United Therapeutics Corporation Announces Ralinepag Achieved 55% Reduction in Risk of Clinical Worsening in Pivotal Pulmonary Arterial Hypertension Study, Delivering Exceptional, Highly Statistically Significant Efficacy

*The phase 3 ADVANCE OUTCOMES study of ralinepag met its primary endpoint and several important secondary endpoints, including increasing odds of clinical improvement by 47%, in predominantly pre-treated patients with pulmonary arterial hypertension (**PAH**)*

Ralinepag has the potential to redefine the PAH treatment landscape as the first and only once-daily oral prostacyclin, combining potent receptor affinity with continuous exposure to deliver long-term, durable efficacy and disease-mitigating outcomes

*United Therapeutics intends to submit a New Drug Application (**NDA**) for ralinepag to the U.S. Food and Drug Administration (**FDA**) by the second half of 2026*

United Therapeutics will host a webcast at 8:30 a.m. Eastern Time today to further discuss the study results

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., March 2, 2026 – United Therapeutics Corporation (Nasdaq: UTHR), a public benefit corporation, today announced that its long-term pivotal phase 3 *ADVANCE OUTCOMES* study met its primary endpoint, with ralinepag reducing the risk of a clinical worsening event by 55% compared with placebo in patients with PAH (hazard ratio 0.45, 95% CI [0.33-0.62]; p<0.0001).

Ralinepag demonstrated durable efficacy in delaying disease progression during the study, in which 80% of patients were on dual background therapy and 70% of patients were considered World Health Organization (**WHO**)/New York Heart Association (**NYHA**) Functional Class (**FC**) II at baseline.

Statistically significant improvements relative to placebo were also observed in important secondary endpoints, including six-minute walk distance (**6MWD**) and change in N-terminal pro-B-type natriuretic peptide (**NT-proBNP**), with ralinepag increasing the odds of achieving clinical improvement by 47% from baseline to Week 28 (p=0.015).

Benefits were consistent across all patient subgroups, including time since diagnosis, disease etiology, baseline 6MWD, and use of background therapies, reinforcing the robustness of the treatment effect and the potential broad therapeutic relevance of ralinepag.

Treatment with ralinepag was well-tolerated and the safety profile was consistent with known prostacyclin-related adverse events. No new safety signals were observed.

"PAH is a progressive, life-threatening disease that has a devastating impact on patients' lives. In the *ADVANCE OUTCOMES* study, ralinepag delayed disease progression in patients with PAH facing significant disease burden at baseline. Ralinepag's potency and once-daily oral dosing make these outcomes highly relevant in real-world settings," said **Vallerie V. McLaughlin, M.D.**, Kim A. Eagle MD Endowed Professor of Cardiovascular Medicine and Director, Pulmonary Hypertension Program at University of Michigan and Chair of the *ADVANCE OUTCOMES* Steering Committee.*

"United Therapeutics was founded on the idea that we could bring transformative therapies to people living with PAH. Our achievement in this pivotal trial is among the most important in our history and strengthens our decades-long commitment to advancing prostacyclin-based science. The strength and

* Dr. McLaughlin has received compensation as a consultant of United Therapeutics.

consistency of these findings give us great optimism that ralinepag could meaningfully improve long-term outcomes and, if approved, usher in a new era of treatment for PAH that brings us closer than ever to addressing the profound unmet needs that persist in this disease. We are grateful for the essential contributions of the study participants and the investigators whose work underpinned this tremendous result," said **Martine Rothblatt, Ph.D.**, Chairperson and Chief Executive Officer of United Therapeutics.

"These results mark a significant advancement for PAH patients. With its extended-release profile and pharmacokinetic characteristics that mimic the steady-state exposure of parenteral therapy, ralinepag provides disease-mitigating capabilities that target underlying PAH pathology and achieve impressive clinical benefits," said **Derek Solum**, **Ph.D.**, Senior Director, Product Development at United Therapeutics and the lead for the global *ADVANCE OUTCOMES* program.

United Therapeutics intends to present full results from the *ADVANCE OUTCOMES* study at an upcoming international conference and to submit an NDA for ralinepag to the FDA by the second half of 2026.

United Therapeutics will host a public webcast today, March 2, 2026, at 8:30 a.m. Eastern Time. The webcast will be accessible via United Therapeutics' website at https://ir.unither.com/events-and-presentations. A rebroadcast of the webcast will be available for one year and can be accessed at the same location.

About Ralinepag

Ralinepag is a highly selective and potent prostacyclin (**IP**) receptor agonist with multiple pathway effects, including vasodilatory, anti-proliferative, and anti-inflammatory effects.[1,2] It demonstrates six-fold higher binding affinity for the IP receptor than MRE-269 (selexipag's active metabolite) and achieves sustained IP receptor occupancy similar to parenteral therapy.[3-6] Ralinepag helps to restore prostacyclin signaling and activates IP receptors on pulmonary artery endothelial and smooth muscle cells to trigger the downstream conversion of ATP to cAMP.[1,7] Ralinepag is six- to eight-fold more potent at increasing in vitro cAMP levels compared with the active metabolite of selexipag.[5] Elevated intracellular cAMP acts on pathways implicated in PAH progression by promoting vasodilation and inhibiting vascular remodeling, suggesting potential for vascular protection.[1,5,7] In a phase 2 study, ralinepag significantly reduced pulmonary vascular resistance compared with placebo in PAH patients on mono (41%) or dual combination (59%) background therapy.[8]

About ADVANCE OUTCOMES

ADVANCE OUTCOMES was a pivotal phase 3 multicenter, global, randomized, double-blind, placebo-controlled, event-driven study to evaluate the efficacy and safety of ralinepag in 687 patients with PAH. Patients who completed the study had the option to enroll in an ongoing open-label extension study, *ADVANCE EXTENSION*.

