therapy** +/- complementary interventions when feasible/beneficial	
Potential Available Tx Options	• Compression garments • Anticoagulants • Pain medication	**Mutant-selective targeting: zovegalisib** +/- complementary local tx: • Surgery, laser therapy • Sclerotherapy (TARA-002) • Topical (QTORIN®)	

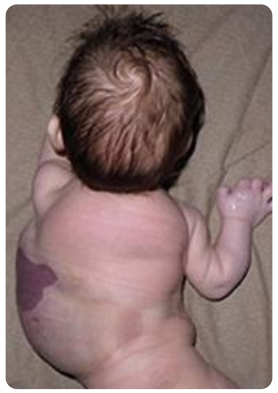
Potential benefits of zovegalisib:
Earlier use, better targeting of disease driver, chronic treatment

Example Case Study #1 – PROS

8-Year-Old Patient With PROS (CLOVES)[1]

Misdiagnosed **at birth**

Large thoraco-abdominal lymphangioma, multiple lipomas, covered by a capillary malformation, and hypertrophy of leg



3 months old: First of three scleroembolization procedures

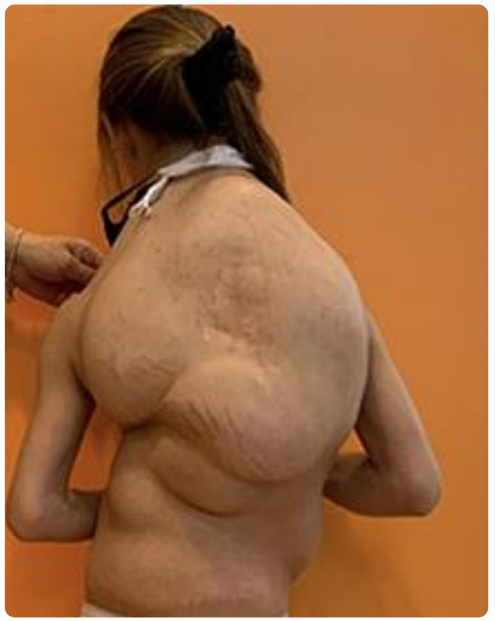
12 months old: Surgery to remove lymphangioma, but residual malformation reactivated

~6 years old: **sirolimus started for 10 months** (0.8 mg/m^2 BID) without improvement; stop due to infection

H1047R (11% of variant allele frequency) identified by whole exome sequencing

~7 years old: **started alpelisib** (50 mg) and has had partial regression

12+ months on alpelisib



KEY:

Clinical milestones | **Systemic treatment**

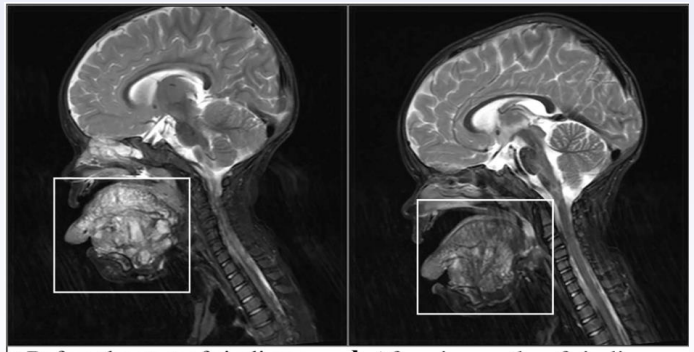
Sources: 1. Pagliazzi et al, 2021

Example Case Study #2 – LM

8-Year-Old Patient with LM

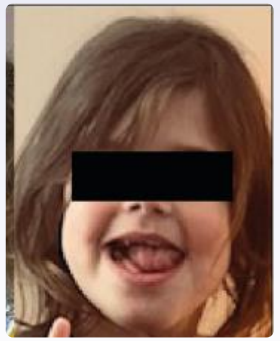
At birth:
Presented with LM of the tongue and mouth

Patient had substantially reduced QoL, experiencing repeated periods of hospitalization; impaired speech development, and challenges feeding

