For Immediate Release

UNITED THERAPEUTICS ANNOUNCES SUBMISSION OF TYVASO DPI™ NEW DRUG APPLICATION TO FDA

NDA submission includes both pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease indications

Priority review voucher applied to the NDA submission

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Monday, April 19, 2021: United Therapeutics Corporation (Nasdaq: UTHR) today announced the submission of a new drug application (**NDA**) to the U.S. Food and Drug Administration (**FDA**) for Tyvaso DPI™, a novel dry powder inhalation formulation of treprostinil, for the treatment of pulmonary arterial hypertension (**PAH**; WHO Group 1 pulmonary hypertension) and pulmonary hypertension associated with interstitial lung disease (**PH-ILD**; WHO Group 3 pulmonary hypertension). There are approximately 45,000 treated PAH patients in the U.S. and United Therapeutics estimates at least 30,000 treatable PH-ILD patients in the U.S.

The submission includes the results of the recently-completed *BREEZE* clinical study evaluating the use of Tyvaso DPI in PAH patients transitioning from Tyvaso® (treprostinil) Inhalation Solution, along with additional pharmacokinetic data from a study in healthy volunteers.

"In the *BREEZE* and pharmacokinetic studies, Tyvaso DPI demonstrated safety, tolerability, and a comparable pharmacokinetic profile to nebulized Tyvaso Inhalation Solution," said Leigh Peterson, Ph.D., Senior Vice President, Product Development at United Therapeutics. "If approved by the FDA, we expect Tyvaso DPI will provide an advancement in the delivery of inhaled treprostinil therapy."

"Since our founding, we've worked hard to ensure our patients have ample choices to deliver treprostinil in various ways to suit their individual needs," said Gil Golden, M.D., Ph.D., Chief Medical Officer of United Therapeutics. "If approved, Tyvaso DPI will enable patients to go about their day with just a small breath-actuated, dry powder inhaler that easily fits inside a pocket and requires no batteries or external power source to operate."

"We're excited for the potential for Tyvaso DPI to be one of our next product launches, assuming a timely approval in December of this year," said Michael Benkowitz, President and Chief Operating Officer of United Therapeutics. "The patient choice afforded by Tyvaso DPI, if approved, will help us achieve our goal of doubling the number of patients on Tyvaso therapy by the end of 2022. We remain committed to investigating, innovating, and delivering multiple therapies and treatments designed to help our patients manage their conditions."

United Therapeutics has applied a priority review voucher to the NDA that could provide for an FDA decision by December 2021. The FDA must first accept the application for review and issue a formal decision date in accordance with the Prescription Drug User Fee Act.

Tyvaso DPI is an investigational therapy that is not approved for any use in any country or indication and the Tyvaso DPI tradename is pending final FDA review. United Therapeutics expects to present data from the *BREEZE* study and the pharmacokinetic study in healthy volunteers at upcoming medical conferences and in forthcoming scientific publications.

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 is developing 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.

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 potential for the approval of Tyvaso DPI and the timing of any such approval, its potential benefits to patients, our goal of doubling the number of patients being treated with Tyvaso by 2022, 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 April 19, 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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