Survival Data From FREEDOM-EV Study of Orenitram Presented at the Pulmonary Vascular Research Institute Annual World Congress

February 1, 2019

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., Jan. 31, 2019 /PRNewswire/ -- United Therapeutics Corporation (Nasdaq: UTHR) today announced that key data from the FREEDOM-EV study of Orenitram® (treprostinil) extended-release tablets were shared during an oral presentation at the Pulmonary Vascular Research Institute Annual World Congress on Pulmonary Vascular Disease in Barcelona, Spain. The presentation was given by R. James White, M.D., Ph.D., Professor of Medicine, Pharmacology & Physiology in the Division of Pulmonary & Critical Care Medicine at the University of Rochester Medical Center and steering committee member for the FREEDOM-EV study.

Presentation Highlights

The primary endpoint of this pivotal, double-blind, placebo-controlled, event-driven trial in patients with pulmonary arterial hypertension (PAH) was met. Orenitram decreased the risk of adjudicated clinical worsening events by 26% compared to placebo (p=0.0391). These results were largely driven by delay in disease progression; Orenitram decreased the risk of disease progression by 61% compared with placebo (p=0.0002). Mortality was similar between Orenitram and placebo groups at the end of randomized treatment. However, in participants for which data are available (89%), Orenitram was associated with a 37% decreased risk of mortality compared with placebo (p=0.0324) at study closure (which includes additional data accrued in the open-label extension study).

"We are thrilled that the FREEDOM-EV study has shown that not only does Orenitram delay disease progression but is the first and only oral prostacyclin-class therapy to indicate a positive impact on survival at study closure," said Martine Rothblatt, Ph.D., Chairman and Chief Executive Officer of United Therapeutics. "These data build off the foundation of the FREEDOM-M study and will bolster Orenitram's perceived value for payors and prescribers, opening the door for more patients to benefit from this medicine."

"I am very excited to share the complete FREEDOM-EV data package at meetings over the next months," said Dr. White. "Orenitram provided clear benefits in the study, and the indication that those assigned to Orenitram treatment had a survival advantage should make prescribers think very differently about the oral form of treprostinil."

United Therapeutics has submitted the FREEDOM-EV study results to the U.S. Food and Drug Administration in support of a potential label amendment for Orenitram and is evaluating whether the results could support marketing applications outside the United States.

Baseline Characteristics

FREEDOM-EV participants were predominantly of lower risk at baseline: World Health Organization (WHO) functional class II (63%). In addition, FREEDOM-EV participants had a median six-minute walk distance (6MWD) of 405 meters, and a median time since PAH diagnosis of 0.54 years at baseline.

Dosing in FREEDOM-EV

Participants received single PAH background therapy of phosphodiesterase type 5 inhibitor/soluble guanylate cyclase stimulator (72%) or endothelin receptor antagonist (28%). Median time on PAH background therapy at baseline was 23.4 weeks. A median Orenitram dose of 2.5 mg and 3.5625 mg three times daily (TID) was achieved at 12 and 24 weeks, respectively.

Safety and Tolerability

Treatment with Orenitram in the FREEDOM-EV study was generally well tolerated and the safety profile was consistent with previous studies and known prostacyclin-related adverse events (see the discussion of adverse events below under "About Orenitram"). Over the course of the long-term study (median exposure of 60.6 and 55.4 weeks for Orenitram and placebo participants, respectively), 19% of Orenitram and 4% of placebo participants discontinued treatment due to adverse events.

Secondary Endpoints

Secondary endpoints are summarized below and will be discussed in detail at upcoming scientific conferences. These include: changes from baseline in 6MWD, Borg dyspnea score (shortness of breath test) and functional class, NT-proBNP levels, and combined 6MWD and Borg dyspnea score:

- **Change in 6MWD:** The median 6MWD trended toward improvement at week 24 (Hodges-Lehmann treatment estimate: 7 meters; p=0.0913). Median 6MWD improved with Orenitram at weeks 36 (13 meters; p=0.0094) and 48 (21 meters; p=0.0008) compared to placebo.