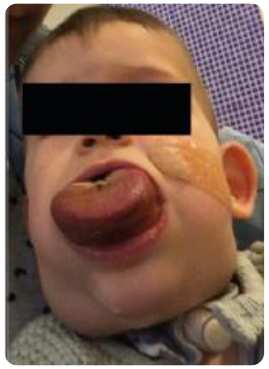


a Before the start of sirolimus **b** After six months of sirolimus

~3 years old:
Underwent a surgical intervention including a partial tongue resection



First few months of life:
A life-threatening situation led to the need for a tracheostomy to provide an airway



~1 year old:
Sirolimus started with some reduction in the LM after 6 months

However, patient experienced adverse events: intermittent aphthous stomatitis, upper airway infections, tonsillitis, and elevation of triglycerides

It was decided to **stop sirolimus** after 6 months

Restarted sirolimus for 21 months

~5 years old:
There was new swelling of the tongue, pain returned, and she developed blisters on the tongue, so **sirolimus again restarted**

KEY:

Clinical milestones | **Systemic treatment**

https://link.springer.com/article/10.1007/s12325-021-01758-y

Vascular Anomalies – Systemic Therapy Options

	1st Generation Non-selective PI3K pathway inhibition	2nd Generation Non-selective PI3Kα inhibition		3rd Generation Mutant-selective PI3Kα inhibition
	Sirolimus ***(mTORi)***	**Serabelisib** ***(KP-001)***	**Alpelisib**	**Zovegalisib**
1st Patent Filing	**1994**[1]	**2007**	**2008**	**2019**
Clinical Dev't in VAs	**2010s:** Early use in VAs **2016:** Ph3 VASE trial starts	**2021:** 1st VAs trial in Japan **2026:** Ph3 trial in US	**2020:** EPIK-P1 for AA	**2024:** ReInspire
Approvals	**1999:** Renal transplant *later LAM ('15), angiofibroma ('22)*	**FIH 2013** for solid tumors (not approved)	**2019:** Breast cancer **2023:** AA in PROS	n/a
	mTOR inhibition leads to immunosuppression: infection risk	**Target coverage limited by WT PI3Kα toxicity: Diarrhea/GI tox, hyperglycemia, rash, hair loss, decreased growth velocity**		**Greater target coverage allowing for lower toxicity from WT PI3Kα and other off-target inhibition**

1. First patents for oncology

Alpelisib – Development & Regulatory Timeline

Breast Cancer:

SOLAR-1 readout + FDA approval in 2019

2020 — 2025 — 2030

Retrospective	1st Confirmatory (failed)	2nd Confirmatory
EPIK-P1	**EPIK-P2**	**EPIK-P4[3]**
outcome Conditional Approval for PROS in 2022[1] at 250mg QD	**outcome** Failed to meet primary endpoint[2] at 125mg QD (with intrapatient dose escalation)	**outcome** Pending, at 250mg QD
timeline 2020-2021	**timeline** 2021-2024	**timeline** 2025-2028
design Retrospective chart review (N=57)	**design** RCT vs placebo (16 wk) then crossover to ALP (N=200)	**design** Single arm (N=104)

Also ongoing[3]:

