Initial Results of Zovegalisib (RLY-2608), a Mutant-Selective PI3Kα Inhibitor in Adult and Adolescent Patients with *PIK3CA*-Driven Vascular Malformations

Bryan Sisk[1], Ionela Iacobas[2], Ahmad Al-Huniti[3], Eulalia Baselga[4], Daniel Willis[1], Joana Mack[5], Vivian Y. Chang[6], Sarah Mc Dermott[7], Adrienne Hammill[8], Michael White[9], Beth Apsel Winger[10], Martin A. Robledo[11], Xiaofeng Wang[11], Rick Blakesley[11], Caitlin Patriquin[11], Sonia Singh[11], Brenton G. Mar[11], Shelley Crary[5]

[1]Washington University School of Medicine, St. Louis, Missouri, USA; [2]Baylor College of Medicine / Texas Children's Hospital, Houston, Texas, USA; [3]The Mayo Clinic, Rochester, Minnesota, USA; [4]Hospital Sant Joan de Deu, Barcelona, Spain; [5]Arkansas Children's Hospital/ University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [6]University of California, Los Angeles Health, Los Angeles, California, USA, [7]University of Wisconsin-Madison Hospital, Madison, Wisconsin; [8]Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; [9]Children's Hospital of Atlanta, Atlanta, Georgia, USA; [10]University of California, San Francisco, Birthmarks and Vascular Center, San Francisco, California, USA; [11]Relay Therapeutics, Cambridge, Massachusetts, USA

Presented at ISSVA, Philadelphia, USA, May 20, 2026

#488

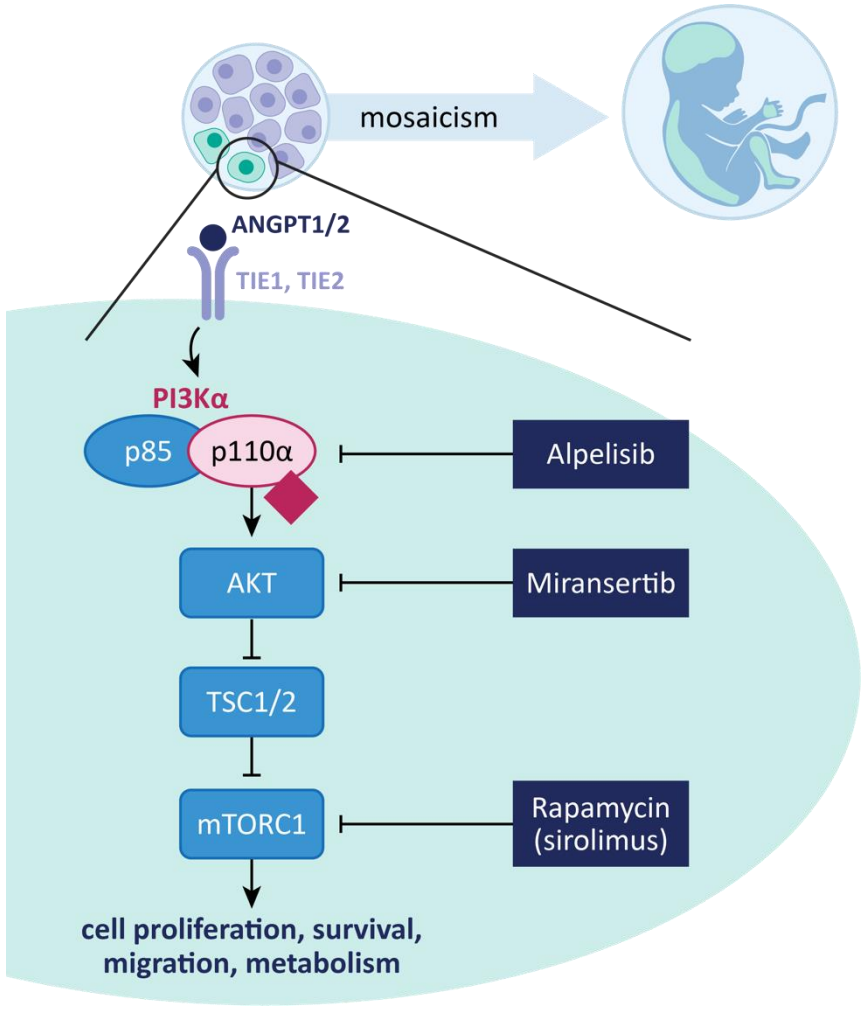
ISSVA WORLD CONGRESS 2026: The Latest in Vascular Anomalies Philadelphia, PA, USA 19-22 May 2026

