UNITED THERAPEUTICS Corp
Form 10-K
February 26, 2010

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

ý **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.**

For the fiscal year ended December 31, 2009

OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.**

For the transition period from to
Commission file number 0-26301

United Therapeutics Corporation

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**52-1984749**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
1040 Spring Street, Silver Spring, MD	**20910**
(Address of Principal Executive Offices)	(Zip Code)

(301) 608-9292
Registrant's Telephone Number, Including Area Code

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $.01 per share and associated preferred stock purchase rights	NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act:

None

(Title of Class)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ý No o

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No ý

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ý No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ý

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ý	Accelerated filer o	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes o No ý

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based on the closing price on June 30, 2009, as reported by the NASDAQ Global Select Market was approximately $1,923,449,000.

The number of shares outstanding of the issuer's common stock, par value $0.01 per share, as of February 19, 2010, was 54,608,343.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for the registrant's 2010 annual meeting of shareholders scheduled to be held on June 28, 2010, are incorporated by reference in Part III of this Form 10-K.

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** Designates management contracts and compensation plans.

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PART I

ITEM 1. BUSINESS

We are 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.

Our key therapeutic platforms are:

Prostacyclin Analogues, which are stable synthetic forms of prostacyclin, an important molecule produced by the body that has powerful effects on blood vessel health and function. Our lead product is Remodulin® (treprostinil) Injection (Remodulin) to be administered subcutaneously or intravenously for the treatment of pulmonary arterial hypertension (PAH). The United States Food and Drug Administration (FDA) initially approved Remodulin in 2002 for subcutaneous (under the skin) administration. Subsequently, the FDA broadened its approval of Remodulin for intravenous (in the vein) use and for the treatment of patients who require transition from Flolan®, the first drug approved by the FDA for the treatment of PAH. In addition to the United States, Remodulin is approved in many other countries, primarily for subcutaneous use. In July 2009, the FDA approved Tyvaso® (treprostinil) Inhalation Solution (Tyvaso), an inhaled prostacyclin therapy for the treatment of PAH. We commenced commercial sales of Tyvaso in the third quarter of 2009. Our oral tablet of treprostinil diethanolamine is in the later stages of development. We are also developing modified release beraprost (beraprost-MR), another oral prostacyclin analogue, for the treatment of PAH;

Phosphodiesterase Type 5 (PDE-5) Inhibitors, which act to inhibit the degradation of cyclic guanosine monophosphate (cGMP) in cells. cGMP is activated by nitric oxide (NO) to signal relaxation of vascular smooth muscle. Our PDE-5 inhibitor product is Adcirca® (tadalafil) tablets (Adcirca), a once-daily oral therapy for the treatment of PAH. We acquired certain exclusive commercialization rights to Adcirca from Eli Lilly and Company (Lilly) in 2008. In May 2009, the FDA approved Adcirca for the treatment of PAH. We commenced commercial sales of Adcirca in the third quarter of 2009;

Monoclonal Antibodies, which act by targeting tumor-associated antigens on cancer cells. We are developing the antibodies 3F8 MAb and 8H9 MAb for the treatment of neuroblastoma and metastatic brain cancer, respectively. We began a Phase II clinical trial in the second quarter of 2009 with 3F8 in primary refractory neuroblastoma; and

Glycobiology Antiviral Agents, which are a novel class of small, sugar-like molecules that have shown pre-clinical indications of efficacy against a broad range of viruses, such as hepatitis C, dengue fever and certain influenza viruses. We are currently conducting preclinical tests on potential compounds for further development.

We devote most of our resources to developing products within our key therapeutic platforms. We also devote our resources to developing products in other therapeutic platforms and to the commercialization and further development of telemedicine products and services, principally for the detection of cardiac arrhythmias (abnormal heart rhythms).

We generate revenues from the sale of Remodulin, Tyvaso and Adcirca (which we refer to as our Commercial Products) and telemedicine products and services. Our sales and marketing staff for our Commercial Products, which is supplemented by our specialty pharmaceutical distributors, supports the commercial availability of our Commercial Products in the countries in which they are approved.