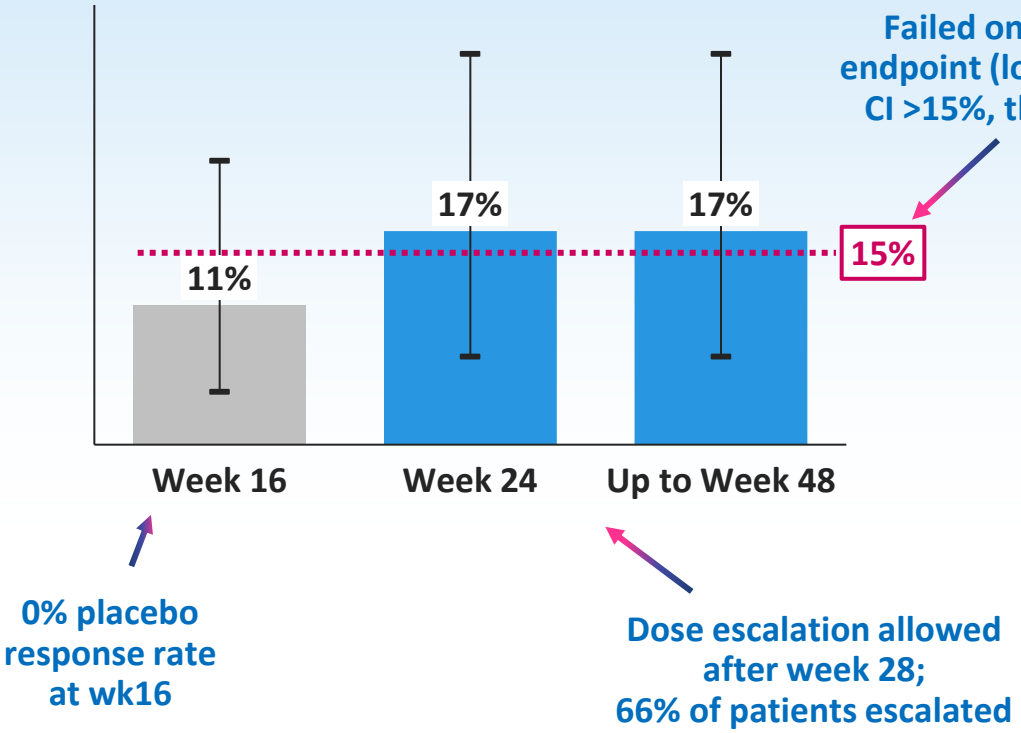
EPIK-L1: Lymphatic malformations

EPIK-P3: Long-term follow-up for EPIK-P1 patients

1. FDA review document; 2. Adults; Canaud 2024 Blood 144:5512; 3. clinicaltrials.gov listing

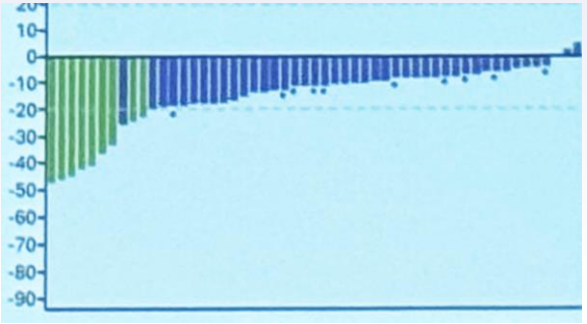
EPIK-P2 Results – Radiological Response Rate

EPIK-P2 Efficacy Results (Adults started at 125mg QD, n=54)[1]



EPIK-P2 Waterfall (presented at ASPHO 2025[2])

- Median depth of reduction: ~11%
- Max depth of reduction: ~46%



1. Canaud 2024 Blood 144:5512 and results from clintrials.gov listing; 2. Hammill, ASPHO 2025 oral presentation.

EPIK-P2 Safety Data in Adults

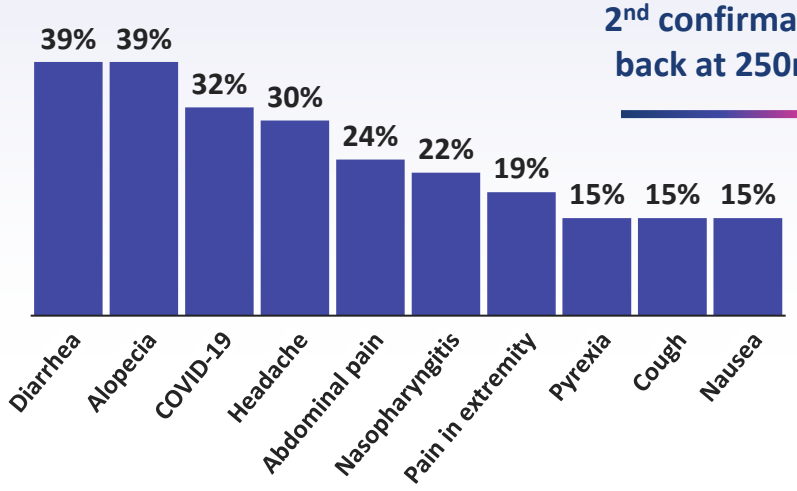
EPIK-P2[1] Up to Week 48

17% ORR

~180mg avg dose[3]

