



## **UNITED THERAPEUTICS ANNOUNCES BREEZE STUDY OF INVESTIGATIONAL TYVASO DPI™ MEETS PRIMARY OBJECTIVE**

*Study demonstrated safety and tolerability of Tyvaso DPI™ in patients with PAH transitioning from Tyvaso® Inhalation Solution*

*A separate study in healthy volunteers demonstrated comparable treprostinil exposure between Tyvaso DPI and Tyvaso Inhalation Solution*

*Tyvaso DPI NDA filing anticipated in April 2021 with priority review*

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Thursday, January 28, 2021: United Therapeutics Corporation (Nasdaq: UTHR) announced today that the BREEZE study of Tyvaso DPI (inhaled treprostinil) met its primary objective of demonstrating safety and tolerability in patients with pulmonary arterial hypertension (PAH) transitioning from Tyvaso (treprostinil) Inhalation Solution. In addition, a pharmacokinetic (PK) study in healthy volunteers demonstrated comparable treprostinil exposure between Tyvaso DPI and Tyvaso Inhalation Solution.

Tyvaso DPI is a next-generation dry powder formulation of Tyvaso currently under development. If approved, Tyvaso DPI is expected to provide a more convenient method of administration as compared with traditional nebulized Tyvaso therapy.

“We are pleased with these results, which demonstrate the safety, tolerability, and pharmacokinetic profiles of treprostinil administered as Tyvaso DPI,” said Dr. Leigh Peterson, Vice President, Product Development at United Therapeutics. “We look forward to submitting our New Drug Application for Tyvaso DPI in April. If approved, we expect Tyvaso DPI will provide a major advancement in the delivery of inhaled treprostinil therapy, offering convenience benefits compared to our existing Tyvaso nebulizer.”

United Therapeutics intends to submit a New Drug Application (NDA) to the FDA for Tyvaso DPI for indications covering PAH and pulmonary hypertension associated with interstitial lung disease in April 2021 and plans to apply a [priority review voucher](#) to the Tyvaso DPI NDA, providing an expedited FDA review period.

### **The BREEZE study demonstrated safety and tolerability of Tyvaso DPI in subjects with PAH transitioning from Tyvaso Inhalation Solution**

The BREEZE study was a single-sequence study in which 51 subjects on a stable regimen of Tyvaso Inhalation Solution 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.

Secondary objectives of the study were to evaluate: (1) the systemic exposure and pharmacokinetics of treprostinil when delivered as Tyvaso Inhalation Solution and Tyvaso DPI; (2) six-minute walk distance (6MWD) at study entry and after three weeks of treatment with Tyvaso DPI; (3) the long-term safety and tolerability of Tyvaso DPI during an optional extension phase (OEP) in patients previously treated with Tyvaso Inhalation Solution; (4) patient satisfaction with and preference for inhaled treprostinil devices assessed at study entry when patients were using Tyvaso Inhalation Solution and after three weeks using Tyvaso DPI; and (5) patient-reported PAH symptoms and impact (PAH-SYMPACT®) assessed at study entry when patients were using Tyvaso Inhalation Solution and after three weeks using Tyvaso DPI.

**Primary safety and tolerability objective.** Transition from Tyvaso Inhalation Solution to Tyvaso DPI was safe and well tolerated. Forty-nine out of 51 patients (96%) completed the treatment phase and 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.

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

- Improvements in 6MWD compared to baseline. These improvements in 6MWD compared to baseline were sustained in the OEP through the data cut-off date.
- Improvements in overall satisfaction with the Tyvaso DPI inhaler compared to the Tyvaso Inhalation Solution nebulizer at baseline using an internally developed satisfaction and preference questionnaire.
- Improvement in patient-reported outcomes using the validated PAH-SYMPACT questionnaire.

**Optional extension phase.** Subjects in BREEZE were given the opportunity to continue in an OEP. All subjects who completed the treatment phase (49/51) elected to continue in the OEP.

PK data collected during the BREEZE study are currently undergoing final analysis. Detailed data from the BREEZE study will be presented in upcoming publications and scientific conferences.