In this event-driven study, patients were randomly assigned (1:1) to receive ralinepag or placebo, in addition to their standard of care PAH-specific background therapy. Once-daily dosing was individualized and titrated based on tolerability and clinical response. No dose ceiling was specified.

The primary endpoint was time to first adjudicated clinical worsening event, defined as death, nonelective hospital admission for worsening PAH, initiation of parenteral or inhaled prostacyclin pathway agent for treatment of worsening PAH, disease progression, or unsatisfactory long-term clinical response.

Secondary endpoints included changes from Baseline to Week 28 in NT-proBNP, 6MWD, and WHO/NYHA FC; shift and proportion of patients with improved risk status, clinical improvement, health-related quality of life (SF-36) as measured by patient-reported outcomes; time to first all-cause nonelective hospitalization; time to all-cause mortality; heart rate recovery following completion of the 6MWT; and safety and tolerability.

About PAH

PAH is a life-threatening disease that affects the blood vessels in the lungs and is characterized by increased pressure in the pulmonary arteries, which are the blood vessels leading from the heart to the lungs. The elevated pressure in the pulmonary arteries strains the right side of the heart as it pumps blood to the lungs. This eventually leads to right heart failure and, ultimately, death. PAH is characterized by structural changes in blood vessel walls, aggregation of platelets, and alteration of smooth muscle cell function. PAH affects about 500,000 individuals worldwide, with around 50,000 people affected in the United States. Increases in the number of people diagnosed with the disease have been observed, but due to the rarity of the disease and the complexity of diagnosing it, only a small fraction of patients with PAH are treated.

About United Therapeutics

Founded by CEO Martine Rothblatt to discover a cure for her daughter's life-threatening rare disease, pulmonary arterial hypertension, United Therapeutics transforms the treatment of rare diseases and pioneers alternatives to expand the supply of transplantable organs. From our innovative therapies to our groundbreaking manufactured organs, we are bold and unconventional. We move quickly from scientific theory to practical technologies that can save lives. As a public benefit corporation, even our legal structure reflects our commitments. We serve patients, act with integrity, create long-term shareholder value, and operate with sustainable practices that protect the future we are working to build. Visit us at www.unither.com and follow us on LinkedIn, Facebook, and Instagram.

Forward-Looking Statements

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, the potential timing and outcome of our efforts to seek FDA approval of ralinepag, including our plan to submit an NDA to the FDA by the second half of 2026; the potential impacts of ralinepag on PAH treatment, including the potential for ralinepag to redefine the PAH treatment landscape; the potential for ralinepag to become the first and only once-daily oral prostacyclin; the potential for ralinepag to deliver long-term, durable efficacy and disease-mitigating outcomes; the potential for ralinepag to meaningfully improve long-term outcomes and usher in a new era of treatment for PAH, bring us closer than ever to addressing unmet needs that persist for PAH patients; our commitment to advancing prostacyclin-based science; and our goals of expanding the supply of transplantable organs, developing practical technologies that can save lives, creating long-term shareholder value, and operating with sustainable practices. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic reports filed with the Securities and Exchange Commission, that could cause actual results to differ materially from anticipated results. Consequently, such forward-looking statements are qualified by the cautionary statements, cautionary language, and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of March 2, 2026, and assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events or any other reason.

For Further Information Contact:
Investor Inquiries
https://ir.unither.com/contact-ir

Media Inquiries
communications@unither.com

References

1. Clapp LH, Abu-Hanna JHJ, Patel JA. Diverse pharmacology of prostacyclin mimetics: implications for pulmonary hypertension. In: Nakanishi T, Baldwin HS, Fineman JR, Yamagishi H, eds. *Molecular Mechanism of Congenital Heart Disease and Pulmonary Hypertension*. Springer; 2020:31-61.
2. Stitham J, Arehart E, Gleim SR, Hwa J. Prostacyclin: an inflammatory paradox. *Front Pharmacol*. 2011;2:24.
3. Asaki T, Kuwano K, Morrison K, Gatfield J, Hamamoto T, Clozel M. Selexipag: An Oral and Selective IP Prostacyclin Receptor Agonist for the Treatment of Pulmonary Arterial Hypertension. *J Med Chem*. 2015;58(18):7128-7137.
4. Tran JQ, Hartung J, Feurer A, et al. Discovery of 2-(((1r,4r)-4-(((4-Chlorophenyl)(phenyl)carbamoyl)oxy)methyl)cyclohexyl)methoxy) acetate (Ralinepag): An Orally Active Prostacyclin Receptor Agonist for the Treatment of Pulmonary Arterial Hypertension. *J Med Chem*. 2017;60(21):8829-8846.
5. Ataya A, Coons JC, Patzlaff N, et al. Safety and pharmacokinetics of ralinepag, a novel oral prostacyclin receptor agonist. *JHLT Open*. 2025;9:100270.
6. Grundy JS, King CD, Adams JW, Cabell CH. Safety, tolerability, and pharmacokinetics of the selective prostacyclin receptor agonist ralinepag in single and multiple dosing studies of an immediate-release oral formulation in healthy volunteers. *Pulm Circ*. 2020;10(2):2045894020922814.
7. Abu-Hanna J, Patel JA, Denton CP, Clapp LH. Prostacyclin mimetics inhibit DRP1-mediated pro-proliferative mitochondrial fragmentation in pulmonary arterial hypertension. *Vasc Pharmacol*. 2023;151:107194.
8. Torres F, Farber H, Ristic A, et al. Efficacy and safety of ralinepag, a novel oral IP agonist, in PAH patients on mono or dual background therapy: results from a phase 2 randomised, parallel group, placebo-controlled trial. *Eur Respir J*. 2019;54(4):1901030.