



UNITED THERAPEUTICS ANNOUNCES U.S. FDA FILING ACCEPTANCE OF SUPPLEMENTAL NEW DRUG APPLICATION FOR TYVASO® FOR PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASE

SILVER SPRING, Md., and RESEARCH TRIANGLE PARK, N.C., August 17, 2020 – United Therapeutics Corporation (Nasdaq: UTHR) today announced that the U.S. Food and Drug Administration (FDA) accepted for review the supplemental New Drug Application (sNDA) for Tyvaso® (treprostinil) Inhalation Solution for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD). United Therapeutics expects the agency's review to be complete in April 2021.

"Tyvaso, if approved by the FDA, would be the first and only therapeutic approved for the treatment of PH-ILD, a condition that afflicts approximately 30,000 people in the United States," said Martine Rothblatt, Ph.D., Chairman and Chief Executive Officer of United Therapeutics. "We look forward to working with the Agency during the regulatory review process, with the goal of expanding the population of patients with pulmonary hypertension who could benefit from this important medicine."

The sNDA is based on data from the phase 3 *INCREASE* clinical study of Tyvaso in adult patients suffering from World Health Organization (WHO) Group 3 PH-ILD. As previously announced on February 24, 2020, the *INCREASE* study met its primary endpoint as Tyvaso increased six-minute walk distance (6MWD) by 21 meters versus placebo ($p=0.0043$, Hodges-Lehmann estimate) after 16 weeks of treatment. In addition, the treatment difference in 6MWD at Week 16 was statistically significant when analyzed using Mixed Model Repeated Measurement (31 meters; $P<0.001$). Benefits of Tyvaso were observed across several key subgroups, including etiology of PH-ILD, disease severity, age, gender, dose, and baseline hemodynamics.

Significant improvements were also observed in each of the study's secondary endpoints, including reduction in the cardiac biomarker NT-proBNP, time to first clinical worsening event, change in peak 6MWD at Week 12, and change in trough 6MWD at week 15. Treatment with Tyvaso of up to 12 breaths per session, four times daily, in the *INCREASE* study was well tolerated. The safety profile was consistent with previous Tyvaso studies in pulmonary arterial hypertension and known prostacyclin-related adverse events (see the Important Safety Information below under "About Tyvaso").

About PH-ILD

Interstitial lung disease (ILD) is a group of lung diseases that are characterized by significant 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.

An estimated 30,000 patients in the United States may suffer from PH-ILD, which 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 *INCREASE*

The phase 3, multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel-group *INCREASE* study evaluated Tyvaso in patients with PH-ILD. A total of 326 patients were enrolled and randomized to Tyvaso (n=163) or placebo (n=163).

The primary endpoint was the change in 6MWD measured at peak exposure from baseline to Week 16. Secondary objectives of the study included:

- Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline to Week 16
- Time to clinical worsening calculated as the time from randomization until one of the following criteria were met:
 - o Hospitalization due to a cardiopulmonary indication
 - o Decrease in 6MWD >15% from baseline directly related to disease under study, at two consecutive visits, and at least 24 hours apart
 - o Death (all causes)
 - o Lung transplantation
- Change in peak 6MWD from baseline to Week 12
- Change in trough 6MWD from baseline to Week 15

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

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 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 timing and outcome of FDA review of our sNDA for Tyvaso, 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 August 17, 2020 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.

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

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