ISSVA International Society for the Study of Vascular Anomalies

Disclosure slide

Dr. Sisk is a consultant for Relay Therapeutics, Novartis, Kaken Pharmaceuticals, Palvella Therapeutics, Palinos Therapeutics, and VasqueBio.

Slow-Flow Vascular Malformations are Highly Symptomatic Diseases Driven by Somatic Mosaic *PIK3CA* Mutations



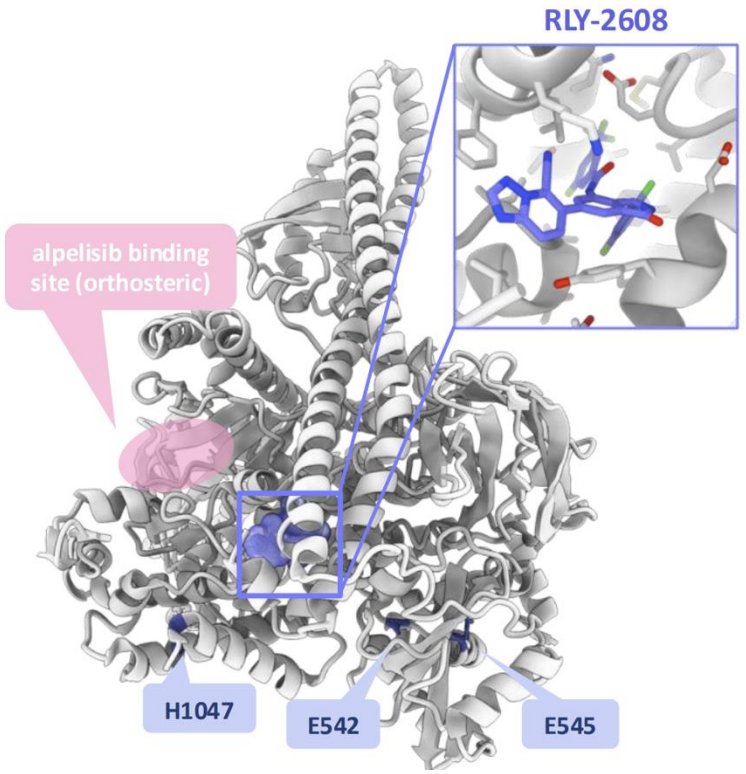
Adapted from Petkova et al, J Clin Invest 2024.

- Isolated and syndromic slow-flow vascular malformations, such as LMs and PROS, are driven by somatic mosaic ***PIK3CA* mutations**
- Non-mutant selective PI3Kα pathway inhibitors can have dose limiting toxicities including **hyperglycemia, rash, stomatitis**[1] and **growth retardation**[2]
- Alpelisib has US accelerated approval based on RWD with a **27% volumetric response rate** (RR)[3]
- Though better tolerated, a starting dose of **125 mg** showed a RR of only **16.7%** in the prospective EPIK-P2 study[4]

LM: Lymphatic Malformation, PROS: PIK3CA-related overgrowth spectrum, RWD: Real-World Data

1. Vijoice USPI, 2. Triana et al. JoVA 2025, 3. Adult RR and dose, 4. Adult data from Canaud, López-Gutiérrez, Hammill et al. ASPHO 2025

Zovegalisib (RLY-2608) is a Novel, Oral, Allosteric Mutant-Selective PI3Kα Inhibitor



