For Immediate Release

United Therapeutics Corporation Announces Full Enrollment of the *TETON 2* Study of Inhaled Treprostinil for the Treatment of Idiopathic Pulmonary Fibrosis

Over 100,000 patients in the United States have IPF, with two approved therapies available that only slow the course of disease progression

Top line data expected in the second half of 2025

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., July 10, 2024: United Therapeutics Corporation (Nasdaq: **UTHR**), a public benefit corporation, announced full enrollment of the *TETON 2* study evaluating the use of Tyvaso® (treprostinil) inhalation solution (**nebulized Tyvaso**) for the treatment of idiopathic pulmonary fibrosis (**IPF**).

The *TETON 2* study enrolled 597 patients and is part of the three-study global *TETON* clinical trial program evaluating the use of inhaled treprostinil in IPF and a similar condition, progressive pulmonary fibrosis (**PPF**). *TETON 1* is evaluating the use of inhaled treprostinil in IPF in patients in the United States and Canada. *TETON 2* is evaluating the use of inhaled treprostinil in IPF in patients outside the United States and Canada. *TETON PPF* is evaluating the use of inhaled treprostinil in PPF in patients globally. Patients in any of the *TETON* program studies may use nebulized Tyvaso alone as a monotherapy or in combination with one background therapy approved for the treatment of IPF or PPF. Enrollment in *TETON 1* and *TETON PPF* is ongoing.

"On behalf of my colleagues at United Therapeutics, I'd like to thank the patients and investigators around the world for the courage and determination to participate in the potentially revolutionary *TETON 2* study," said **Peter Smith, Pharm. D.**, Vice President, Product Development at United Therapeutics and the lead for the global *TETON* program. "Our continued goal with the *TETON* program is to demonstrate that inhaled treprostinil can lead to better patient outcomes in this underserved, vulnerable patient population with fibrotic lung disease."

The *TETON* program in IPF and PPF was prompted by data from the *INCREASE* study of nebulized Tyvaso for the treatment of pulmonary hypertension associated with interstitial lung disease (**PH-ILD**), which demonstrated in a post-hoc analysis that treatment with nebulized Tyvaso resulted in significant improvements in percent predicted forced vital capacity (**FVC**) at weeks 8 and 16, with subjects having an underlying etiology of IPF showing the greatest improvement (week 8: 2.5%; p=0.038 and week 16: 3.5%; p=0.015).

Further, open label extension data published in 2023 showed these improvements in FVC were sustained for at least 64 weeks. For those patients who received placebo during the *INCREASE* study, marked improvements in FVC were observed following transition to nebulized Tyvaso during the open-label extension study. These data points, combined with substantial preclinical evidence of antifibrotic activity of treprostinil, suggest that nebulized Tyvaso may offer a treatment option for patients with IPF and PPF.

The *TETON* program is evaluating the use of nebulized Tyvaso, which is approved to improve exercise ability in patients with pulmonary arterial hypertension and PH-ILD. Tyvaso DPI® (treprostinil) Inhalation Powder is not being evaluated in the *TETON* program, but United Therapeutics intends to seek U.S. Food and Drug Administration (**FDA**) approval to expand the Tyvaso DPI label to include IPF and PPF following completion of the *TETON* studies and any FDA-required bridging studies. Tyvaso Inhalation Solution and Tyvaso DPI are not approved in any jurisdiction for the treatment of IPF or PPF patients who do not have documented pulmonary hypertension.

About *TETON 2*

The *TETON 2* study is a 597-patient, multicenter, randomized, double-blind, placebo-controlled phase 3 registration study to evaluate the safety and efficacy of nebulized Tyvaso in subjects with IPF over a 52-week period at sites outside of the United States and Canada. The study reached full enrollment in July 2024 and top-line data is expected in the second half of 2025.

Subjects will be randomly allocated 1:1 to receive nebulized Tyvaso or placebo. All subjects will initiate nebulized Tyvaso or placebo at a dose of three breaths administered four times daily (**QID**) and will titrate to a target dosing regimen of 12 breaths QID. Study drug doses may be titrated up as tolerated, until the target dose or maximum clinically tolerated dose is achieved.

The primary endpoint of the study is the change in FVC from baseline to week 52. Secondary endpoints include: (1) time to clinical worsening; (2) time to first acute exacerbation of IPF; (3) overall survival at week 52; (4) change in percent predicted FVC from baseline to week 52; and (5) change in the King's Brief Interstitial Lung Disease questionnaire.

