FREEDOM-M Trial of Oral Treprostinil in Pulmonary Arterial Hypertension Meets Primary Endpoint

Preliminary Analysis Demonstrates a 23-meter Improvement in Six-Minute Walk Distance (p=0.0125) Conference Call to be Held at 9:00 a.m. Eastern Time on June 6, 2011

SILVER SPRING, Md., June 6, 2011 /PRNewswire/ -- United Therapeutics Corporation (NASDAQ: UTHR) announced today the completion of its FREEDOM-M Phase 3 trial of treprostinil diethanolamine (oral treprostinil), an investigational sustained release oral formulation of treprostinil, a stable synthetic form of prostacyclin, in patients with pulmonary arterial hypertension (PAH). Preliminary analysis demonstrates that the trial has met its primary endpoint.

FREEDOM-M was a randomized, double-blind, placebo-controlled trial of patients with PAH, a chronic, life-threatening illness. The study enrolled 349 patients who were not receiving any approved PAH medication, with the population for the primary analysis consisting of the 228 patients who had access to the 0.25 mg tablet at randomization. These patients were administered oral treprostinil or placebo twice daily, with the doses titrated to effect over the course of the 12-week trial. The majority of patients were in World Health Organization (WHO) Functional Class II (~33%) and Class III (~66%) of varied etiologies, including idiopathic or familial PAH (~75%), collagen vascular disease associated PAH (~19%), and PAH associated with HIV or other associated conditions (~6%). The patients' mean baseline six-minute walk distance (6MWD) was approximately 330 meters.

The primary efficacy endpoint of the trial was the change in 6MWD at 12 weeks for the 228 patients. Preliminary analysis of the FREEDOM-M results demonstrates that those patients receiving oral treprostinil improved their median 6MWD by approximately 23 meters (p=0.0125, Hodges-Lehmann estimate and non-parametric analysis of covariance in accordance with the trial's pre-specified statistical analysis plan) as compared to patients receiving placebo. The median change from baseline was 25 meters for oral treprostinil and -5 meters for placebo at week 12.

The combined 6MWD and Borg Dyspnea Score rating (shortness of breath test) was significantly improved (p=0.0497). Preliminary analysis of other secondary efficacy measures, including change in Borg Dyspnea Score rating, trough walk at Week 11, change in Dyspnea Fatigue Index, change in WHO functional class, time to clinical worsening (as defined by death, transplant, atrial septostomy, hospitalization due to PAH *or* at least a 20% decrease in six-minute walk *and* initiation of another approved PAH therapy), and PAH signs and symptoms did not differ significantly between oral treprostinil and placebo (p>0.05).

An analysis of all 349 FREEDOM-M patients demonstrates that those patients receiving oral treprostinil improved their median 6MWD by approximately 25.5 meters (p=0.0001, Hodges-Lehmann estimate and non-parametric analysis of covariance) as compared to patients receiving placebo.

Adverse events seen in the trial included headache, nausea, diarrhea, and flushing, which are common in patients receiving prostanoid therapy. Detailed analysis of adverse events is ongoing. All patients in the trial had the option to continue receiving oral treprostinil in an open-label continuation study after completion of the 12-week period. Of the 287 patients who were eligible to enroll, approximately 279 patients entered the open-label continuation study. Of these, approximately 183 patients are currently being treated with oral treprostinil, with the longest duration of treatment exceeding three years.

"This is my dream come true," said Martine Rothblatt, Ph.D., Chairman and Chief Executive Officer of United Therapeutics. "PAH patients have approved therapies available to them by only three routes of administration — parenteral, inhaled and oral — and no therapy other than treprostinil is available by two of these. The FREEDOM-M trial presents a potentially transformative opportunity to extend treprostinil across all available approved routes of administration."

"These results build upon the treprostinil franchise we have established with Remodulin and Tyvaso. We are excited that the primary efficacy analysis of this trial confirms the benefits of oral treprostinil on 6MWD, as the delivery of treprostinil via a twice daily oral tablet, if it secures regulatory approval, would provide a critically important additional treatment option for patients with this severe disease," said Roger Jeffs, Ph.D., President and Chief Operating Officer of United Therapeutics. "We will now focus our energies on finishing our FREEDOM-C(2) trial and completing the necessary regulatory filings next year so that patients can have access to oral treprostinil as a prescribed route of delivery."

The 313-patient FREEDOM-C(2) trial is studying oral treprostinil in PAH patients who are receiving an endothelin receptor

antagonist and/or a PDE-5 inhibitor. Preliminary analysis of the results of the trial are expected to be announced in September 2011.