- **Zovegalisib (RLY-2608)** is a novel, **pan-mutant-selective PI3Kα inhibitor** that binds an allosteric pocket in activated PI3Kα
- Zovegalisib has demonstrated **8-12 fold selectivity** for PI3Kα helical and kinase mutants over wildtype PI3Kα[1]
- Zovegalisib has demonstrated **greater lesion regression** and **less insulin induction** compared to alpelisib in vivo xenograft and genetic vascular malformation models (See presentation #404, **Graupera et al. ISSVA 2026** on Friday, 22 May)
- Zovegalisib has **FDA Breakthrough Therapy Designation** in HR+ HER2- breast cancer and is currently in pivotal Phase 3 development

1. Varkaris et al. Cancer Dis 2024

ReInspire: a Phase 2 Trial of Zovegalisib in Pediatric and Adult Patients with PIK3CA-driven Vascular Malformations

Part 1: Dose Selection
(Data shown today)

Group 1: Adults and Adolescents (≥12yrs)

(N=32)

R

- 400mg BID *(n=10)*
- 300mg BID *(n=11)*
- 100mg BID *(n=11)*

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

- In **Part 1 Group 1** patients ≥12 yo were **randomized to 3 biologically active doses** up to the **oncology dose of 400mg BID**
- Intended to explore a **broad range** of safety and efficacy and **identify dose(s)** to expand for further exploration in Part 2

Part 2: Dose Expansion

Expansion cohorts opened at:
- **300mg BID**
- **400mg QD**

Key Inclusion Criteria

- Clinical diagnosis of PROS or a malformation within the ISSVA classification
- Activating *PIK3CA* mutation by local assessment
- Severe, symptomatic, and/or progressive disease
- ≥ 1 target lesion amenable to volumetric assessment

Key Study Endpoints

- Safety, tolerability, RP2D selection per group
- Efficacy: 20% reduction in target lesion volume by BICR
- Changes in reported clinical outcome assessments

BICR: Blinded Independent Central Review; RP2D: Recommended Phase 2 Dose; PROS: PIK3CA-related overgrowth spectrum

ReInspire preliminary data as of 4/15/2026

Zovegalisib – RelnspireTrial Demographics (Part 1, Group 1)

	Total (N=32)	100mg BID (N=11)	300mg BID (N=11)	400mg BID (N=10)
Age (years), median (range)	**24.5 (12, 63)**	31 (13, 50)	24 (13, 54)	19.5 (12, 63)
12-17 / ≥18, n (%)	**10 (31) / 22 (69)**	4 (36) / 7 (64)	2 (18) / 9 (82)	4 (40) / 6 (60)
Sex, M/F, n (%)	**14 (44) / 18 (56)**	6 (55) / 5 (45)	5 (45) / 6 (55)	3 (30) / 7 (70)
Disease Classification, n (%)				
PROS	**22 (69)**	8 (73)	6 (54)	8 (80)
CLOVES	**5 (16)**	1 (9)	3 (27)	1 (10)
KTS	**10 (31)**	4 (36)	2 (18)	4 (40)
Other	**7 (22)**	3 (27)	1 (9)	3 (30)
LM	**8 (25)**	3 (27)	4 (36)	1 (10)
VeM	**2 (6)**	0	1 (9)	1 (10)
Performance Status at Baseline, 50-70/ ≥80[1], n (%)	**5 (16) / 27 (84)**	2 (18) / 9 (82)	1 (9) / 10 (91)	2 (20) / 8 (80)
Pre-diabetic[2], n (%)	**8 (25)**	1 (9)	6 (55)	1 (10)
Local PIK3CA Status at Baseline, n (%)				
Kinase mutation	**10 (31)**	4 (36)	4 (36)	2 (20)
Non-Kinase mutation	**16 (50)**	4 (36)	6 (55)	6 (60)
No mutation documented	**6 (19)**	3 (27)	1 (9)	2 (20)
Prior disease-related systemic treatment, median	**1**	1	2	1
None, n (%)	**9 (28)**	3 (27)	3 (27)	3 (30)
Prior alpelisib / sirolimus, n (%)	**23 (72)**	8 (73)	8 (73)	7 (70)
Prior disease-related surgery, n (%)	**19 (59)**	5 (45)	6 (55)	8 (80)
Prior catheter-based procedures, n (%)	**18 (56)**	6 (55)	8 (73)	4 (40)

