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

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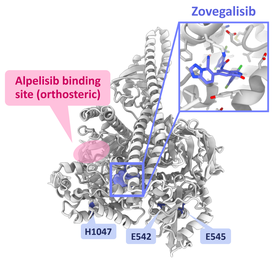
BACKGROUND & SIGNIFICANCE

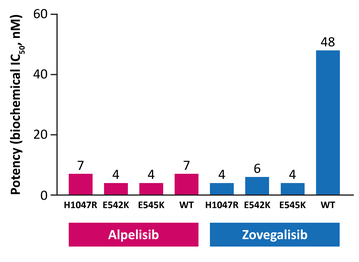
- Somatic, gain-of-function mutations in the *PIK3CA* gene can result in a range of vascular malformations. These rare disorders include lymphatic malformations, *PIK3CA*-related overgrowth spectrum (PROS), and venous malformations, with an estimated prevalence of 170,000 patients with a *PIK3CA*-mutant vascular malformation in the U.S.[1] Affected patients have limited options for systemic therapy. Inhibition of wild-type (WT) PI3Kα results in significant toxicity that can be dose-limiting, including hyperglycemia, diarrhea, rash, and potential for growth delay.
- **Zovegalisib (RLY-2608) is a novel, allosteric, mutant-selective oral PI3Kα inhibitor** designed to have greater potency and improved tolerability than other PI3Kα inhibitors (**Figure 1**).[2] Zovegalisib demonstrates enhanced selectivity for the mutant form of PI3Kα and less inhibition of WT protein. Zovegalisib was designed to target a hidden pocket that enables it to be more selective for the mutant protein and overcome limitations of traditional orthosteric inhibitors.[3]

Figure 1. Zovegalisib Structure and Mutant Selectivity

a. Zovegalisib binds in a novel allosteric binding site in PI3Kα



b. Mutant vs. wild-type PI3Kα selectivity



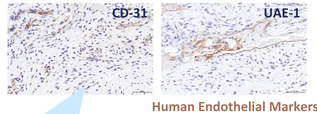
- In a *PIK3CA*^{H1047R} HUVEC (human umbilical vein endothelial cells) xenograft mouse model to assess the effect of zovegalisib on mutant and WT PI3Kα *in vivo* (**Figure 2**), animals developed highly vascularized lesions resembling vascular malformations.[2] Histopathological analysis revealed that lesions had mixed cell populations including a subset of mutant cells, consistent with the mosaic pattern of clinical disease.

Figure 2. Development of *PIK3CA*^{H1047R} HUVEC Xenograft Model

a. *PIK3CA*^{H1047R} HUVEC xenograft model informing mutant and WT PI3Kα inhibition

b. Highly vascularized lesions

c. Histopathology (untreated animals)

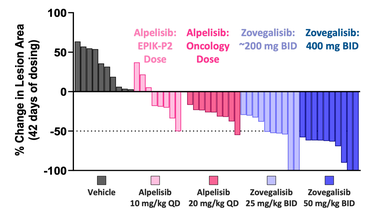


PIK3CA^{H1047R} HUVECs Populate Only a Fraction of the *In Vivo* Xenograft Lesions

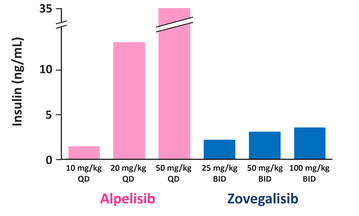
- Treatment of study animals with zovegalisib demonstrated superior lesion regression and less insulin induction across clinically relevant dose levels than alpelisib (**Figure 3**).

