



**UNITED THERAPEUTICS ANNOUNCES NEW ENGLAND JOURNAL OF MEDICINE PUBLICATION OF THE INCREASE STUDY EVALUATING TYVASO® IN PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASE**

*INCREASE Study is First to Demonstrate a Clear Benefit in Patients with PH-ILD, a Life-threatening Disease with No Currently FDA-Approved Treatments*

*Company to host a webcast detailing the INCREASE study results on Tuesday, January 19, 2021 at 4:30 p.m. E.T.*

SILVER SPRING, Md., and RESEARCH TRIANGLE PARK, N.C., January 13, 2021 – United Therapeutics Corporation (Nasdaq: UTHR) today announced that results from the INCREASE clinical study of Tyvaso® (treprostinil) Inhalation Solution for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD) have been [published](#) online in the New England Journal of Medicine. Results from INCREASE, the largest and most comprehensive completed study of adult patients with PH-ILD, showed that treatment with inhaled Tyvaso was well tolerated and improved the exercise capacity measure of six-minute walk distance (6MWD) by 31 meters relative to placebo at Week 16 ( $p < 0.001$ ) using the mixed model repeated measurement analysis. Additionally, patients treated with Tyvaso experienced significant improvements in other clinically meaningful outcomes, including a decreased risk of clinical worsening, an improvement in forced vital capacity, and a reduction in exacerbation of underlying lung disease.

Interstitial lung disease (ILD) is a group of lung diseases in which marked scarring occurs within the lungs. It is often complicated by pulmonary hypertension (PH; high blood pressure in the lungs). PH 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. Currently, no therapy is approved by the U.S. Food and Drug Administration (FDA) to treat this serious, life-threatening disease.

“Patients with both interstitial lung disease and pulmonary hypertension are more likely to have a worse course of disease and worse survival rate than patients with interstitial lung disease alone. They often have a very poor quality of life and are significantly limited because of severe shortness of breath despite supplemental oxygen,” said Steven D. 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. “With no therapies currently approved for PH-ILD, the positive efficacy and notable safety outcomes demonstrated in the INCREASE study are very encouraging. Having an approved inhaled treatment to offer my patients with PH-ILD would be transformational for the medical community and, importantly, for patients living with this disease.”

United Therapeutics submitted a supplemental New Drug Application (sNDA) for Tyvaso for the treatment of PH-ILD based on the results of the INCREASE study. The sNDA was accepted by the FDA for review, and the company expects the agency’s review to be complete in April 2021.

“We are thrilled that the positive pivotal INCREASE study results were published in such a prestigious journal,” said Leigh Peterson, Ph.D., Vice President, Product Development at United Therapeutics. “Based on the final data set from INCREASE, we are confident that Tyvaso will provide clinical benefit to patients with PH-ILD, who are in need of a safe and effective therapy. If approved, Tyvaso will be the first and only therapy approved for the treatment of this serious disease, heralding a significant advance in the way these patients are managed.”

## **INCREASE Study Design and Results**

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 (n=163). United Therapeutics previously announced [topline 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. Results showed that Tyvaso significantly increased 6MWD by 31 meters as analyzed using the Mixed Model Repeated Measurement ( $p<0.001$ ). When analyzed using a pre-specified worst case imputation for missing data and Hodges-Lehmann estimate, Tyvaso improved 6MWD by 21 meters relative to placebo over the same time period ( $p=0.0043$ ). 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 versus 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").

## **Webcast information**

United Therapeutics will host a Science Session webcast on Tuesday, January 19, 2021 at 4:30 p.m. Eastern Standard Time, to discuss the results of the *INCREASE* study and United Therapeutics' commercial plans in PH-ILD once FDA approved.

The webcast will feature members of United Therapeutics' management team, including Michael Benkowitz, President and Chief Operating Officer, and will feature Steven D. 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.

Those interested in listening to the webcast can register for the event [here](#) or can visit the "Events and Presentations" page at [ir.unither.com](http://ir.unither.com). A replay of the webcast will be available on the United Therapeutics Investor Relations website after the conclusion of the event.

## **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; however, no treatments are approved by the FDA for patients with this disease.

## **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 timing and outcome of FDA review of our sNDA for Tyvaso, the potential for Tyvaso to treat PH-ILD patients if the sNDA is approved, our ability to create value and sustain our success in the long-term, and 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 13, 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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