1. Lansky performance status for patients <16 years old or Karnofsky performance status for patients ≥16 years old; 2. Baseline HbA1c ≥5.7, glucose ≥100, or medical history of pre-diabetes mellitus

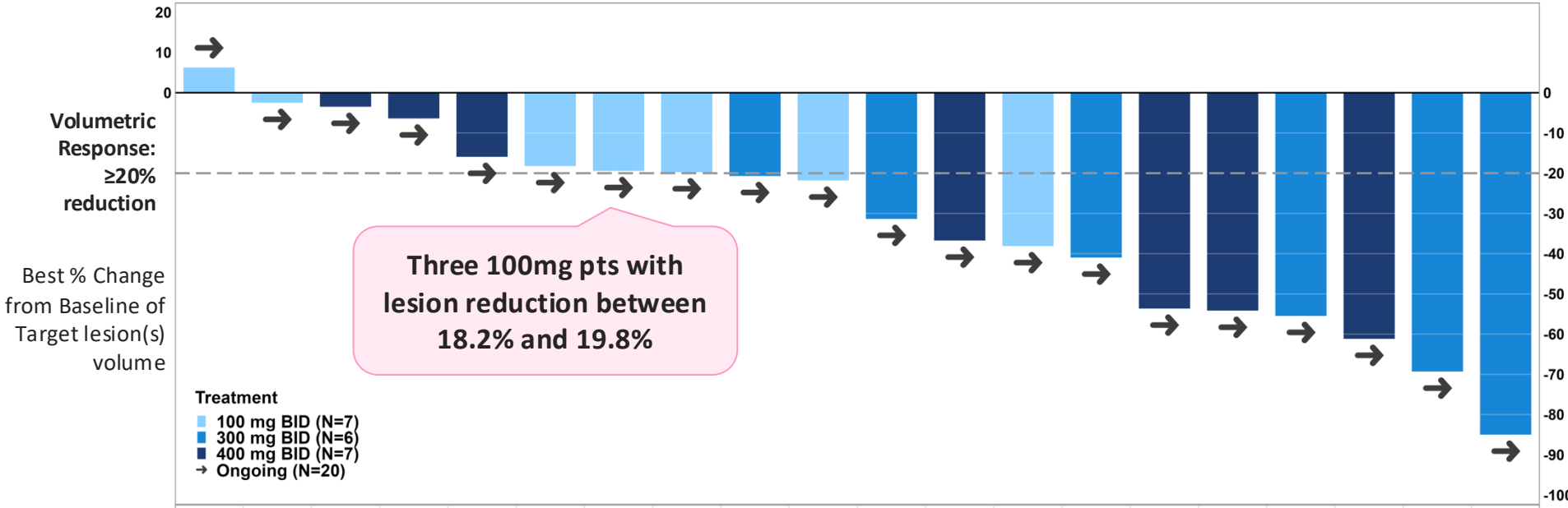
RelnspirepreliminarydataasofRelnspire preliminary data as of 04/15/2026

Zovegalisib – 60% Volumetric Response Rate by BICR Across All Doses

Volumetric Response Rate (VRR)[1]

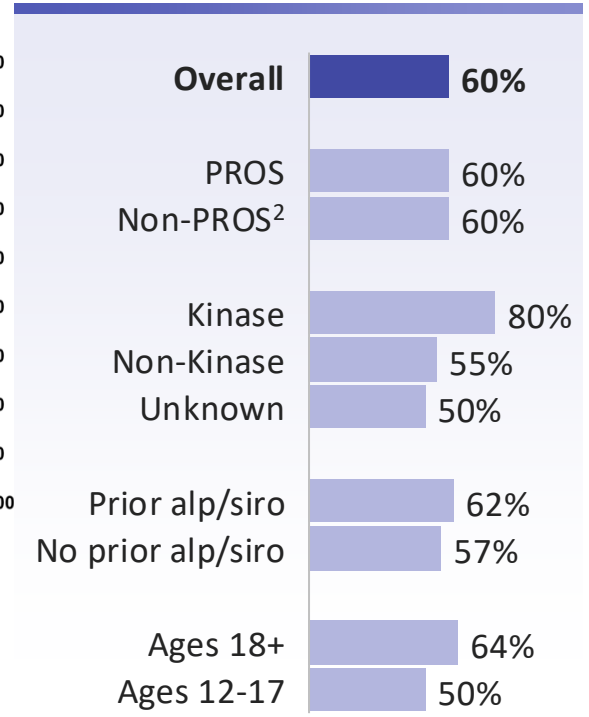
Overall: 60% (12/20)

