

Preliminary results of zovegalisib, a mutant-selective PI3Kα inhibitor, in adult and adolescent patients with *PIK3CA*-driven vascular malformations from the ReInspire Study

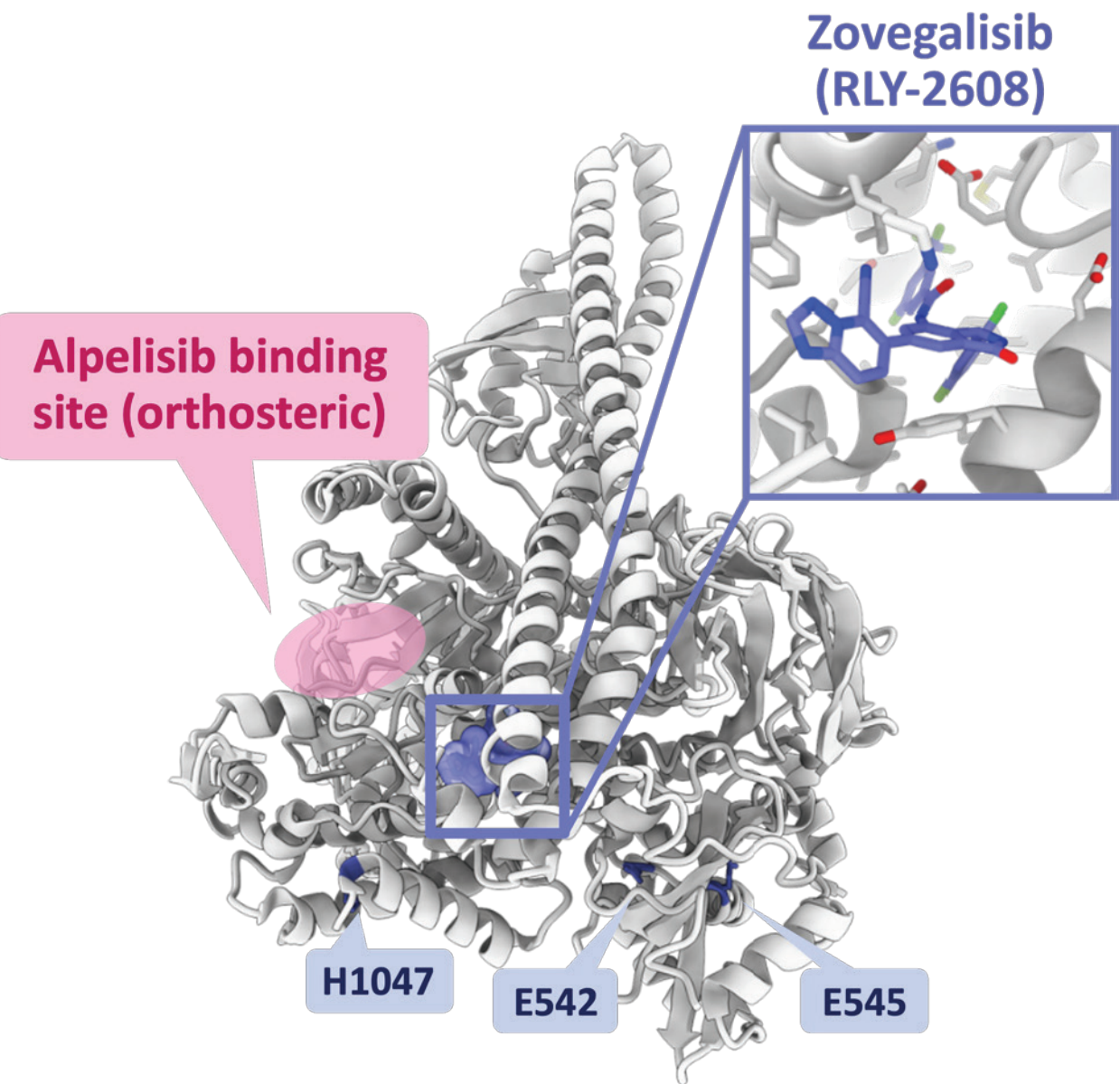
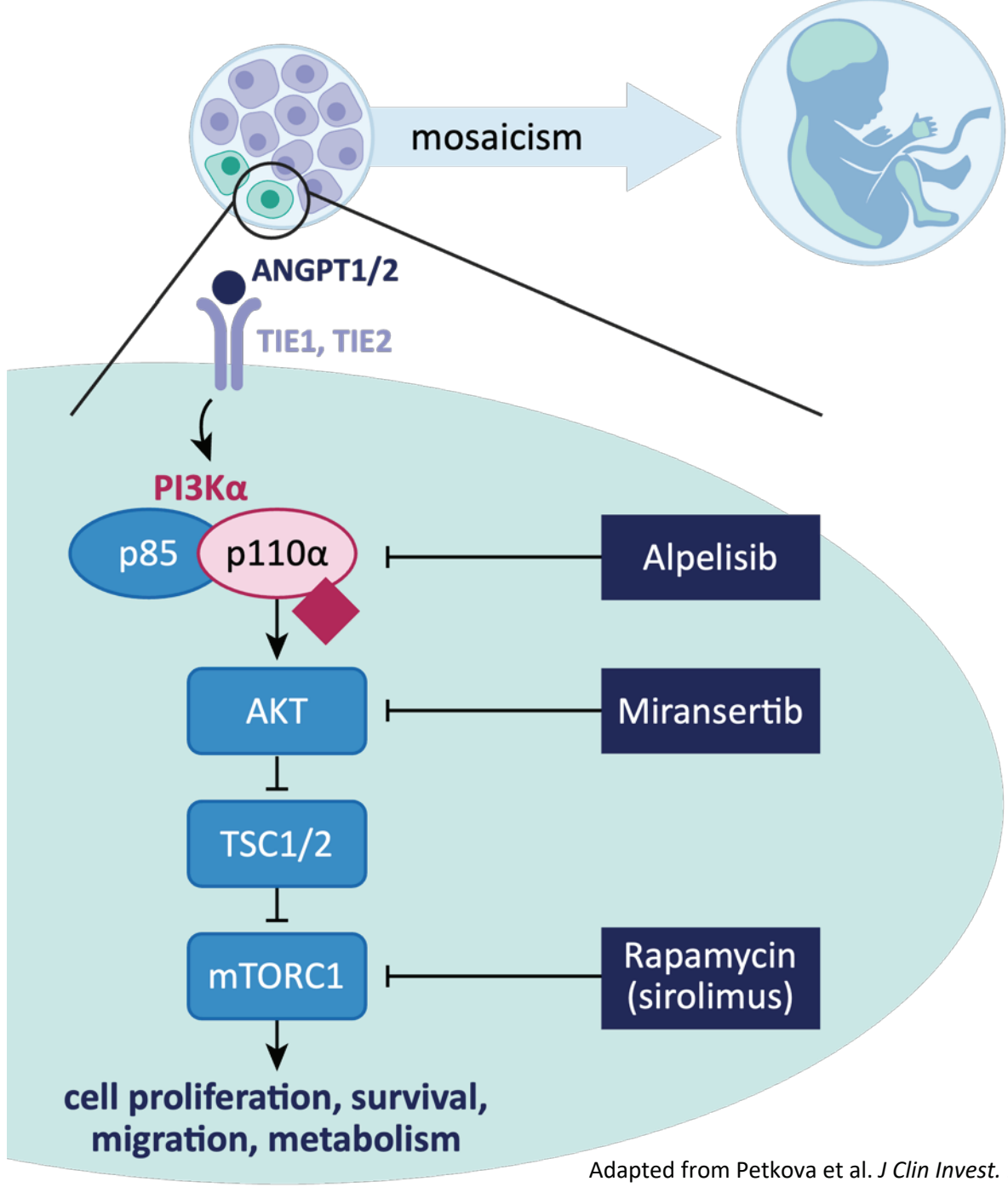