30% SAEs

66% of pts escalated dose up from 125mg after Week 28



2nd confirmatory trial back at 250mg dose

EPIK-P4[1] initiated 2025

250mg starting dose

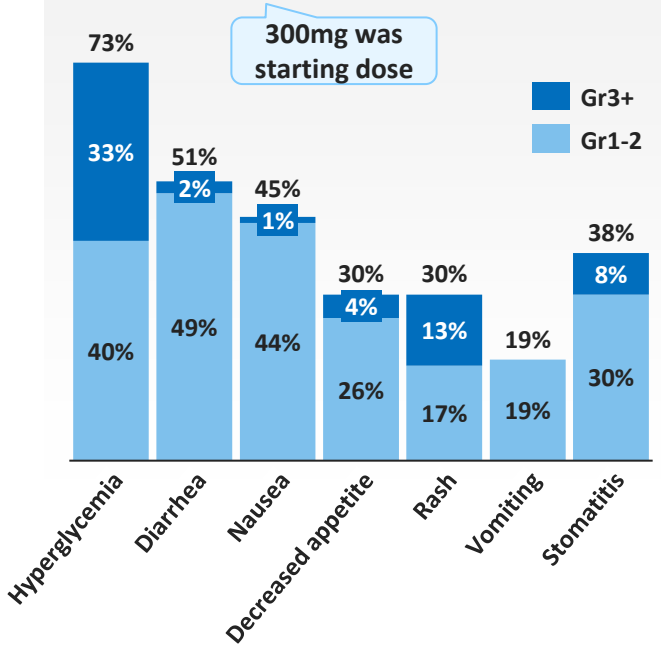
Trial ongoing

EPIK-B5[2] (breast cancer)

~220mg avg dose[4]