100mg BID	300mg BID	400mg BID
29% (2/7)	100% (6/6)	57% (4/7)



Subtype	LM	PROS	VeM	PROS	PROS	PROS	PROS	PROS	PROS	PROS	LM	PROS	PROS	PROS	PROS	PROS	PROS	PROS	LM	LM
PROS subtype		KTS		FAO	KTS	FAO	FAVA	KTS	CLOVES	CLOVES		KTS	KTS	KTS	CLOVES	FAVA	CLOVES	KTS		
PIK3CA mutation	NK	NK	NK	NK	Unk	K	Unk	NK	NK	K	NK	Unk	K	NK	K	NK	NK	NK	K	Unk
Prior alp/siro	S	A + S	S	—	A + S	—	A + S	—	[illegible]	A	A + S	—	—	—	A + S	A + S	A + S	S	—	S
BL volume (L)	0.4	5.4	0.5	0.9	1.2	0.4	0.8	18.0	3.4	0.9	0.2	2.7	0.4	1.0	1.2	0.1	0.2	0.3	0.1	0.1
%CFB W12	6.3	-2.5	-3.5	-6.4	-15.9	-18.2	-1.4	-12.7	-20.7	-21.8	-31.4	-36.7	-38.1	-41.0	-53.7	-44.1	-49.0	-50.7	-69.3	-70.9
%CFB W24		3.5					-19.5	-19.8								-54.2	-55.5	-54.4		-75.6
%CFB W36		8.9																-61.2		-85.0
BOR	SD	SD	SD	SD	SD	SD	SD	SD	uVR	uVR	uVR	uVR	uVR	uVR	uVR	cVR	cVR	cVR	uVR	cVR

