For Immediate Release

UNITED THERAPEUTICS ANNOUNCES FIRST PATIENT ENROLLED IN PHASE 3 TETON 2 STUDY OF TYVASO IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSISLITIGATION

Second registration study of Tyvaso® (treprostinil) Inhalation Solution for patients with IPF

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., October 11, 2022: United Therapeutics Corporation (Nasdaq: **UTHR**), a public benefit corporation, announced today that the first patient has enrolled in the phase 3 *TETON 2* study which will evaluate Tyvaso in 396 adult patients with idiopathic pulmonary fibrosis (**IPF**) at sites outside the United States and Canada. This second registration study is part of the broader global *TETON* program evaluating Tyvaso for the treatment of IPF. The 52-week study will evaluate the impact of Tyvaso on a key prognostic indicator for IPF known as forced vital capacity (**FVC**). IPF is a progressive lung disease characterized by the loss of the ability of the lungs to transfer oxygen into the blood, ultimately resulting in respiratory failure and death.

"Despite the availability of two approved products in this therapeutic category, there remains a critical unmet need in IPF," 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. "As is now widely known in the pulmonology community, the safety data collected from the *INCREASE* study showed a positive impact of inhaled treprostinil on FVC in IPF patients with pulmonary hypertension. In follow-up to this, the *TETON 1* and *TETON 2* studies have been designed to further investigate the potential antifibrotic effects of inhaled treprostinil in IPF patients."

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, was added to the Tyvaso label in March 2021 based on the successful results of the *INCREASE* study. Tyvaso is not approved in any jurisdiction for use for IPF patients without documented PH. Additionally, Tyvaso DPI® (treprostinil) inhalation powder is not being evaluated in the *TETON* program.

"The expansion of the *TETON* program demonstrates our excitement about the potential for Tyvaso in IPF," said **Peter Smith, Pharm.D.**, United Therapeutics' Vice President of Global Product Development. "Like with *TETON 1,* the *TETON 2* study is an example of our flexible development model to expand beyond PH to potentially help us better understand the impact of treprostinil as a potential treatment option for this vulnerable group of patients."

About *TETON 2*

Parallel in design to the *TETON 1* study, the *TETON 2* study is a 396-patient, multicenter, randomized, double-blind, placebo-controlled phase 3 registration study to evaluate the safety and efficacy of Tyvaso in subjects with IPF over a 52-week period. This second registration study is part of the broader global *TETON* program evaluating Tyvaso for the treatment of IPF and will be conducted at sites outside of the United States and Canada. The *TETON 1* study is being conducted at sites in the United States and Canada.

Subjects will be randomly allocated 1:1 to receive Tyvaso or placebo. All subjects will initiate 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

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[1]. Further, United Therapeutics estimates there are around 100,000 IPF patients in the United States alone.

About TYVASO® (treprostinil) Inhalation Solution and TYVASO DPI® (treprostinil) 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 (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, statements relating our plans to conduct the *TETON 1* and *TETON 2* studies, including our plan to enroll 396 patients in the *TETON 2* study, the potential for inhaled treprostinil to become a treatment option for patients with idiopathic pulmonary fibrosis, our commitment to fulfilling our purpose and promise to our patients, our employees, and all of humankind, our ability to create value and sustain our success in the long-term, and our efforts to develop technologies that either delay the need for transplantable organs or expand the supply 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 11, 2022 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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[1] Maher et al. *Respir Res* (2021) 22:197 https://doi.org/10.1186/s12931-021-01791-z

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