For Immediate Release

United Therapeutics Announces First Patient Enrolled in Phase 3 *TETON PPF* Study of Nebulized Tyvaso in Patients with Progressive Pulmonary Fibrosis

Up to 60,000 patients in the United States may have PPF, with only one approved therapy available

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., October 31, 2023: United Therapeutics Corporation (Nasdaq: **UTHR**), a public benefit corporation, announced today that the first patient has enrolled in the registration-phase *TETON* PPF study, which will evaluate nebulized Tyvaso® (treprostinil) Inhalation Solution in 698 adult patients with progressive pulmonary fibrosis (**PPF**). This is in addition to two separate ongoing registration-phase studies, *TETON 1* and *TETON 2*, of nebulized Tyvaso in patients with another type of pulmonary fibrosis (**PF**) known as idiopathic pulmonary fibrosis (**IPF**).

The 52-week study will evaluate the impact of nebulized Tyvaso on a key prognostic indicator for PPF known as forced vital capacity (**FVC**). PPF is a progressive form of interstitial lung disease (**ILD**) characterized by the loss of the ability of the lungs to transfer oxygen into the blood, ultimately resulting in respiratory failure and death.

Nebulized Tyvaso is currently approved by the U.S. Food and Drug Administration (**FDA**) to treat both pulmonary arterial hypertension and pulmonary hypertension (**PH**) associated with interstitial lung disease (**PH-ILD**). The PH-ILD indication, which includes patients with PH associated with IPF and PPF, was added to the nebulized Tyvaso label in March 2021 based on the successful results of the *INCREASE* study. Nebulized Tyvaso is only approved for use for PPF patients who may also have documented PH, to improve exercise capacity. The *TETON PPF* study seeks to evaluate the use of nebulized Tyvaso in PPF patients irrespective of whether or not they have PH.

"The progressive pulmonary fibrosis phenotype represents a group of ILD patients who only have limited treatment options currently available to them," said **Steven Nathan, M.D.**, Medical Director of the Advanced Lung Disease and Lung Transplant Program at Inova Fairfax Hospital in Falls Church, Virginia, who is also chair of the *TETON* program steering committee. "The broader ILD data set from the *INCREASE* study showed improvements in FVC beyond just IPF patients, and the data provide the foundation for further study of inhaled treprostinil's anti-fibrotic and disease modifying mechanism of action in patients with other forms of fibrotic lung disease like PPF."

"The initiation of the global *TETON PPF* study illustrates confidence in nebulized Tyvaso as a potential treatment option for patients with fibrotic lung disease," said **Natalie Breytenbach, Pharm.D.**, Associate Director, Global Product Development at United Therapeutics and the company's lead for the *TETON PPF* study. "The expansion of *TETON* into the PPF patient population allows us to continue to evaluate inhaled treprostinil's potential for treating this vulnerable group of patients in a robust global pivotal study."

The *TETON* program in IPF and PPF was prompted by data from the *INCREASE* study of nebulized Tyvaso for the treatment of PH-ILD, which demonstrated improvements in certain key parameters of lung function in pulmonary hypertension patients with fibrotic lung disease (improved absolute FVC and reduced exacerbations of underlying lung disease). Specifically, in the *INCREASE* study, treatment with nebulized Tyvaso resulted in significant improvements in percent predicted FVC at weeks 8 and 16, with subjects having an underlying etiology of IPF showing the greatest improvement (week 8: 2.5%; p=0.0380 and week

16: 3.5%; p=0.0147). In May 2022, data from the *INCREASE* open-label, long-term extension trial were presented at a medical conference, indicating that improvements in FVC were sustained for at least 64 weeks for PH-ILD patients with underlying IPF. 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.

Tyvaso DPI® (treprostinil) Inhalation Powder is not being evaluated in the *TETON* program, but United Therapeutics intends to seek 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.

About *TETON PPF*

The *TETON PPF* study is a 698-patient, multicenter, randomized, double-blind, placebo-controlled phase 3 registration study to evaluate the safety and efficacy of nebulized Tyvaso in subjects with progressive pulmonary fibrosis (**PPF**) over a 52-week period. This third registration study is part of the global *TETON* program evaluating nebulized Tyvaso for the treatment of idiopathic pulmonary fibrosis (**IPF**) and PPF and will be conducted at sites globally.

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 interstitial lung disease (**ILD**); (3) overall survival at week 52; (4) change in percent predicted FVC from baseline to week 52; (5) change in the King's Brief Interstitial Lung Disease questionnaire; and (6) change in the diffusing capacity of the lungs for carbon monoxide.

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

About PPF

Progressive pulmonary fibrosis (**PPF**) is a group of interstitial lung disease (**ILD**) conditions that exhibit progressive, self-sustaining fibrosis, and display a similar disease course to idiopathic pulmonary fibrosis (**IPF**). PPF includes idiopathic interstitial pneumonias (other than IPF), autoimmune ILDs, chronic fibrosing hypersensitivity pneumonitis, and fibrotic ILDs related to environmental or occupational exposure. It is estimated that 13% to 40% of patients with these various ILDs will go on to develop PPF[1]. Patients with PPF exhibit decreased lung function, poor quality of life, and increased mortality despite usual treatments for the underlying ILD. Estimates for median transplant free survival and overall survival are approximately 2.9 years and 3.7 years, respectively.[2,3] Further, United Therapeutics estimates there are up to 60,000 PPF patients in the United States.

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[1] Olson AL, Patnaik P, Hartmann N, et al. Prevalence and incidence of chronic fibrosing interstitial lung diseases with a progressive phenotype in the United States estimated in a large claims database analysis. Adv Ther. 2021;38:4100-4114.

[2] Platenburg MGJP, van der Vis JJ, Grutters JC, van Moorsel CHM. Decreased survival and lung function in progressive pulmonary fibrosis. Medicina. 2023;59:296.

[3] Cottin V, Teague R, Nicholson L, et al. The burden of progressive-fibrosing interstitial lung disease. Front Med. 2022;9:799912.

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).

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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. Our public benefit purpose is *to provide a brighter future for patients through the development of novel pharmaceutical therapies; and 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, statements regarding the planned enrollment, conduct, and design of the *TETON 1*, *TETON 2*, and *TETON PPF* clinical studies, the potential for Tyvaso to become a treatment option for patients with fibrotic lung disease, our plans to seek IPF and PPF indications for the Tyvaso DPI label, and our goals of innovating for the unmet medical needs of our patients and to benefit our other stakeholders and furthering 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 October 31, 2023, 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/