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BACKGROUND

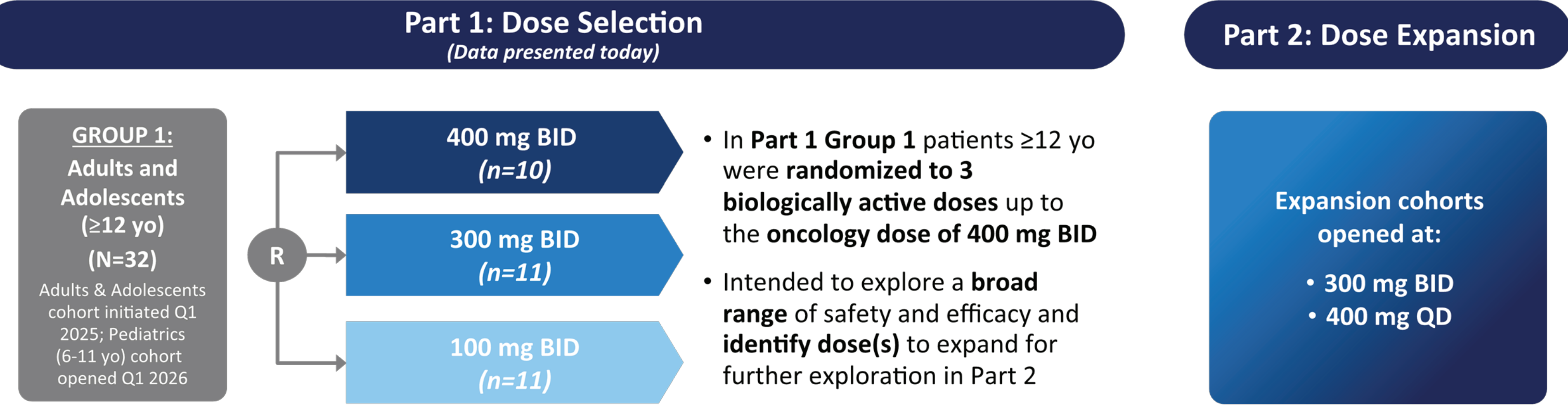
- Slow-flow vascular malformations are highly symptomatic diseases driven by somatic mosaic *PIK3CA* mutations
- Isolated and syndromic slow-flow vascular malformations, such as LMs and PROS, are driven by somatic mosaic *PIK3CA* mutations (right figure)
- Non-mutant selective PI3Kα pathway inhibitors can have dose-limiting toxicities including **hyperglycemia**, **rash**, **stomatitis**,¹ and **growth retardation**²
- Alpelisib has US-accelerated approval based on real-world data 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 study⁴



- Zovegalisib (RLY-2608)** is a novel, **pan-mutant-selective PI3Kα inhibitor** that binds an allosteric pocket in activated PI3Kα (left figure)
- Zovegalisib has demonstrated **8- to 12-fold selectivity** for PI3Kα helical and kinase mutants over wild-type PI3Kα⁵
- Zovegalisib has demonstrated **greater lesion regression** and **less insulin induction** compared with alpelisib in vivo xenograft and genetic vascular malformation models
- Zovegalisib has **FDA Breakthrough Therapy Designation** in HR+, HER2- breast cancer and is currently in pivotal Phase 3 development

STUDY DESIGN

A Phase 2 Trial of Zovegalisib in Pediatric and Adult Patients with *PIK3CA*-Driven Vascular Malformations



RESULTS

Zovegalisib – ReInspire Trial Demographics (Part 1, Group 1)

	Total (N=32)	100 mg BID (N=11)	300 mg BID (N=11)	400 mg 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 (55)	8 (80)
KTS	10 (31)	4 (36)	2 (18)	4 (40)
CLOVES	5 (16)	1 (9)	3 (27)	1 (10)
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, ^a n (%)	5 (16) / 27 (84)	2 (18) / 9 (82)	1 (9) / 10 (91)	2 (20) / 8 (80)
Prediabetic, ^b n (%)	8 (25)	1 (9)	6 (55)	1 (10)
Local <i>PIK3CA</i> 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)

ReInspire preliminary data as of 04/15/2026. ^a Lansky performance status for patients <16 years old or Karnofsky performance status for patients ≥16 years old. ^b Baseline A1C ≥5.7%, glucose ≥100 mg/dL, or medical history of prediabetes mellitus.

