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

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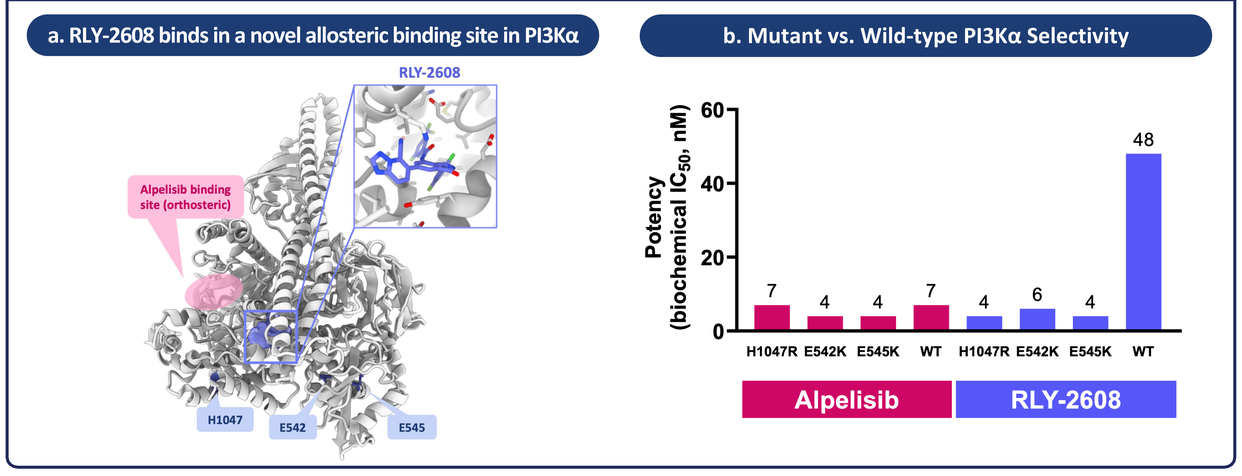
Background & Significance

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 PI3Kα results in significant toxicity that can be dose-limiting, including hyperglycemia, diarrhea, rash, and potential for growth delay.

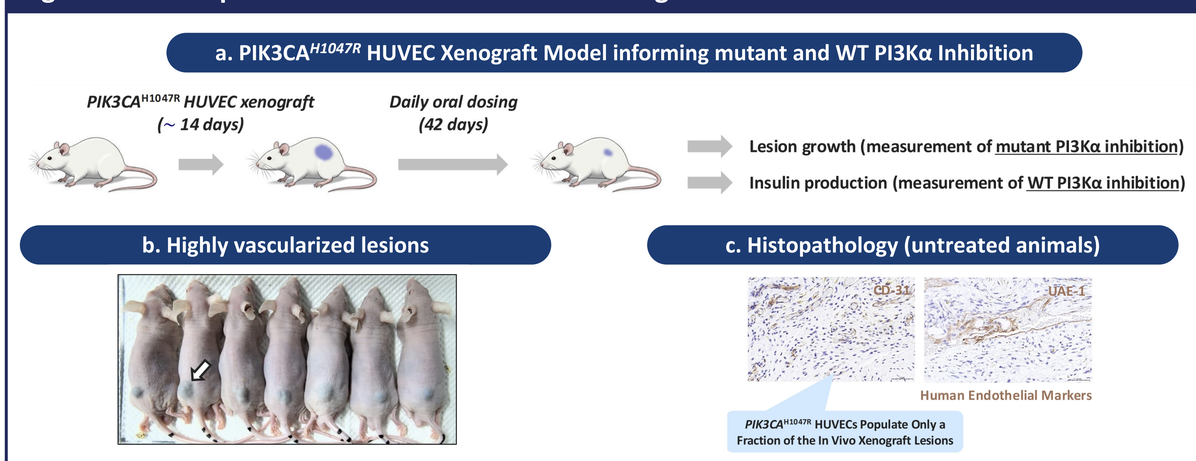
RLY-2608 is a novel, allosteric, mutant-selective oral PI3Kα inhibitor designed to have greater potency and improved tolerability than other PI3Kα inhibitors (Figure 1).[2] RLY-2608 demonstrates enhanced selectivity for the mutant form of PI3Kα and less inhibition of wild-type (WT) protein. Using the Dynamo™ platform to analyze conformational differences, RLY-2608 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. RLY-2608 Structure and Mutant Selectivity



