For Immediate Release

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

In subjects with PAH, transition from Tyvaso® to Tyvaso DPI™ demonstrated safety and tolerance with significant improvements in six-minute walk distance, device preference and satisfaction, and patient reported outcomes

FDA action on New Drug Application for Tyvaso DPI expected in October 2021

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Tuesday, September 7, 2021: United Therapeutics Corporation (Nasdaq: UTHR) today presented new clinical data from the *BREEZE* study evaluating Tyvaso DPI™ (treprostinil) in patients with pulmonary arterial hypertension (**PAH**) at the European Respiratory Society (**ERS**) International Congress 2021.

Tyvaso DPI is a next-generation dry powder formulation of Tyvaso® (treprostinil) Inhalation Solution (**Tyvaso**), which is currently under review by the U.S. Food and Drug Administration (**FDA**). If approved, Tyvaso DPI is expected to provide a more convenient method of administration as compared with traditional nebulized Tyvaso therapy.

"The transition from nebulized Tyvaso to Tyvaso DPI demonstrated safety and tolerance with significant improvements in six-minute walk distance and other key factors," said Leslie Spikes, M.D., Associate Professor of Pulmonary and Critical Care Medicine at the University of Kansas Medical Center. "The results of the study, even when taken into the context of the unblinded study design, indicate that Tyvaso DPI is a convenient, tolerable treprostinil formulation that could increase prostacyclin accessibility, with the potential to improve patient outcomes."

"At United Therapeutics, we continue to strive to make treprostinil therapy more accessible for our pulmonary hypertension patients," said Peter Smith, PharmD, Vice President, Product Development at United Therapeutics. "As such, we are thrilled to share the *BREEZE* study data demonstrating the safety and tolerability of treprostinil administered as Tyvaso DPI, which, if approved by the FDA, could represent a more convenient formulation of inhaled treprostinil."

The *BREEZE* study

The *BREEZE* study enrolled 51 subjects on a stable regimen of Tyvaso 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 of the study included changes in six-minute walk distance (**6MWD**), device preference and satisfaction as evaluated through the Preference Questionnaire for Inhaled Treprostinil Devices (**PQ-ITD**), and patient reported PAH symptoms and impact (**PAH-SYMPACT®**).

Primary safety and tolerability objective. Transition from Tyvaso to Tyvaso DPI demonstrated safety and tolerance. Forty-nine out of 51 patients (96%) completed the three-week treatment phase, while two subjects discontinued due to treatment-related adverse events during the treatment phase. There were no study drug-related serious adverse events. Most adverse events experienced during the study were mild to moderate in severity and occurred at severities and frequencies consistent with those seen in other inhaled treprostinil studies in patients with PAH. Please see Important Safety Information about Tyvaso at the end of this press release.

Secondary objectives. Three weeks after switching from Tyvaso to Tyvaso DPI, patients in the *BREEZE* study demonstrated:

- **Significant improvements in 6MWD compared to baseline.** Improvements of 11.5 meters (p=0.0217) in 6MWD compared to baseline were observed through the three-week treatment phase.
- **Significant improvements in overall satisfaction with the Tyvaso DPI inhaler.** Using the PQ-ITD, significant improvements (p<0.0001) were observed in overall satisfaction with the Tyvaso DPI inhaler.
- **Significant improvements in PAH Impact.** The SYMPACT questionnaire includes domains on physical impacts, cognitive/emotional impacts, cardiopulmonary symptoms, and cardiovascular symptoms. Significant improvements in PAH impacts were observed in physical impacts (p=0.0438) and cognitive/emotional impacts (p=0.0048) at week three.

Optional extension phase. Subjects in *BREEZE* were given the opportunity to continue in an optional extension phase (**OEP**). All subjects who completed the treatment phase (49/51) elected to continue in the OEP. Improvements in 6MWD compared to baseline were sustained in the OEP through the data cut-off date.

The *BREEZE* data presented at ERS will be available on the United Therapeutics Pipeline website following the conclusion of the congress. Additional pharmacokinetic (**PK**) data from *BREEZE* and a separate healthy volunteer study will be presented at future medical congresses.

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 adult 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 pending NDA for Tyvaso DPI, the potential clinical benefits of Tyvaso DPI if and when it is approved by the FDA, our planned presentations of additional Tyvaso DPI clinical data, 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 September 7, 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.

TYVASO DPI is a trademark of United Therapeutics Corporation.

AFREZZA, BLUHALE, and DREAMBOAT are registered trademarks of MannKind Corporation.

PAH-SYMPACT is a registered trademark of Actelion Pharmaceuticals Ltd société anonyme.

For Further Information Contact:
Dewey Steadman at (202) 919-4097
Email: ir@unither.com

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