References

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- Singh S, et al. *Clin Cancer Res.* 2024;30(1):23-28.
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Abbreviations

A/Alp, alpelisib; A1C, hemoglobin A1C; AE, adverse event; AKT, protein kinase B; ANGPT1/2, angiotensin-1 and -2; BICR, blinded independent central review; BID, twice daily; BL, baseline; BOR, best overall response; CFB, change from baseline; CLOVES, congenital lipomatous overgrowth with vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies; cVR, confirmed volumetric response; FAO, fibroadipose overgrowth; FAVA, fibroadipose vascular anomaly; Gr, grade; IADRSS, Investigator Assessment of Disease-Related Signs and Symptoms; IGIC, Investigator Global Impression of Change; ISSVA, International Society for the Study of Vascular Anomalies; K, kinase; KTS, Klippel-Trenaunay syndrome; LM, lymphatic malformation; NK, non-kinase; mTORC1, mechanistic target of rapamycin complex 1; PGIC, Patient Global Impression of Change; PI3Kα, phosphoinositide 3-kinase alpha; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROS, PIK3CA-related overgrowth spectrum; Pts, patients; Q, quarter; QD, once daily; R, randomization; RP2D, recommended phase 2 dose; RR, response rate; S/Siro, sirolimus; SAE, serious AE; SD, stable disease; TRAE, treatment-related AE; Unk, unknown; US, United States; uVR, unconfirmed VR; VeM, venous malformation; VR, volumetric response; VRR, volumetric RR; yo, years old.

Acknowledgments

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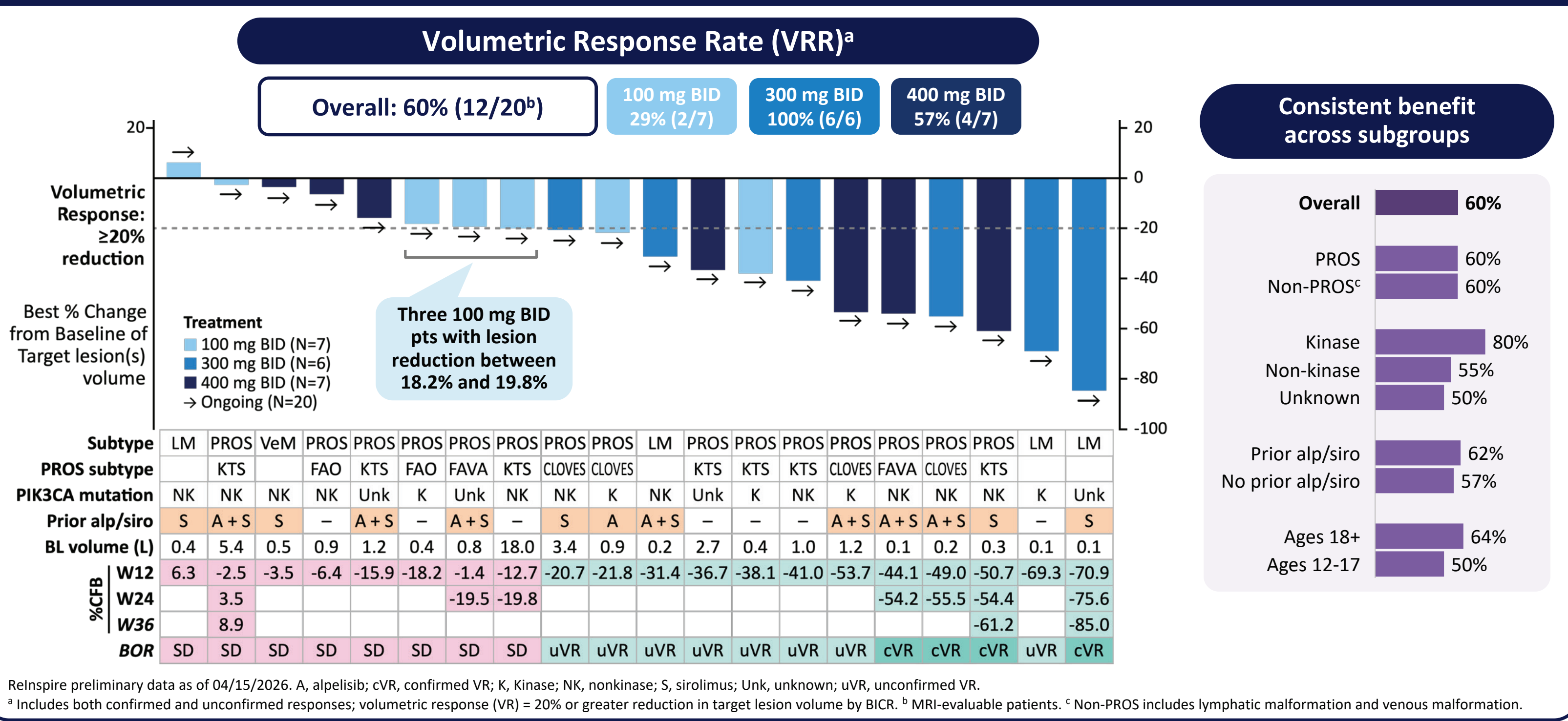
ReInspire: A Phase 2 Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, in Adults and Children with PIK3CA-Related Overgrowth Spectrum (PROS) and Malformations Driven by PIK3CA Mutation https://clinicaltrials.gov/study/NCT06789913
Previously presented at the ISSVA World Congress; May 2026.

