For Immediate Release

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

First pivotal study of Tyvaso® (treprostinil) Inhalation Solution outside pulmonary hypertension

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Thursday, June 3, 2021: United Therapeutics Corporation (Nasdaq: UTHR) announced today that the first patient has enrolled in the phase 3 *TETON* study, which is expected to evaluate approximately 396 adult patients with idiopathic pulmonary fibrosis (**IPF**). This 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 absorb oxygen, ultimately resulting in respiratory failure and death. IPF is estimated to affect 100,000 people in the United States.

"Despite the availability of two approved products in the therapeutic category, there remains a critical unmet need in IPF," said Steven Nathan, M.D., the 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* trial steering committee. Dr. Nathan further added, "We were pleasantly surprised to note the intriguing post-hoc analysis of safety data collected from the *INCREASE* study that showed a positive impact of inhaled treprostinil on FVC in IPF patients with pulmonary hypertension. In follow-up to this, the *TETON* study has been designed to validate 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 for use for IPF patients without documented PH.

"The initiation of the *TETON* study is an important milestone in potentially bringing an improved treatment option to patients with IPF" said Leigh Peterson, Ph.D., United Therapeutics' Senior Vice President of Global Product Development. "The *TETON* study is an example of our company's flexible development model to expand beyond PH and will help us to better understand the impact of treprostinil in mitigating the FVC decline seen in IPF patients."

The FDA has granted Tyvaso orphan drug designation for the treatment of IPF. As a result, if the FDA updates Tyvaso's labeling to include an IPF indication following a successful *TETON* study, the FDA should confer seven years of market exclusivity in the United States following marketing approval by FDA.

About *TETON*

The *TETON* study is a 396-patient, multicenter, randomized, double-blind, placebo-controlled phase 3 registration study to evaluate the safety and efficacy of inhaled treprostinil in subjects with IPF over a 52-week period.

Subjects will be randomly allocated 1:1 to receive inhaled treprostinil or placebo. All subjects will initiate inhaled treprostinil 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 (**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 absorb oxygen, 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. IPF is estimated to affect approximately 100,000 patients in the United States and the median survival of patients with IPF ranges from 2 to 3 years.

About TYVASO® (treprostinil) Inhalation Solution

INDICATION

TYVASO (treprostinil) is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies 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 controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience 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 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 is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, TYVASO may produce symptomatic hypotension.
- TYVASO inhibits platelet aggregation and increases 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.

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of TYVASO 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 in the placebo-controlled study 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.

- 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 were similar to the experience in studies of PAH.

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

United Therapeutics: Enabling Inspiration

United Therapeutics Corporation focuses on the strength of a balanced, value-creating biotechnology model. We are confident in our future thanks to our fundamental attributes, namely our obsession with quality and innovation, the power of our brands, our entrepreneurial culture, and our bioinformatics leadership. We also believe that our determination to be responsible citizens – having a positive impact on patients, the environment, and society – will sustain our success in the long term.

Through our wholly owned subsidiary, Lung Biotechnology PBC, we are focused on addressing the acute national shortage of transplantable lungs and other organs with a variety of technologies that either delay the need for

such organs or expand the supply. Lung Biotechnology is the first public benefit corporation subsidiary of a public biotechnology or pharmaceutical company.

Please visit unither.com to learn more.

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 to the *TETON* study including the target enrollment, the potential for the *TETON* study to demonstrate FVC improvements in IPF patients and lead to an expansion of the Tyvaso label to include an IPF indication, the potential for obtaining orphan drug exclusivity from FDA for an IPF indication for Tyvaso, our ability to create value and sustain our success in the long-term, as well as 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 June 3, 2021, 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.

TYVASO is a registered trademark of United Therapeutics Corporation.

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