Further review and analysis of the FREEDOM-M preliminary results are ongoing. A summary of the preliminary analysis conducted thus far can be accessed via United Therapeutics' website at http://ir.unither.com/events.cfm beginning at 6:00 a.m. Eastern Time on June 6, 2011. Full data from FREEDOM-M will be presented at an upcoming medical meeting and will also be available through the publication of peer-reviewed journal articles.

Conference Call

On Monday, June 6, 2011 at 9:00 a.m. Eastern Time, Lewis J. Rubin, MD, FCCP, the Chair of the FREEDOM-M Steering Committee and Professor Emeritus of Medicine at University of California San Diego Medical Center, will join United Therapeutics' management on a one-hour conference call to answer questions related to FREEDOM-M.

The conference call is accessible by dialing 1-877-351-5881, with international callers dialing 1-970-315-0533. A rebroadcast of the conference call will be available for two weeks and can be accessed by dialing 1-800-642-1687, with international callers dialing 1-706-645-9291, and using conference code: 72976350.

This conference call is also being webcast and can be accessed via our website at http://ir.unither.com/events.cfm.

About Tyvaso (treprostinil) Inhalation Solution

Indication

Tyvaso 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

- TYVASO is intended for oral inhalation only. TYVASO is approved for use only with the TYVASO Inhalation System.
- The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
- TYVASO may increase the risk of bleeding, particularly in patients receiving anticoagulants.
- In patients with low systemic arterial pressure, TYVASO may cause symptomatic hypotension. The concomitant use of TYVASO with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Hepatic or renal insufficiency may increase exposure to TYVASO and decrease tolerability. TYVASO dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn.
- The most common adverse events seen with TYVASO in greater than or equal to 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%).
- TYVASO should be used in pregnancy only if clearly needed. Caution should be exercised when TYVASO is administered to nursing women.

For more information about TYVASO, please see the Full Prescribing Information, Patient Package Insert, and the TYVASO Inhalation System Instructions for Use manual at www.Tyvaso.com or call 877-UNITHER (877-864-8437).

About Remodulin (treprostinil) Injection

Indication

Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to

diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). It may be administered as a continuous subcutaneous infusion or continuous intravenous infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

In patients with PAH requiring transition from Flolan® (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

Important Safety Information

- Chronic intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSI) and sepsis, which may be fatal. Therefore, continuous subcutaneous infusion is the preferred mode of administration.
- Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH. Remodulin is a potent pulmonary and systemic vasodilator. It lowers blood pressure, which may be further lowered by other drugs that also reduce blood pressure. Remodulin inhibits platelet aggregation and therefore, may increase the risk of bleeding, particularly in patients on anticoagulants. Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.
- Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered.
- Remodulin dosage should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms.
- Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided. Caution should be used in patients with hepatic or renal insufficiency.
- The most common side effects of Remodulin included those related to the method of infusion. For subcutaneous infusion, infusion site pain and infusion site reaction (redness and swelling) occurred in the majority of patients. These symptoms were often severe and could lead to treatment with narcotics or discontinuation of Remodulin. For intravenous infusion, line infections, sepsis, arm swelling, tingling sensations, bruising, and pain were most common. General side effects (>5% more than placebo) were diarrhea, jaw pain, vasodilatation, and edema.

For more information about Remodulin, please see the Full Prescribing Information at www.Remodulin.com or call 877-UNITHER (877-864-8437).

About United Therapeutics Corporation

United Therapeutics is a biotechnology company focused on the development and commercialization of unique products to address the unmet medical needs of patients with chronic and life-threatening conditions. [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, our expectations regarding our pursuit and potential success in obtaining regulatory approvals for oral treprostinil, including our filing for regulatory approval in 2012, the future commercial availability of oral treprostinil to patients, that preliminary analysis of the results of the FREEDOM-C(2) trial will be announced in September 2011 and that full data from the trial will be presented at an upcoming medical meeting and will also be available in peer-reviewed journal articles. 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. These risks and uncertainties include, among others, the failure of oral treprostinil to receive regulatory approval at all, or on the schedule expected; the possible inaccuracies of our analysis with respect to the FREEDOM-M preliminary trial results and market opportunity; and our or our suppliers' inability to manufacture oral treprostinil in accordance with all applicable regulatory requirements and in sufficient quantity to support patient demand. 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 June 6, 2011, 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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