- **Change in Borg dyspnea score and WHO functional class:** When classified categorically as 'improved', 'no change', or 'deteriorated', participants in the Orenitram group exhibited a positive shift in Borg dyspnea score and WHO functional class compared to placebo at weeks 24, 36, and 48 (p<0.05, all).

- **Change in NT-proBNP levels:** NT-proBNP levels were significantly improved with Orenitram at weeks 24 and 36 (p<0.0001, both).

- **Change in combined 6MWD and Borg dyspnea score:** Combined 6MWD and Borg dyspnea score was significantly improved with Orenitram when assessed at week 24 compared to placebo (p=0.0057).

Additional Information

The complete presentation of FREEDOM-EV data has been filed by United Therapeutics with the SEC as Exhibit 99.2 to its Current Report on Form 8-K filed with the U.S. Securities and Exchange Commission on January 31, 2019.

Additional detailed data from the FREEDOM-EV study will be made available through oral presentations at the upcoming International Society for Heart and Lung Transplantation (Apr. 3-6, 2019; Orlando, FL) and American Thoracic Society (May 17-22, 2019; Dallas, TX) conferences and through scientific publications.

About FREEDOM-EV

FREEDOM-EV was a phase 3, international, multi-center, randomized, double-blind, placebo-controlled, event-driven clinical worsening study of oral treprostinil in patients with PAH receiving background oral monotherapy (a phosphodiesterase type 5 inhibitor, an endothelin receptor antagonist or a soluble guanylate cyclase stimulator). Global enrollment was completed in December 2017 with a total of 690 patients. Patients were randomized 1:1 to receive three daily doses of Orenitram or placebo. This event-driven study was conducted in 152 centers from 23 countries in North and Latin America, Europe, and Asia-Pacific, with 214 patients having an adjudicated clinical worsening (morbidity or mortality) event: death, hospitalization due to worsening of PAH, initiation of inhaled or infused prostacyclin treatment for PAH, disease progression, or unsatisfactory long-term clinical response. Disease progression was defined as a decrease in 6MWD by ≥15% and an increase in functional class or the appearance or worsening of right-heart failure. Dosing in FREEDOM-EV was initiated at 0.125 mg TID and increased to a maximum of 12 mg TID. This event-driven study was designed to demonstrate a prolongation of time to the first adjudicated clinical worsening event for patients treated with Orenitram compared with placebo and to further establish the safety of Orenitram in PAH patients. Investigator-reported clinical worsening events were adjudicated by an independent committee blinded to study treatment. Mortality was analyzed at the end of randomized treatment and study closure, which included open-label treatment. Vital status was assessed at six-month intervals for consenting individuals who discontinued participation.

About Orenitram

Indication

Orenitram is a prostacyclin vasodilator indicated for treatment of PAH (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

Important Safety Information for Orenitram

CONTRAINDICATIONS

- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

WARNINGS AND PRECAUTIONS

- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum

DRUG INTERACTIONS / SPECIFIC POPULATIONS

- Concomitant administration of Orenitram with diuretics, antihypertensive agents, or other vasodilators increases the risk of symptomatic hypotension
- Orenitram inhibits platelet aggregation; there is an increased risk of bleeding, particularly among patients receiving anticoagulants
- Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients
- Pregnancy Category C. Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans
- It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding
- Safety and effectiveness in patients under 18 years of age have not been established
- There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients

ADVERSE REACTIONS

- In the 12-week placebo-controlled monotherapy study, adverse reactions that occurred at rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and

abdominal discomfort.

Please see Full Prescribing Information and Patient Information for Orenitram. For additional information about Orenitram, visit www.orenitram.comor call 1-877-UNITHER (1-877-864-8437).

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. [uthr-g]

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 regarding the impact of the FREEDOM-EV results on physicians, payers and patients, our pending application to the FDA to include the FREEDOM-EV results in the Orenitram label, and the potential for the FREEDOM-EV results to support marketing applications for Orenitram outside the U.S. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic and other reports filed with the Securities and Exchange Commission that could cause actual results to differ materially from anticipated results. The forward-looking statements in this press release 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 31, 2019 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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James Edgemond, Phone: (301) 608-9292, E-mail: jedgemond@unither.com