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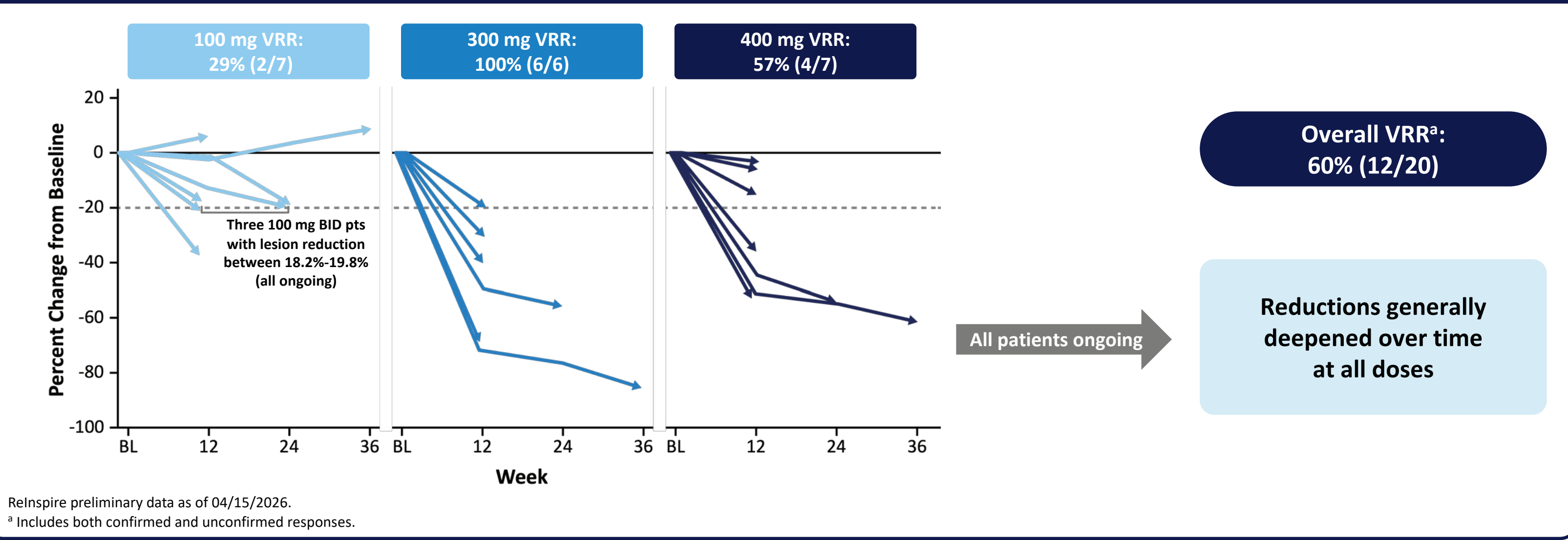


RESULTS (CONT'D)