71% Gr3+ AEs

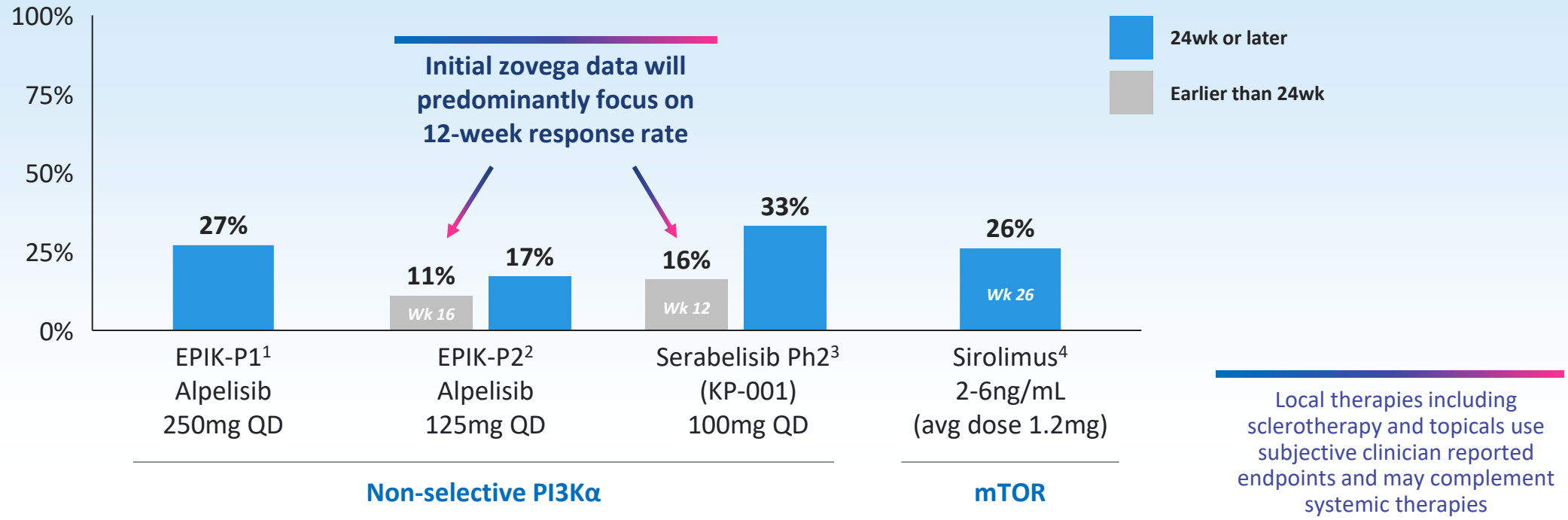
300mg was starting dose



1. Results posted at clintrials.gov listing; 2. SABCS 2025 #RF7-02 3. approximated from data on clintrials.gov listing. 4. approximated from dose modification data from SABCS 2025 #RF7-02

All Current Treatments Leave Large Unmet Medical Need

Volumetric Response Rates for Systemic Therapies in VAs



Local therapies including sclerotherapy and topicals use subjective clinician reported endpoints and may complement systemic therapies

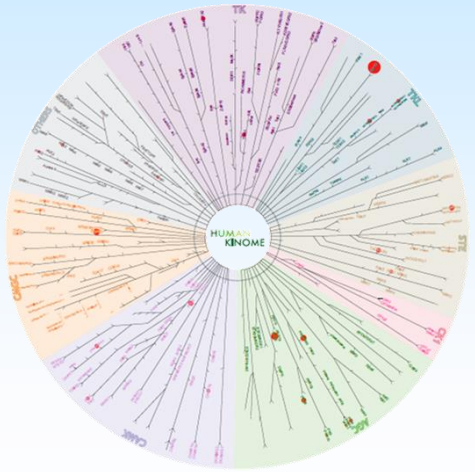
Need for a more efficacious systemic therapy for PIK3CA-driven VAs

1. FDA review document; 2. Adults; Canaud 2024 Blood 144:5512; 3. Adults and pediarics; Ozeki 2025, Orphanet Journal of Rare Diseases 20:64; 4. Parker 2019, Genet Med 21, 1189–1198; response determined using difference in affected tissue growth between the run-in and sirolimus treatment phases, and includes both pediatric and adult patients. Note: These data are derived from different clinical trials at different points in time, with differences in molecule composition, trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