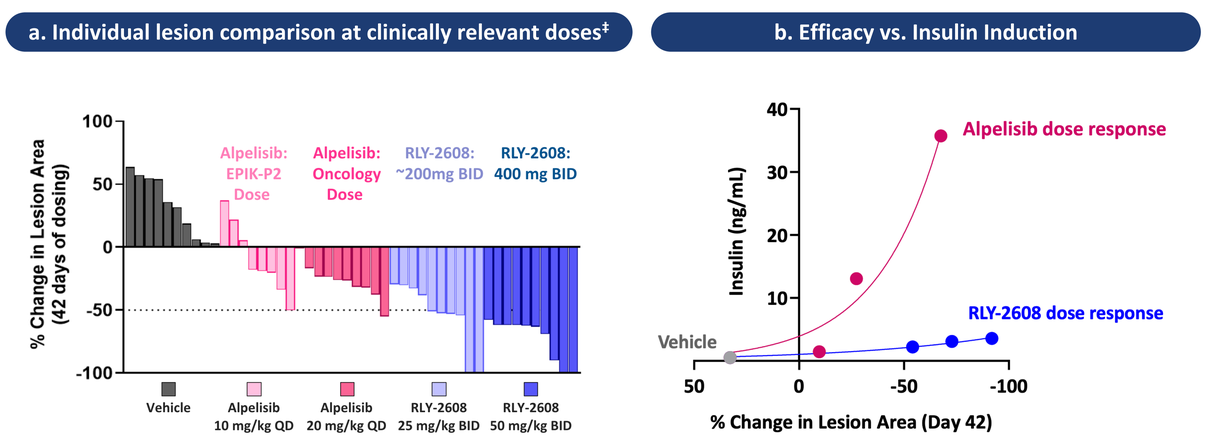
In a *PIK3CA*^{H1047R} HUVEC xenograft mouse model to assess the effect of RLY-2608 on mutant and WT PI3Kα *in vivo* (Figure 2), animals developed highly vascularized lesions resembling vascular malformations.[2] Histopathological analysis revealed that lesions had mixed cell populations including a subset of mutant cells, consistent with the mosaic pattern of clinical disease.

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



Treatment of study animals with RLY-2608 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†



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

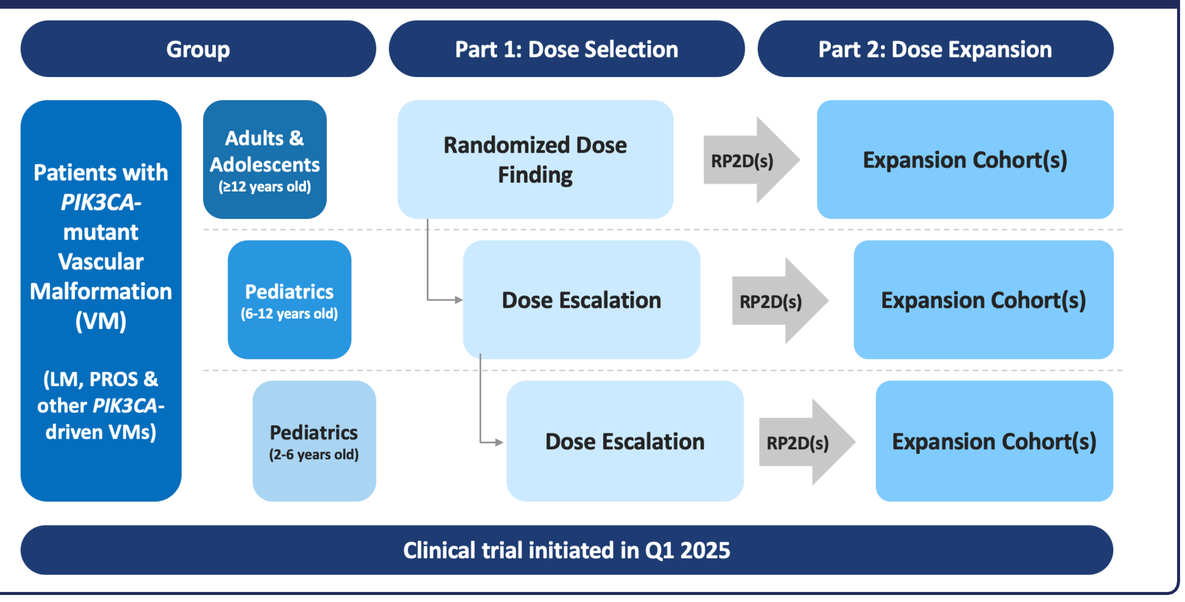
Clinical Experience with RLY-2608 in Adults with Advanced Breast Cancer

