For Immediate Release

# UNITED THERAPEUTICS TO PRESENT TYVASO DPI™ *BREEZE* CLINICAL DATA AT THE EUROPEAN RESPIRATORY SOCIETY INTERNATIONAL CONGRESS 2021

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., August 24, 2021 -- United Therapeutics Corporation (Nasdaq: UTHR) today announced it will present data from a clinical trial studying Tyvaso DPI™ (treprostinil) in patients with pulmonary arterial hypertension (**PAH**) at the European Respiratory Society (**ERS**) International Congress 2021, which will be held virtually from September 5-8, 2021.

Data from the *BREEZE* study of Tyvaso DPI, a dry powder inhaled formulation of treprostinil, will be presented in a poster session on September 6, 2021. The *BREEZE* study enrolled 51 subjects on a stable regimen of Tyvaso® Inhalation Solution who were transitioned to Tyvaso DPI at a corresponding treprostinil dose.

The primary objective of the study was to evaluate the safety and tolerability of Tyvaso DPI during a three-week treatment phase in PAH patients previously treated with Tyvaso Inhalation Solution. Top line data showing the *BREEZE* study met its primary objective were released in January 2021.

Secondary objectives highlighted at the congress will include: (1) change in six-minute walk distance (**6MWD**); (2) patient satisfaction with and preference for inhaled treprostinil devices; and (3) patient-reported PAH symptoms and impact (PAH-SYMPACT®). Each objective was assessed at study entry when patients were using Tyvaso Inhalation Solution and after three weeks using Tyvaso DPI.

Additional pharmacokinetic (**PK**) data from the *BREEZE* and healthy volunteer studies will be presented at future medical congresses.

"We look forward to presenting important new data that serve as the basis of our pending New Drug Application for Tyvaso DPI," said Leigh Peterson, Ph.D., Senior Vice President, Product Development, at United Therapeutics. "If approved by the FDA, Tyvaso DPI will provide a more convenient formulation of inhaled treprostinil that may increase prostacyclin accessibility."

Details for the poster presentation at ERS 2021 are as follows:

**Title:** *BREEZE*: Open-label, Clinical Study to Evaluate the Safety and Tolerability of a Treprostinil Dry Powder inhaler in Patients with Pulmonary Arterial Hypertension Currently using Tyvaso
**Lead Author:** Leslie Spikes, M.D.

The poster will be available on the United Therapeutics Pipeline website following the conclusion of the congress.

**About PAH**
Also known as World Health Organization (WHO) Group 1 Pulmonary Hypertension, PAH is life-threatening high blood pressure in the arteries of the lungs, affecting the ability of the heart and lungs to work properly in afflicted patients. PAH is a serious, progressive disease for which there is no known cure.

**About Tyvaso DPI**
Tyvaso DPI™ is an investigational drug-device combination therapy comprised of a dry powder formulation of treprostinil and a small, portable, dry powder inhaler. If approved, Tyvaso DPI is expected to provide a more convenient method of administration compared with traditional nebulized Tyvaso® therapy. United Therapeutics has developed Tyvaso DPI under a collaboration and license agreement with MannKind Corporation (Nasdaq:

MNKD). Tyvaso DPI incorporates the dry powder formulation technology and Dreamboat® inhalation device technology used in MannKind's Afrezza® (insulin human) Inhalation Powder product, which was approved by the FDA in 2014.

United Therapeutics and MannKind are also developing BluHale®, a Bluetooth-connected accessory for the Tyvaso DPI inhaler with a companion mobile application intended to help the patient track information about inhaler use.

United Therapeutics has submitted a New Drug Application (**NDA**) to the U.S. Food and Drug Administration (**FDA**) seeking approval of Tyvaso DPI to treat patients with PAH and pulmonary hypertension associated with interstitial lung disease. FDA action on the NDA is anticipated in October 2021.

**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 our planned presentations regarding Tyvaso DPI clinical data, our pending

NDA for Tyvaso DPI, and the potential clinical benefits of Tyvaso DPI if and when it is approved by the FDA, 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 August 24, 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.



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