Figure 3. Lesion Regression and Insulin Impact in *PIK3CA*^{H1047R} HUVEC Xenograft Model*

a. Individual lesion comparison at clinically relevant doses†



b. Insulin Induction



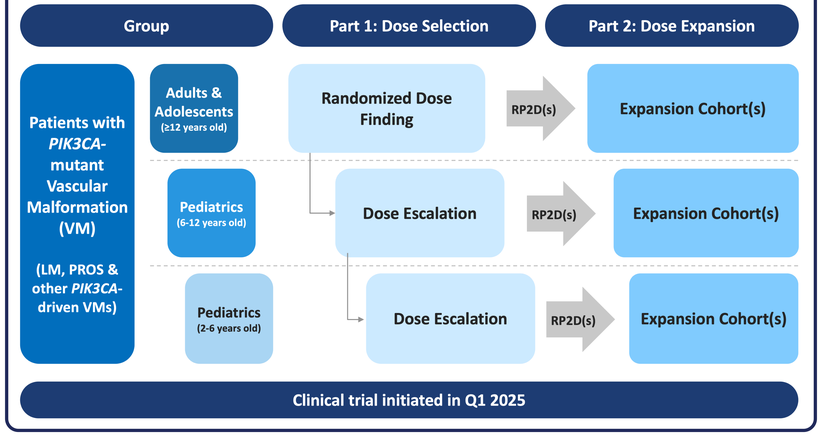
* Data presented at International Conference on Vascular Anomalies, Feb. 2025.
† HUVEC PIK3CA-H1047R Xenograft Vascular Malformation Mouse Model.

Clinical Experience With Zovegalisib in Adults With Advanced Breast Cancer

- Zovegalisib has been studied in adult participants with *PIK3CA*-mutant advanced solid tumors including HR+/HER2- breast cancer in ReDiscover, a global, multicenter, dose-escalation and expansion study of zovegalisib as a single agent and in combination with fulvestrant and CDK 4/6 inhibitor (NCT05216432).[4] Zovegalisib has demonstrated clinical proof-of-concept with favorable efficacy and an improved safety profile in patients with advanced or metastatic breast cancer previously treated with CD4/6 inhibitor.
- Zovegalisib is currently being further investigated in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer with *PIK3CA* mutation in the Phase 3 randomized study ReDiscover-2 (NCT06982521).

STUDY DESIGN & METHODS

Figure 4. ReInspire Study Schema for Parts 1 & 2



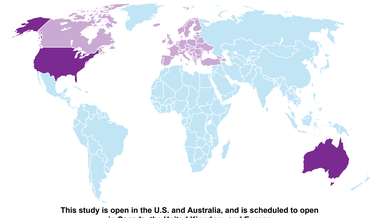
Study Synopsis

- ReInspire (RLY-2608-201; NCT06789913) is an ongoing, 3-part, global study in approximately 277 participants ≥2 years with PIK3CA-driven vascular malformations including lymphatic malformations, PROS, and venous malformations (**Figure 4**). ReInspire includes open-label dose selection (Part 1), open-label dose expansion (Part 2), and a double-blinded, placebo-controlled, 2:1 randomized study (Part 3). Zovegalisib is administered orally in continuous cycles.
- Study objectives are to evaluate the:
  - Safety, tolerability, pharmacokinetics, and recommended adult and pediatric dosing in Parts 1 and 2, and
  - Efficacy of zovegalisib based on reduction in target lesion volume by blinded independent central review and age-appropriate clinical outcome assessments (PROMIS, EQ-5D, PGI-S, PGI-C, and IGIC) in Part 3
- Participants are enrolled in a staggered fashion by age, beginning with adult and adolescent participants ≥12 years (Group 1), and may be extended to pediatric participants 6 to <12 years (Group 2) and 2 to <6 years (Group 3), based on review of cumulative clinical data.
  - Part 1 initiates with randomization of Group 1 participants (n=45) to one of three dose levels with stratification according to prior alpelisib use, and will be followed by weight-based dose escalation using a Bayesian optimal interval (BOIN) design in Groups 2 and 3, if opened.
  - Part 2 is a basket-style dose expansion that will evaluate the clinical activity of zovegalisib at one or more recommended Phase 2 doses (RP2Ds) in various populations in cohorts of 20 participants each based on Part 1 findings.
  - Depending on the results of Parts 1 and 2, Part 3 (n=90) may be opened to participants ≥6 years.
- The design of this study, including dose selection, was informed by clinical data from the first-in-human study of RLY-2608 in adult participants with advanced solid tumors, including HR+/HER2-, *PIK3CA*-mutated breast cancer.