Zovega – Inhibits The Core Driver of The Disease

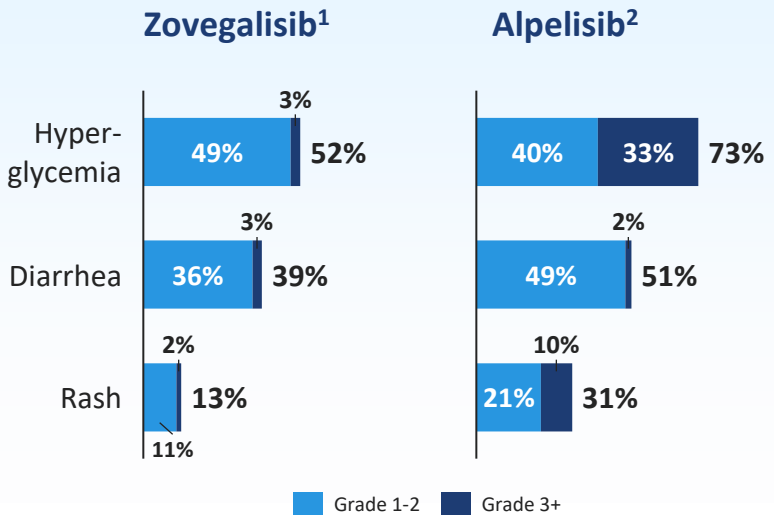
Favorable Selectivity

Selective for mutant PI3Kα



Favorable Tolerability

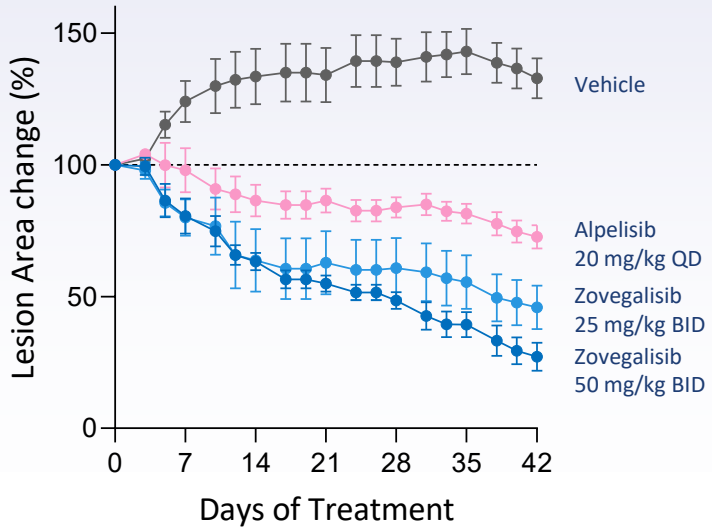
Fewer key common PI3K class AEs



*interim data from oncology trials[1-2]

Favorable Efficacy

Reduction of lesions in vivo[3]



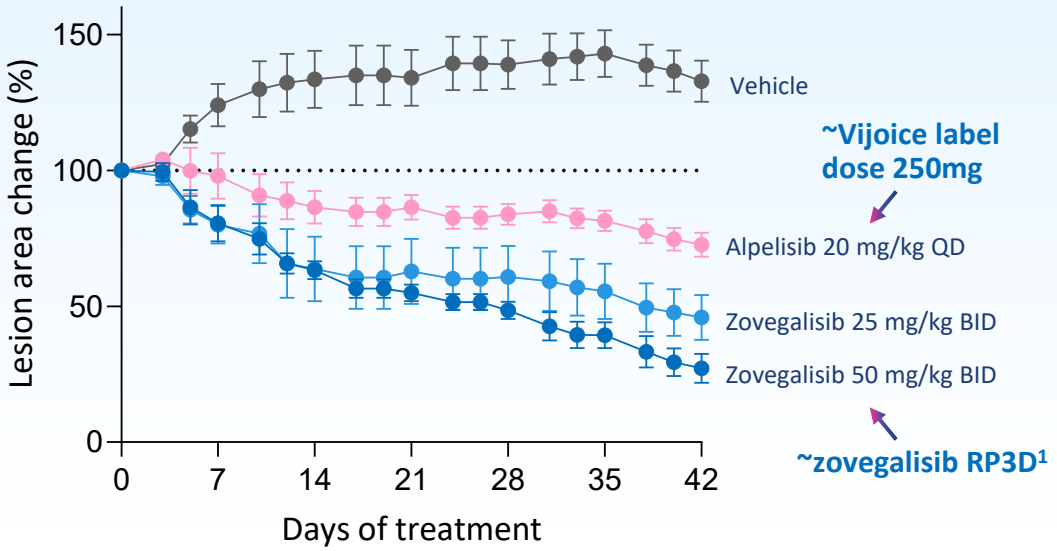
Zovegalisib is the only known clinical-stage mutant-selective PI3Kα inhibitor for vascular anomalies

1. Interim AE rates for zovegalisib part of ongoing ReDiscover trial studying solid tumors (oncology); 2. Alpelisib AE rates from EPIK-B5 study (oncology), SABCS 2025 #RF7-02; 3. HUVEC PIK3CA-H1047R Xenograft VM Mouse Model;
Note: These data are derived from different clinical trials at different points in time, with differences in molecule composition, trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