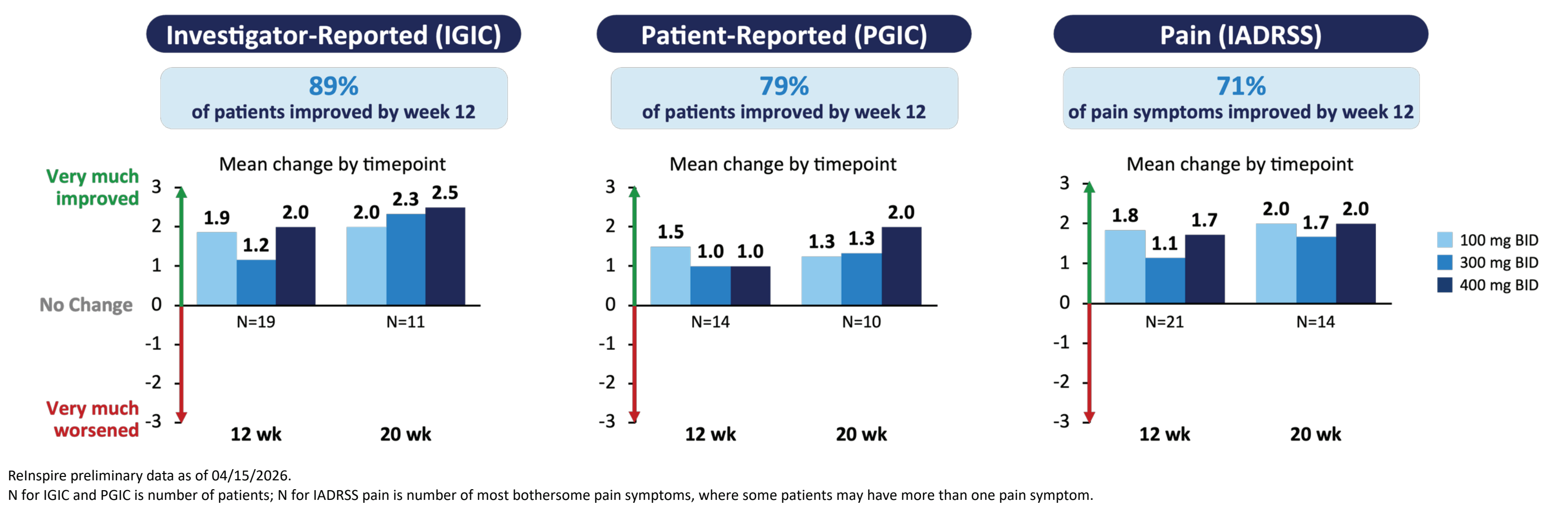
Zovegalisib – 60% Volumetric Response Rate by BICR Across All Doses



Zovegalisib – Volumetric Response Over Time (BICR)



Zovegalisib Efficacy Data – Clear Symptomatic Benefit



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

		100 mg BID (N=11)				300 mg BID (N=11)				100 mg+300 mg BID (N=22)				400 mg BID (N=10)				No discontinuations for any reason
		All Gr	Gr1	Gr2	Gr3+	All Gr	Gr1	Gr2	Gr3+	All Gr	Gr1	Gr2	Gr3+	All Gr	Gr1	Gr2	Gr3+	
TRAE ≥15%	Any TRAE	82%	36%	45%	-	91%	55%	18%	18%	86%	45%	32%	9%	90%	20%	50%	20%	
	Headache	18%	18%	-	-	73%	73%	-	-	45%	45%	-	-	50%	30%	20%	-	
	Fatigue	18%	9%	9%	-	55%	36%	18%	-	36%	23%	14%	-	20%	10%	10%	-	
	Nausea	27%	18%	9%	-	45%	36%	9%	-	36%	27%	9%	-	70%	40%	30%	-	
	Diarrhea	27%	27%	-	-	18%	18%	-	-	23%	23%	-	-	10%	-	10%	-	
	Hyperglycemia	-	-	-	-	45%	18%	27%	-	23%	9%	14%	-	40%	20%	10%	10%	
Other select TRAE	Decreased appetite	18%	9%	9%	-	18%	9%	9%	-	18%	9%	9%	-	20%	10%	10%	-	
	Rash	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Stomatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
						Most hyperglycemia observed in patients prediabetic at baseline ^a				No Grade 3 hyperglycemia								
Median relative dose intensity		100%				99%				99%				77%				
Dose reduction due to TRAE, n (%)		1 (9%) ^a				4 (36%)				5 (23%)				7 (70%)				

Reinspire preliminary data as of 04/15/2026.
^a Baseline A1C ≥5.7%, glucose ≥100 mg/dL, or medical history of prediabetes mellitus. [†] Patient later increased back up to original dose of 100 mg BID.

ReInspire preliminary data as of 04/15/2026. ^a Baseline A1C ≥5.7%, glucose ≥100 mg/dL, or medical history of prediabetes mellitus. ^b Patient later increased back up to original dose of 100 mg BID.

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 **100 mg 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 **300 mg BID**, zovegalisib achieved **100% volumetric response** with a manageable 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 400 mg QD and 300 mg 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)