Key Eligibility Criteria

- Clinical diagnosis of PROS or a malformation within the ISSVA classifications.
- One or more documented activating *PIK3CA* mutation(s) that are targeted by selective PI3Kα inhibitors in lesional tissue and/or cell-free DNA from the lesion or blood. Some participants may be eligible without a documented *PIK3CA* mutation as long as no other genetic driver has been documented.
- Participants with other known pathogenic somatic or germline driver mutations (e.g., *TIE2 [TEK], AKT1*) are not eligible.
- Participants must be a candidate for investigational systemic therapy; have severe, symptomatic, and/or progressive disease; and at least one target lesion amenable for volumetric assessment.
- Participants who have received disease-directed therapy (e.g., alpelisib, sirolimus) must undergo a washout period for systemic treatment and local therapies including radiation, surgery and other procedures.
- Participants with Type 1 or 2 diabetes requiring antihyperglycemic medication or fasting plasma glucose ≥140 mg/dL, or glycosylated hemoglobin (HbA1c) ≥7.0% (≥53 mmol/mol) are not eligible.
- Participants with any risk factors that increase the risk of QTc prolongation or risk of arrhythmic events are not eligible.

Figure 5. ReInspire Active Study Sites & Enrollment Status



This study is open in the U.S. and Australia, and is scheduled to open in Canada, the United Kingdom, and Europe

Active Sites:

USA
- Arkansas
  - Arkansas Children's Hospital, Little Rock
- California
  - Stanford University, Palo Alto
  - University of California, Los Angeles
  - University of California, San Francisco
- Colorado
  - Children's Hospital of Colorado, Aurora
- Georgia
  - Children's Healthcare of Atlanta
- Massachusetts
  - Boston Children's Hospital
- Minnesota
  - The Mayo Clinic, Rochester
- Missouri
  - Washington University School of Medicine, St. Louis
- Ohio
  - Cincinnati Children's Hospital Medical Center
  - Cleveland Clinic Children's Hospital
- Texas
  - Texas Children's Hospital, Houston
- Wisconsin
  - University of Wisconsin, Madison

Australia
- Murdoch Children's Research Institute, Parkville, Australia

Trial Status:
- ReInspire has been actively enrolling patients since June 2025.
- Patients ≥12 years are now enrolling in Part 1. Currently 14 centers are active.

Summary

- Zovegalisib is a novel allosteric mutant-selective PI3Kα inhibitor.
- *In vivo*, zovegalisib induces greater lesion regression than alpelisib at clinically relevant concentrations with sustained PI3Kα suppression and without hyperinsulinemia.
- Zovegalisib has demonstrated efficacy and an improved safety profile over available options in adult participants with CDK4/6 inhibitor pretreated HR+/HER2- *PIK3CA*-mutant advanced breast cancer.
- **ReInspire is enrolling participants with PIK3CA-driven vascular malformations including lymphatic malformations, PROS, and venous malformations.**

References

1. Behravesh S, 2016; Choquet H, 2015; Engel-Nitz NM, 2022; Fereydooni A, 2019; Gallagher JR, 2022; Keppler-Noreuil, 2015; Limaye N, 2015; Luks VL, 2015; Pagliacci A, 2021; Peyre M, 2021; Pennington A, 2023; Poget M, 2023; Rodriguez-Laguna L, 2022; Shah GH & Deshpande MD, 2010; Stor MLE, 2024; Ten Broek RW, 2019; Venot Q, 2018; Vogel SA, 2013. (full citations available on request)
2. Data presented at International Conference on Vascular Anomalies (ISVA), Feb 2025.
3. Varkaris A, et al. *Cancer Discov*. 2024;14(2):240-257.
4. Sammons SL, et al. *J Clin Oncol*. 2025;43:1086.

Abbreviations

CDK 4/6, cyclin-dependent kinases 4/6; EQ-5D, EuroQol 5 dimension; HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; HUVEC, human umbilical vein endothelial cell; IGIC, investigator global impression of change; ISSVA, International Society for the Study of Vascular Anomalies; LM, lymphatic malformation; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; PROMIS, patient-reported outcomes measurement information system; PROS, PIK3CA-related overgrowth spectrum; QTc, corrected QT interval; RP2D, recommended phase 2 dose; VM, vascular malformation; WT, wild-type

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For more information, please contact ClinicalTrials@RelayTx.com

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