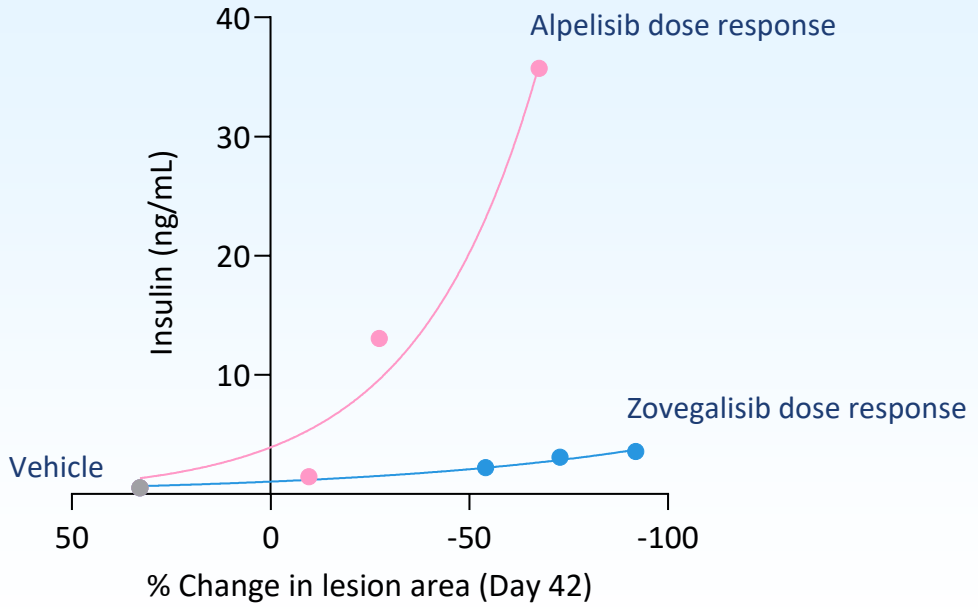
Zovega – Preclinical Data

Zovegalisib's greater target coverage pre-clinically leads to greater lesion size reduction

PIK3CA-Driven VM PDX (H1047R)[1]



Efficacy vs. Insulin induction



Mutant-selective approach allows for greater target coverage and reduced off-target toxicity in VAs

Note: Preclinical data based on HUVEC PIK3CA-H1047R Xenograft VM Mouse Model;
1. mouse exposure approximately equivalent to human exposures for 400mg BID fed and 600mg BID fasted (data presented at International Conference on Vascular Anomalies, Feb. 2025).

ReInspire – Zovegalisib Study Design

Part 1: Dose Selection

All PIK3CA-driven Vascular Anomalies
(primary focus: PROS and LMs)

Adults & Adolescents
(≥12 years old)

→

Initial clinical data

Randomized dose finding:
400mg, 300mg, 100mg BID fed dosing
(N=~15 each)

RP2D(s) →

Part 2: Dose Expansion

Expansion patient population
to be confirmed

Expansion cohort(s)

Pediatrics
(6-11 years old)

→

Pediatrics cohort opened Q1 2026

Dose Escalation

RP2D(s) →

Expansion Cohort(s)

Adults & Adolescents cohort initiated Q1 2025; Pediatrics (6-11 y/o) cohort opened Q1 2026

Note: ReInspire trial also includes a cohort for pediatrics ages 2-5 years old which is not yet opened

Endpoints

Regulatory Endpoint: Radiographic Response (MRI)

Response defined as ≥20% volumetric reduction

Used in EPIK-P1, -P2, -P3, -P4, and -L1 trials of alpelisib in PROS and LMs

Reported Outcome Endpoints

Caregiver/patient reported outcomes have been explored by other groups, but not yet validated