### **Tyvaso DPI demonstrated comparable treprostinil exposure to Tyvaso Inhalation Solution in healthy volunteers**

The healthy volunteer PK study was a randomized six-period, six-sequence crossover study of three dose levels of Tyvaso DPI and three dose levels of Tyvaso Inhalation Solution in 36 healthy volunteers. The primary objective of the study was to evaluate the systemic exposure and PK of treprostinil administered as Tyvaso DPI and Tyvaso Inhalation Solution. Secondary objectives of the study evaluated the safety and tolerability of Tyvaso DPI.

**Study results.** Subjects demonstrated comparable systemic treprostinil exposure for each corresponding Tyvaso DPI and Tyvaso Inhalation Solution dose level. Between-subject variability for both  $AUC_{0-5h}$  and  $C_{max}$  was approximately 50% less for Tyvaso DPI compared to Tyvaso Inhalation Solution, suggesting a more precise dosing profile for Tyvaso DPI relative to nebulized Tyvaso.

**Safety.** The adverse event profile for Tyvaso DPI in healthy volunteers was consistent with known prostacyclin effects and previous studies of Tyvaso Inhalation Solution.

Detailed data from the healthy volunteer PK study will be presented in upcoming publications and scientific conferences.

### **About Tyvaso DPI**

Tyvaso DPI™, previously referred to as Treprostinil Technosphere®, 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. 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 plans to submit the Tyvaso DPI NDA with an indication to treat pulmonary arterial hypertension (PAH), as well as pulmonary hypertension associated with interstitial lung disease (PH-ILD). Tyvaso is indicated to treat World Health Organization (WHO) Group 1 PAH, and the FDA is currently reviewing a supplement to the Tyvaso NDA to reflect the [results](#) of the *INCREASE* study and expand its labeling to include PH-ILD.

Tyvaso DPI is an investigational combination product that is not approved for any use in any country, and the Tyvaso DPI tradename is pending final FDA review.

## **About TYVASO® (treprostinil) Inhalation Solution**

### **INDICATION**

TYVASO (treprostinil) is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately 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.

### **IMPORTANT SAFETY INFORMATION FOR TYVASO**

#### **WARNINGS AND PRECAUTIONS**

- The efficacy of TYVASO has not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- TYVASO is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, TYVASO may cause symptomatic hypotension
- Titrate slowly in patients with hepatic or renal insufficiency, as exposure to treprostinil may be increased in these patients
- TYVASO inhibits platelet aggregation and increases the risk of bleeding
- Co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil may increase exposure to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events, 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
- Co-administration of the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to oral treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to oral 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
- It is unknown if geriatric patients respond differently than younger patients. Caution should be used when selecting a dose for geriatric patients

#### ADVERSE REACTIONS

- The most common adverse reactions seen with TYVASO in  $\geq 4\%$  of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical 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  $\geq 10\%$  of patients were dizziness and diarrhea

**Please see the Full Prescribing Information, Patient Product Information, and the [TD-100](#) and [TD-300](#) TYVASO® Inhalation System Instructions for Use manuals. For additional information about TYVASO, visit [www.tyvaso.com](http://www.tyvaso.com) or call 1-877-UNITHER (1-877-864-8437).**

For Consumer Important Safety Information, please see <https://www.tyvaso.com/dtc/isi>

#### **About United Therapeutics**

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.

#### **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 anticipated timing and outcome of the New Drug Application for Tyvaso DPI and our pending supplemental New Drug Application for Tyvaso to update its labeling to include a PH-ILD indication, the potential indications for Tyvaso DPI, the expected benefits of Tyvaso DPI to patients, our plan to seek both PAH and PH-ILD indications when we submit our Tyvaso DPI NDA, our expectation that Tyvaso DPI will represent a major advancement in the delivery of inhaled treprostinil therapy, our commitment to bring a new generation of treatments to patients with PAH, and the timing thereof, 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 January 28, 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, DREAMBOAT, and TECHNOSPHERE are registered trademarks of MannKind Corporation.

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

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