United Therapeutics announces the Lancet Respiratory Medicine publication of post-hoc analysis of FVC change from the Tyvaso® INCREASE study

For Immediate Release

UNITED THERAPEUTICS ANNOUNCES THE LANCET RESPIRATORY MEDICINE PUBLICATION OF POST-HOC ANALYSIS OF FVC CHANGE FROM THE TYVASO® INCREASE STUDY

Forced vital capacity improvement observed during the INCREASE study in patients with idiopathic pulmonary fibrosis represents the basis of the TETON registration study of Tyvaso in IPF

Silver Spring, Md. and Research Triangle Park, N.C., Wednesday, June 30, 2021: United Therapeutics Corporation (Nasdaq: UTHR) today announced the publication in The Lancet Respiratory Medicine of a post-hoc analysis of forced vital capacity (FVC) change in patients during the INCREASE study of Tyvaso® (treprostinil) Inhalation Solution in patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3 pulmonary hypertension).

The analysis demonstrated that inhaled treprostinil was associated with improvements in FVC compared to placebo over 16 weeks. The improvement was most evident in patients with idiopathic pulmonary fibrosis (IPF), a progressive, irreversible, and life-threatening lung disease of unknown cause with a median survival of 2-3 years.1,2 This analysis, together with literature demonstrating the in vitro antifibrotic effects of treprostinil, represent the basis of the pivotal TETON study of Tyvaso in patients with IPF.3,4

“I am encouraged by the improvement in FVC observed in subgroups such as IPF in this post-hoc analysis of the INCREASE study data,” said Steven Nathan, M.D., an INCREASE study investigator and Steering Committee member, Director of the Advanced Lung Disease Program and Director of the Lung Transplant Program at Inova Fairfax Hospital in Falls Church, Va., and Professor of Medicine at Virginia Commonwealth University-Inova Campus. “These data, collected in patients presenting with IPF plus pulmonary hypertension, warrant the further investigation of inhaled treprostinil’s effects in patients diagnosed with IPF alone, before their disease progresses and they develop pulmonary hypertension.”

“Patients with IPF have generally used two therapies that modestly slow the progression of their disease but come with challenging side effects that can make treatment difficult,” said Gil Golden, M.D., Ph.D., Chief Medical Officer at United Therapeutics. “This analysis is exciting because rather than slowing down the rate of FVC deterioration, Tyvaso actually improved FVC in the relatively short 16-week duration of the INCREASE study. If the TETON study supports eventual approval of Tyvaso in patients with IPF, we look forward to providing a new treatment option for these patients with few current treatment options for this life-threatening medical condition.”

“We measured FVC in the INCREASE study as a safety endpoint to make sure treatment with Tyvaso was not exacerbating patients’ underlying lung diseases. What we found was quite the contrary, as we saw improvement in lung function among several subgroups including those with PH associated with IPF,” said Leigh Peterson, Ph.D., Senior Vice President, Product Development at United Therapeutics. “We are looking to expand on these results in the TETON study, in hopes of demonstrating a label-enabling FVC improvement in patients with IPF. We enrolled the first patients in the TETON study this month.”

Tyvaso is approved by the U.S. Food and Drug Administration to treat pulmonary arterial hypertension (PAH; WHO Group 1) and PH-ILD.

About INCREASE
The multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel group INCREASE study evaluated Tyvaso in adult patients suffering from World Health Organization (WHO) Group 3 PH-ILD. A total of 326 patients were enrolled at 93 centers and randomized to inhaled Tyvaso (n=163) four times daily or placebo.
United Therapeutics previously announced data from INCREASE showing it met all primary and secondary endpoints.

The primary efficacy endpoint was the change in six-minute walk distance (6MWD) measured at peak exposure from baseline to Week 16. The study showed that treatment with inhaled Tyvaso was well tolerated and improved 6MWD by 21 meters versus placebo (p=0.0043) at week 16 when using a pre-specified worst-case imputation for missing data and Hodges-Lehmann estimate. Tyvaso increased 6MWD by 31 meters relative to placebo after 16 weeks of treatment (p<0.001) using the mixed model repeated measurement analysis. The benefits of Tyvaso were observed across subgroups, including etiology and severity of PH-ILD, age group, gender, baseline hemodynamics and dose group.

Secondary endpoints included change in plasma concentration of the cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline to Week 16; time to clinical worsening as measured by various metrics including hospitalization due to a cardiopulmonary indication, death (all causes) or lung transplantation; change in peak 6MWD from baseline to Week 12; and change in trough 6MWD from baseline to Week 15. Results showed significant improvements in each of the secondary endpoints:

- A 42% reduction in NT-proBNP with Tyvaso versus placebo at Week 16 (p<0.001)
- A 39% reduction in the risk of a clinical worsening event with Tyvaso versus placebo (p=0.04); 22.7% of patients treated with Tyvaso experienced a clinical worsening event vs. 33.1% of placebo patients
- Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (26.4% versus 38.7%, p=0.02)
- Significant Improvements in peak 6MWD at Week 12 with Tyvaso compared with placebo (31.29 m, p<0.001) and trough 6MWD at week 15 (21.99, p=0.005)

Treatment with Tyvaso of up to 12 breaths per session, four times daily, was well tolerated. Most treatment-related adverse events were mild to moderate in intensity and included cough, headache, dyspnea, dizziness, nausea, fatigue and diarrhea, consistent with the existing Tyvaso label. The safety profile was similar to previous studies of Tyvaso in pulmonary arterial hypertension and known prostacyclin-related adverse events (see the Important Safety Information below under “About TYVASO® (treprostinil) Inhalation Solution”).

**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 PH-ILD
Interstitial lung disease (ILD) is a group of lung diseases that are characterized by marked scarring or fibrosis of the bronchioles and alveolar sacs within the lungs. Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs, and the condition can present with a wide range of symptoms, including shortness of breath with activity, labored breathing and fatigue. Pulmonary hypertension (PH) frequently complicates the course of patients with interstitial lung disease and is associated with worse functional status measured by exercise capacity, greater supplemental oxygen needs, decreased quality of life, and worse outcomes.

PH-ILD is estimated to affect at least 15% of patients with ILD (approximately 30,000 PH-ILD patients) and may affect up to 86% of patients with more severe ILD. PH-ILD is included within Group 3 of the World Health Organization (WHO) classification of PH.

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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $\geq4\%$ of PAH patients and more than 3% greater than placebo in the placebo-controlled study were cough (56% 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 $\geq4\%$ 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](https://www.tyvaso.com), the [TD-100](https://www.tyvaso.com) and [TD-300](https://www.tyvaso.com) TYVASO® Inhalation System Instructions for Use manuals, and other additional information at [www.tyvaso.com](http://www.tyvaso.com) or call 1-877-UNITHER (1-877-864-8437).

**References**
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](http://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, 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 to provide Tyvaso as a new treatment option for IPF patients, 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 30, 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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