Consistent benefit across subgroups

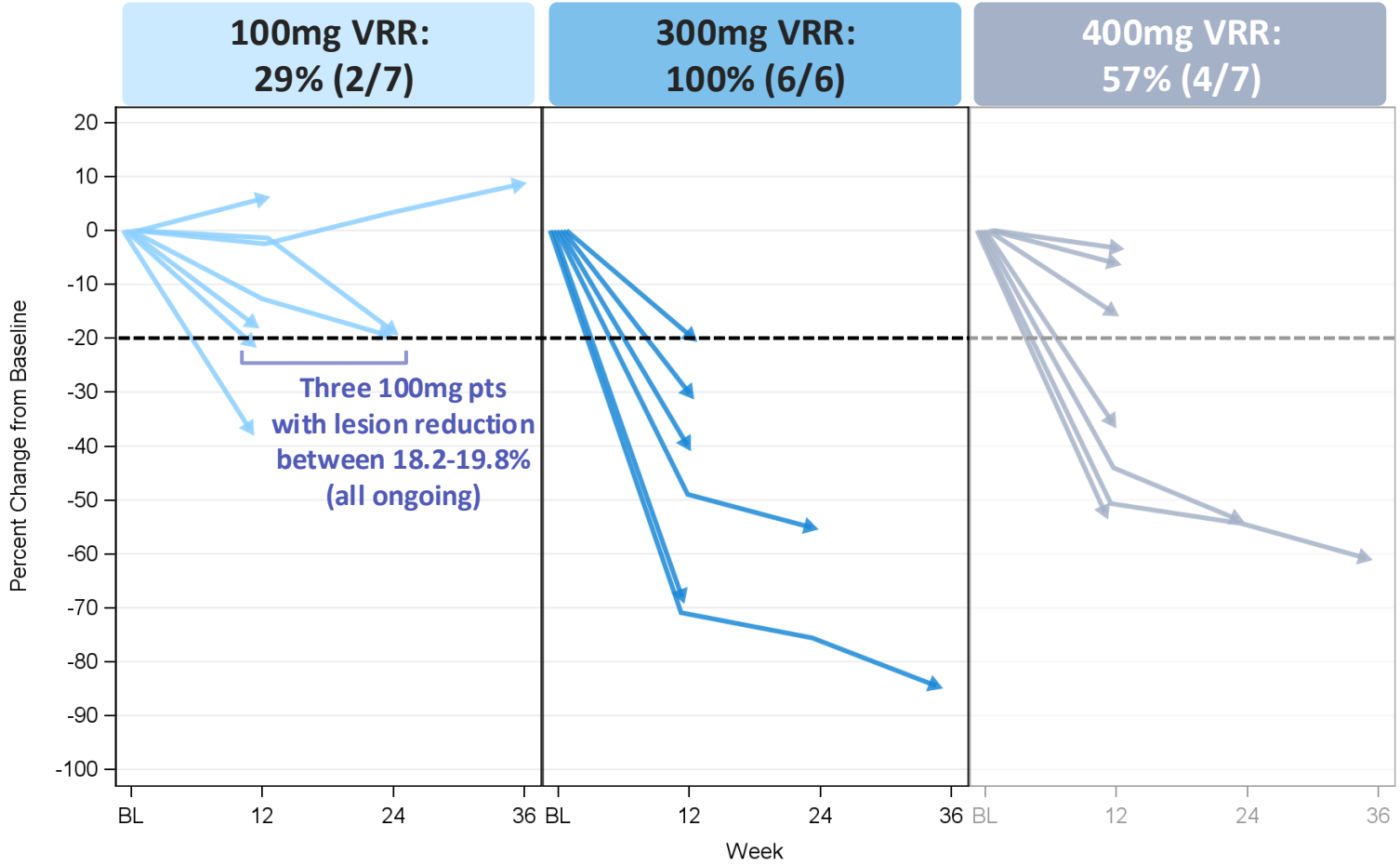


1. Includes both confirmed and unconfirmed responses; Volumetric Response (VR) = 20% or greater reduction in target lesion volume by blinded independent central review (BICR); cVR = Confirmed Volumetric Response (VR with 2nd scan to confirm response), uVR = Unconfirmed Volumetric Response (VR without confirmatory scan), SD = Stable Disease; 2. Non-PROS includes lymphatic malformation and venous malformation.

RelnspIre preliminary data as of 04/15/2026

#488

Zovegalisib - Volumetric Response Over Time (BICR)



Overall VRR[1]: 60% (12/20)

All patients ongoing

Reductions generally deepened over time at all doses

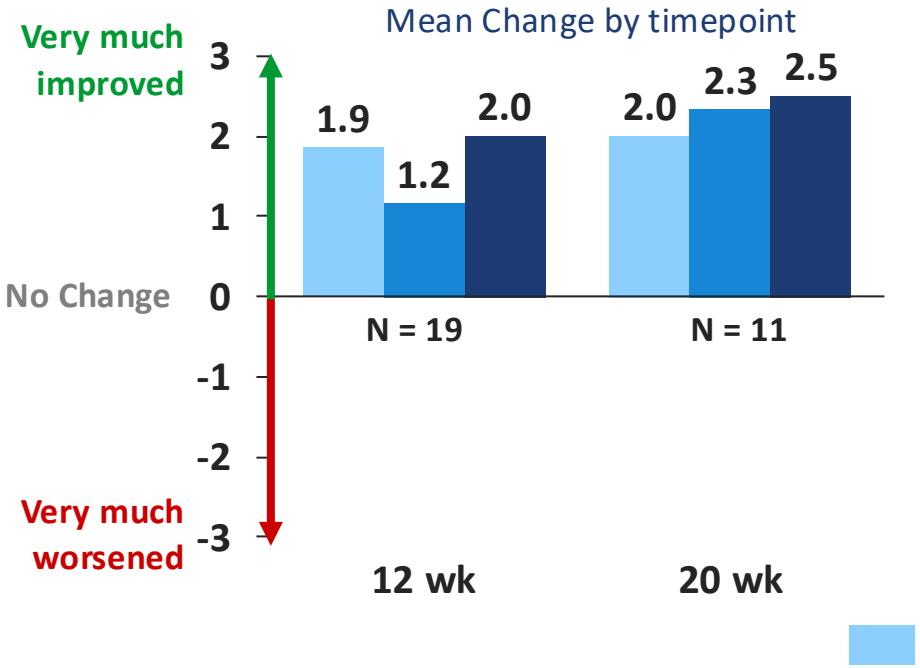
1. Includes both confirmed and unconfirmed responses