RLY-2608 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 RLY-2608 as a single agent and in combination with fulvestrant and CDK 4/6 inhibitor (NCT05216432).[4] RLY-2608 has demonstrated proof-of-concept with substantial efficacy and an improved safety profile in patients with advanced or metastatic breast cancer previously treated with CD4/6 inhibitor.

RLY-2608 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



ReInspire (RLY-2608-201; NCT06789913) is an ongoing, 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).

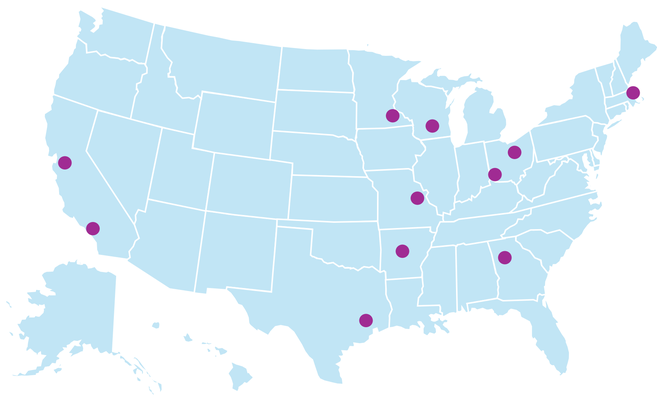
Study objectives are to evaluate the:
- Safety, tolerability, pharmacokinetics, and recommended adult and pediatric dosing in Parts 1 and 2, and
- Efficacy of RLY-2608 based on reduction in target lesion volume by blinded independent central review and age-appropriate clinical outcome assessments (PROMIS, 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. 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



Active Sites:
- Arkansas Children's Hospital (Little Rock, AR)
- Boston Children's Hospital (Boston, MA)
- Children's Hospital of Atlanta (Atlanta, GA)
- Cincinnati Children's Hospital Medical Center (Cincinnati, OH)
- Cleveland Clinic Children's Hospital (Cleveland, OH)
- The Mayo Clinic (Rochester, MN)
- Texas Children's Hospital (Houston, TX)
- University of California, Los Angeles (Los Angeles, CA)
- University of California, San Francisco (San Francisco, CA)
- University of Wisconsin, Madison (Madison, WI)
- Washington University School of Medicine (St. Louis, MO)

Trial Status
- ReInspire has been actively enrolling patients since June 2025.
- Patients ≥12 years are now enrolling in Part 1. Currently 11 centers are active.
- The study will be open internationally including sites in Canada, the United Kingdom, Europe, and Australia.

Summary

- RLY-2608 is a novel allosteric mutant-selective PI3Kα inhibitor.
- *In vivo*, RLY-2608 induces greater lesion regression than alpelisib at clinically relevant concentrations with sustained PI3Kα suppression and without hyperinsulinemia.
- RLY-2608 has demonstrated efficacy and an improved safety profile over available options in adult participants with CDK4/6-inhibitor pre-treated 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; Pagliazzi A, 2021; Peyre M, 2021; Penington 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 (VAC), 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; **IGIC**, investigator global impression of change; **ISSVA**, international Society for the Study of Vascular Anomalies; **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; **WT**, wild-type

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For more information, please contact ClinicalTrials@RelayTx.com

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