Other data collected in the study will include the plasma N-terminal pro-brain natriuretic peptide (**NT-proBNP**) concentration, supplemental oxygen use, and lung diffusion capacity. Safety assessments include the development of adverse events, serious adverse events, vital signs, clinical laboratory parameters, and electrocardiogram parameters.

About IPF

Idiopathic pulmonary fibrosis, or IPF, is a scarring disease of the lungs of an unknown (idiopathic) cause and is the most common of the idiopathic interstitial pneumonias. IPF is characterized by the progressive loss of the ability of the lungs to transfer oxygen into the blood, ultimately resulting in respiratory failure and death. While the precise causes of IPF remain unknown, IPF rarely presents before age 50 and can be associated with cigarette smoking and certain genetic dispositions. In addition, some evidence suggests that gastroesophageal reflux (acid reflux, or heartburn), certain viral infections, air pollution, and some exposures in the workplace may be risk factors for IPF. According to recent research, IPF is estimated to affect between 0.33 and 4.51 people per 10,000 persons worldwide. Further, United Therapeutics estimates there are over 100,000 IPF patients in the United States alone.

Just two therapies are approved in the United States to treat IPF, and studies for both therapies have shown only a reduction in the rate of forced vital capacity, or FVC, decline in IPF patients.

About Tyvaso® Inhalation Solution and Tyvaso DPI® Inhalation Powder

INDICATION

TYVASO (treprostinil) Inhalation Solution and TYVASO DPI (treprostinil) Inhalation Powder are prostacyclin mimetics indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with TYVASO establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

  The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

  While there are long-term data on use of treprostinil by other routes of administration, nearly all clinical experience with inhaled treprostinil has been on a background of an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor. The controlled clinical experience with TYVASO was limited to 12 weeks in duration.

- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study with TYVASO establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- TYVASO and TYVASO DPI are pulmonary and systemic vasodilators. In patients with low systemic arterial pressure, either product may produce symptomatic hypotension.
- Both products inhibit platelet aggregation and increase the risk of bleeding.
- Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.
- Like other inhaled prostaglandins, TYVASO and TYVASO DPI may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with TYVASO and TYVASO DPI.

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of either product with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8.

- Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality. There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.
- Safety and effectiveness in pediatric patients have not been established.
- Across clinical studies used to establish the effectiveness of TYVASO in patients with PAH and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

- Pulmonary Arterial Hypertension (WHO Group 1)

  In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most common adverse reactions seen with TYVASO in ≥4% of PAH patients and more than 3% greater than placebo were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%). In addition, adverse reactions occurring in ≥4% of patients were dizziness and diarrhea.

  In a 3-week, open-label, single-sequence, safety and tolerability study (BREEZE) conducted in 51 patients on stable doses of TYVASO who switched to a corresponding dose of TYVASO DPI, the most commonly reported adverse events seen with TYVASO DPI in ≥4% of PAH patients during the 3-week treatment phase included cough (35.3%), headache (15.7%), dyspnea (7.8%), and nausea (5.9%).

- Pulmonary Hypertension Associated with ILD (WHO Group 3)

  In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse reactions with TYVASO were similar to the experience in studies of PAH.

Please see Full Prescribing Information for TYVASO or TYVASO DPI, Instructions for Use manuals for TD-100 and TD-300 TYVASO® Inhalation System and TYVASO DPI™ Inhalation Powder, and additional information at www.TYVASOHCP.com or call 1-877-UNITHER (1-877-864-8437).

TYVISIhcpMAY2022revised

United Therapeutics: Enabling Inspiration

At United Therapeutics, our vision and mission are one. We use our enthusiasm, creativity, and persistence to innovate for the unmet medical needs of our patients and to benefit our other stakeholders. We are bold and unconventional. We have fun, we do good. We are the first publicly-traded biotech or pharmaceutical company to take the form of a public benefit corporation (**PBC**). Our public benefit purpose is to provide a brighter future for patients through (a) the development of novel pharmaceutical therapies; and (b) technologies that expand the availability of transplantable organs.

You can learn more about what it means to be a PBC here: unither.com/pbc.

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, our plans concerning the *TETON* program, including our plans to release top-line data from the *TETON 2* study in 2025, our plans to seek FDA approval of nebulized Tyvaso and Tyvaso DPI to treat IPF and PPF, the potential for inhaled treprostinil to lead to better patient outcomes in patients with fibrotic lung disease, our efforts to innovate for the unmet medical needs of our patients, to benefit our other stakeholders, and to pursue our public benefit purpose of developing novel pharmaceutical therapies and technologies that expand the availability of transplantable organs. 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 10, 2024, 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:

Dewey Steadman at (202) 919-4097

https://ir.unither.com/contact-uthr/