United Therapeutics Corporation Announces *ADVANCE OUTCOMES* Study of Ralinepag Published in *The Lancet*

The long-term, pivotal, phase 3 ADVANCE OUTCOMES *study of ralinepag in predominantly pre-treated patients with pulmonary arterial hypertension (**PAH**) met its primary endpoint and important secondary endpoints with statistical significance*

*The results support the use of ralinepag as a once-daily oral prostacyclin receptor agonist upon approval by the U.S. Food and Drug Administration (**FDA**)*

Investigational ralinepag combines potent receptor binding affinity with continuous exposure to deliver long-term, durable efficacy, and clinically meaningful outcomes

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., July 29, 2026 – United Therapeutics Corporation (Nasdaq: UTHR), a public benefit corporation, today announced that *The Lancet* has published full results of its *ADVANCE OUTCOMES* study, available here. Ralinepag has not been approved for use in any indication by the FDA and remains investigational for PAH.

Ralinepag reduced 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), meeting the study's primary endpoint with statistical significance. 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**) Functional Class (**FC**) II at baseline.

Ralinepag achieved statistically significant improvements relative to placebo from baseline to week 28 in change in N-terminal pro-B-type natriuretic peptide (**NT-proBNP**; 24.3% reduction over placebo; p=0.0013) and six-minute walk distance (**6MWD**; +20.4 m placebo-corrected difference; p=0.0033), two key secondary endpoints. Ralinepag increased the odds of achieving clinical improvement by 47% (p=0.015) compared to placebo, another important secondary endpoint.

These findings were consistent across all patient subgroups, including time since diagnosis, disease etiology, 6MWD, WHO FC, NT-proBNP levels, and use of background therapies.

The adverse event profile of ralinepag was consistent with known prostacyclin pathway effects. The most commonly reported adverse events in the ralinepag group were headache, diarrhea, nausea, and myalgia. No new safety signals were observed.

"Ralinepag reduced the risk of a first clinical worsening event and increased clinical improvement, maintaining durability of effect in this long-term clinical trial in PAH patients who were on dual background therapy. These findings support ralinepag as an oral, once-daily prostacyclin pathway treatment option upon FDA approval and suggest that the addition of prostacyclin pathway therapy can reduce clinical worsening even in a largely pretreated population with relatively preserved baseline functional capacity," 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.[1]

"We are honored that our *ADVANCE OUTCOMES* study has been published in the prestigious *Lancet* medical journal. Although PAH treatment has improved over the last thirty years, long-term survival remains low and additional treatment options are needed. The incredibly positive results of the study indicate that ralinepag has the potential to meaningfully improve long-term outcomes for people living

[1]Dr. McLaughlin has received compensation as a consultant of United Therapeutics.

with PAH," said **Martine Rothblatt, Ph.D.**, Chairperson and Chief Executive Officer of United Therapeutics.

"Ralinepag is an oral, highly selective, non-prostanoid, prostacyclin IP receptor agonist that promotes vasodilation and anti-proliferation and may counter the inflammatory mechanisms implicated in pulmonary vascular disease. Ralinepag combines potent receptor binding affinity and pharmacokinetic characteristics that mimic the steady-state exposure of parenteral therapy, which support its clinically meaningful and durable benefits," said **Derek Solum**, **Ph.D.**, Associate Vice President, Product Development at United Therapeutics, and the lead for the global *ADVANCE OUTCOMES* program.

United Therapeutics submitted a New Drug Application for ralinepag to the FDA in June 2026. Ralinepag has not been approved for use in any indication by the FDA and remains investigational for PAH.

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.[9] 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/New York Heart Association (**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; the potential impacts of ralinepag on PAH treatment, including the potential for ralinepag to meaningfully improve long-term outcomes for people living with PAH; 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 July 29, 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.

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