RelInspire preliminary data as of 04/15/2026

Zovegalisib Efficacy Data – Clear Symptomatic Benefit

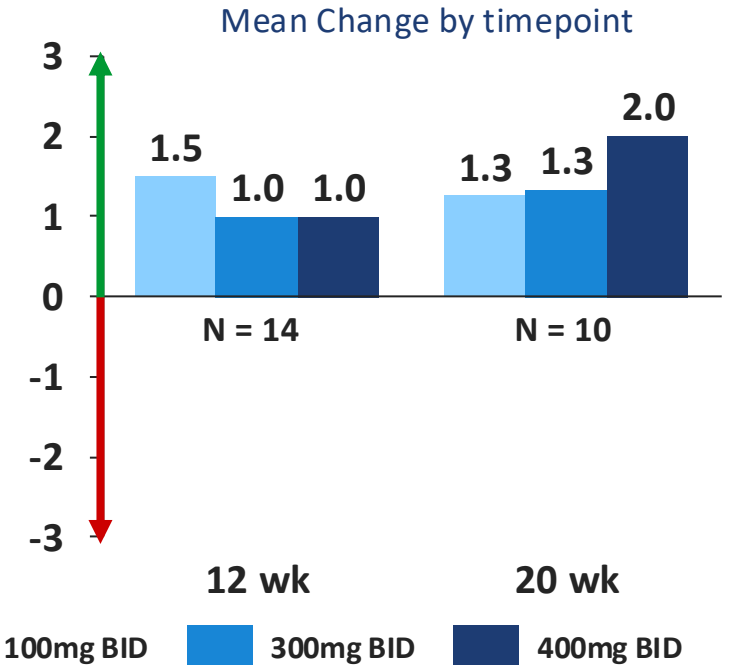
Investigator-Reported (IGIC)

89%
of patients improved by week 12



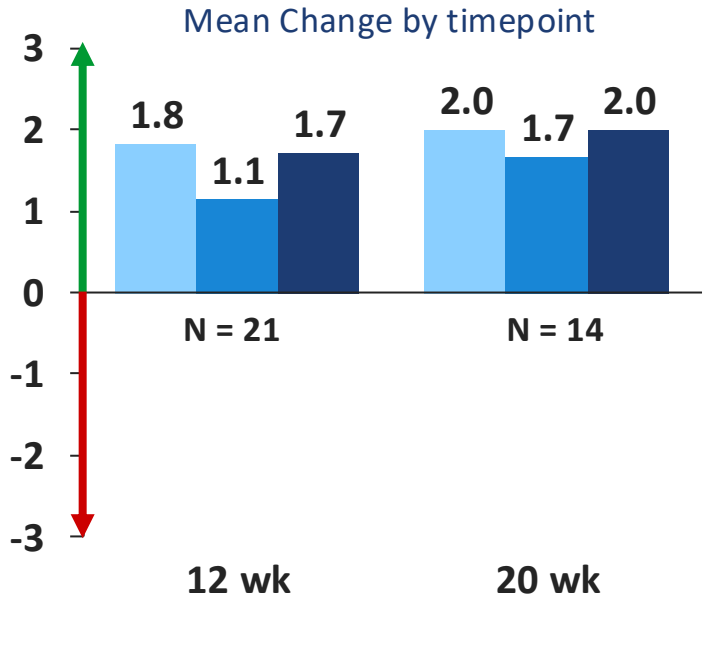
Patient-Reported (PGIC)

79%
of patients improved by week 12



Pain (IADRSS)

71%
of pain symptoms improved by week 12



100mg BID 300mg BID 400mg BID

IGIC = Investigator Global Impression of Change, PGIC = Patient Global Impression of Change, IADRSS = Investigator Assessment of Disease-Related Signs and Symptoms.
Note: N for IGIC and PGIC is number of patients; N for IADRSS pain is number of most bothersome pain symptoms, where some patients may have more than one pain symptom.