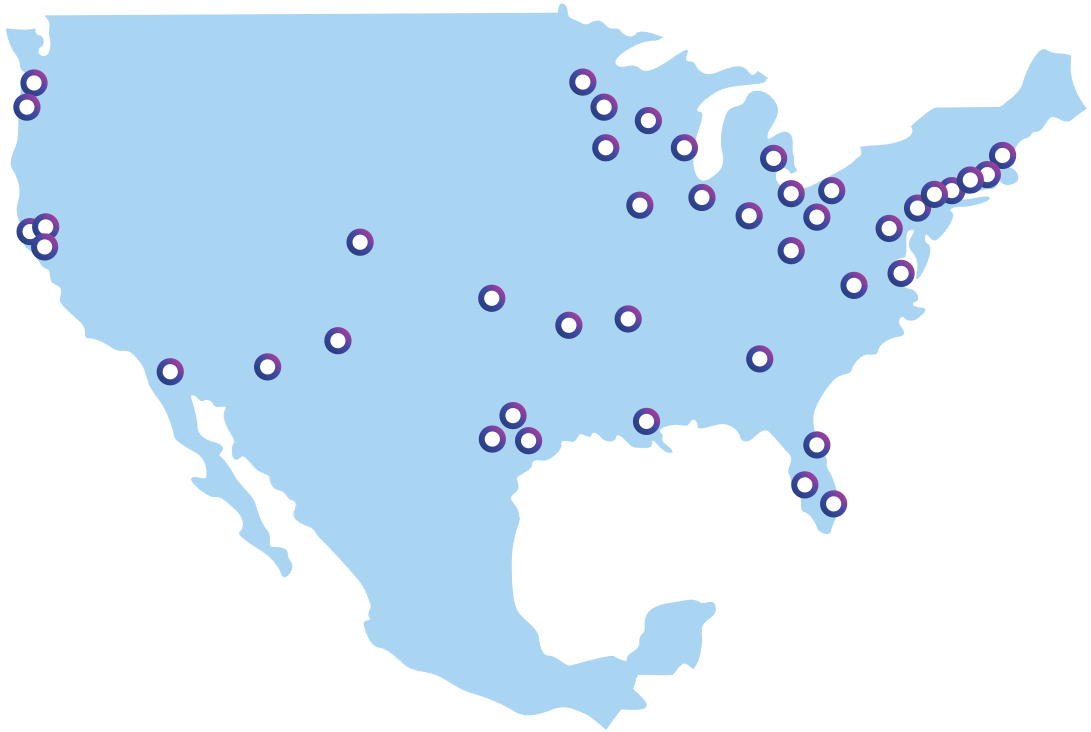
Relay Tx in process of validating a fit-for-purpose PRO tool for use in ReInspire trial

Radiographic response is a precedented regulatory endpoint, though PRO validation may be supportive

Blockbuster Potential Across Concentrated Centers

Vascular Anomaly Centers (VACs) identified by ISSVA

United States



Europe

Primary treatment for VAs patients is concentrated in <100 multidisciplinary VACs across US and Europe

Source: ISSVA https://www.issva.org/resources/multidisciplinary-teams

ReInspire – Potential Regulatory Approach

Part 1: Dose Selection

All PIK3CA-driven Vascular Anomalies (primary focus: PROS and LMs)

Adults & Adolescents
(≥12 years old)

→ **Randomized dose finding:**
3 Doses: N=15 each

RP2D(s) →

Part 2: Dose Expansion

Expansion patient population to be confirmed

Expansion cohort(s)

Alpelisib registrational path:
- Accelerated approval: EPIK-P1 (N=57)
- Confirmatory trial (failed): EPIK-P2 (N=110*)

Pediatrics
(6-11 years old)

Dose Escalation

RP2D(s) →

Expansion Cohort(s)

No systemic therapy currently has full FDA approval for Vascular Anomalies; Potential for Accelerated Approval pathway

* EPIK-P2 also included 55 patients in the placebo arm, none of whom responded at the 16 week timepoint (primary endpoint)

Vascular Anomalies Overview

~170k US patients with PIK3CA-driven Vascular Anomalies

Somatic PIK3CA mutation → **drives malformed vasculature** → **leading to vascular anomalies**

Current treatment options are limited

Local Treatments: temporary, only treat symptoms → **Systemic Treatments: non-selective, limited toxicity/efficacy** → **Large unmet medical need**

Zovegalisib is uniquely positioned to address driver of disease

First mutant-selective PI3Kα inhibitor

Initial clinical data showing:

- Selectivity
- Tolerabilit
- y
- Efficacy

Potential for chronic systemic treatment option

Sources: ISSVA classification, NORD, Mayo Clinic, Novartis, Penington et al 2023, Gallagher et al 2022, Luks et al 2015, Limaye et al 2015, Peyre et al 2021, Hong et al 2021, and company primary market research

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