RelInspire preliminary data as of 04/15/2026

Zovegalisib – Treatment-Related Adverse Events ≥15% of Patients

No discontinuations for any reason

		100mg BID (N=11)				300mg BID (N=11)				100mg+300mg BID (N=22)				400mg BID (N=10)			
		All Gr	Gr1	Gr2	Gr3+	All Gr	Gr1	Gr2	Gr3+	All Gr	Gr1	Gr2	Gr3+	All Gr	Gr1	Gr2	Gr3+
	Any TRAE	82%	36%	45%	-	91%	55%	18%	18%	86%	45%	32%	9%	90%	20%	50%	20%
TRAE ≥15%	Headache	18%	18%	-	-	73%	73%	-	-	45%	45%	-	-	50%	30%	20%	-
TRAE ≥15%	Fatigue	18%	9%	9%	-	55%	36%	18%	-	36%	23%	14%	-	20%	10%	10%	-
TRAE ≥15%	Nausea	27%	18%	9%	-	45%	36%	9%	-	36%	27%	9%	-	70%	40%	30%	-
TRAE ≥15%	Diarrhea	27%	27%	-	-	18%	18%	-	-	23%	23%	-	-	10%	-	10%	-
TRAE ≥15%	Hyperglycemia	-	-	-	-	45%	18%	27%	-	23%	9%	14%	-	40%	20%	10%	10%
TRAE ≥15%	Decreased appetite	18%	9%	9%	-	18%	9%	9%	-	18%	9%	9%	-	20%	10%	10%	-
Other select TRAE	Rash	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other select TRAE	Stomatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Median Relative Dose Intensity	100%				99%				99%				77%			
	Dose Reduction due to TRAE, n (%)	1 (9%)[2]				4 (36%)				5 (23%)				7 (70%)			

Majority of hyperglycemia observed in patients prediabetic at baseline[1]

No Grade 3 hyperglycemia

1. Baseline HbA1c ≥5.7, glucose ≥100, or medical history of pre-diabetes mellitus; 2. Patient later increased back up to original dose of 100mg BID

RelInspire preliminary data as of 04/15/2026

Part 1 Group 1 of RelnspireTM: Conclusions

- Zovegalisib (RLY-2608) is the **first known mutant-selective PI3Kα inhibitor** studied in patients with vascular anomalies
- Across all doses, investigators assessed average overall symptoms to be between **much and very much improved** at 20 weeks **with 60% achieving volumetric response,** regardless of PIK3CA mutation status, diagnosis or prior therapy
- The lowest dose of **100mg BID** was generally well tolerated with no hyperglycemia, and investigators assessed mean overall symptom improvement to be **much improved** at 20 weeks **with 29% volumetric response**
- At the dose of **300mg BID**, zovegalisib achieved **100% volumetric response** with a manageable adverse event (AE) profile
- AEs were generally dose-dependent, low grade, reversible, with no treatment-related SAEs, with all patients remaining on treatment
- **Expansion cohorts have begun enrollment at 400mg QD and 300mg BID in patients 12 and older (Part 2, Group 1)**
- **Weight-based dose escalation is ongoing in patients 6 to 11 years old (Part 1, Group 2)**

RelnspireTM preliminary data as of 04/15/2026

Acknowledgments

We would like to thank the patients and their families and caregivers, study investigators, sub-investigators, and research staff.

ReInspire: A Phase 2 Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, in Adults and Children with PIK3CA Related Overgrowth Spectrum (PROS) and Malformations Driven by *PIK3CA* Mutation

The Phase 2 ReInspire Trial is a global trial evaluating RLY-2608 in children (>2yr old), adolescents and adults with PIK3CA-related Overgrowth Spectrum and *PIK3CA*-mutated Vascular Malformations.

https://clinicaltrials.gov/study/NCT06789913