United Therapeutics was incorporated in Delaware in June 1996. Our principal executive offices are located at 1040 Spring Street, Silver Spring, Maryland 20910. We also maintain executive offices at 55 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709.

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Unless the context requires otherwise or unless otherwise noted, all references in this Annual Report on Form 10-K to "United Therapeutics" and to the "company", "we", "us" or "our" are to United Therapeutics Corporation and its subsidiaries.

Our Products

Our product portfolio includes the following as of February 15, 2010:

Product	Mode of Delivery	Indication/Market	Current Status	Our Territory
Remodulin	Continuous subcutaneous	Pulmonary arterial hypertension	Commercial in the U.S., most of Europe*, Canada, Israel, Australia, Mexico, Argentina and Peru	Worldwide
Remodulin	Continuous intravenous	Pulmonary arterial hypertension	Commercial in the U.S., Canada, Israel, Mexico, Argentina and Peru	Worldwide
Tyvaso	Inhaled	Pulmonary arterial hypertension	Commercial in the U.S.	Worldwide
Adcirca (tadalafil) Tablets	Oral	Pulmonary hypertension	Commercial in the U.S. and Puerto Rico	United States/Puerto Rico
CardioPAL® SAVI and Decipher Cardiac Monitors	Telemedicine	Cardiac arrhythmias and ischemic heart disease	Commercial in the U.S.	Worldwide
CardioPAL SAVI Wireless Cardiac Event Monitors	Telemedicine	Cardiac arrhythmias and ischemic heart disease	Commercial in the U.S.	Worldwide
Oral Treprostinil	Oral	Pulmonary arterial hypertension	Phase III	Worldwide
Beraprost-MR	Oral	Pulmonary arterial hypertension	Phase II	North America/Europe
3F8 MAb	Intravenous	Neuroblastoma	Phase II	Worldwide
Oral Treprostinil	Oral	Peripheral vascular disease	Phase II	Worldwide
Aviptadil	Inhaled	Pulmonary hypertension and other pulmonary diseases	Phase II	Worldwide
8H9 MAb	Intravenous	Metastatic brain cancer	Phase I	Worldwide
IW001	Oral	Idiopathic Pulmonary Fibrosis and Primary Graft Dysfunction	Phase I	Worldwide
Glycobiology Antiviral Agents	Oral	Hepatitis C and other infectious diseases	Pre-Clinical	Worldwide

* We have obtained approval in 23 member countries of the European Union (EU), as well as in certain European countries that are not members of the EU. We have received formal approval letters and pricing approval in most of these countries.

Pulmonary Arterial Hypertension

PAH is a life-threatening disease that affects the blood vessels in the lungs and is characterized by increased blood pressure from the heart to the lungs. The elevated pressure in the pulmonary arteries strains the right side of the heart as it pumps blood to the lungs, which eventually leads to right heart failure and, ultimately, death. PAH is characterized by structural changes in blood vessel walls, the aggregation of platelets and an alteration of smooth muscle cell function. It is estimated that PAH affects between 100,000 and 200,000 individuals worldwide. In recent years, as awareness of PAH has

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grown, we have seen an increase in the number of people diagnosed with the disease. However, only a small fraction of patients with PAH are being treated due to the rarity of the disease and the complexity of diagnosing it. There is scientific interest in identifying easier, less invasive methods of diagnosing PAH. If this research is successful, more patients could be diagnosed at an earlier stage of the disease.

The complexity of diagnosing PAH reflects in part the current uncertainties surrounding the etiology and pathophysiology of the condition. Currently, treatment of PAH focuses on three distinct molecular pathways that have been implicated in the disease process: the endothelin (ET) pathway, the nitric oxide (NO) pathway, and the prostacyclin pathway.

Endothelin Receptor Antagonists. PAH patients have been shown to have elevated levels of ET-1, a naturally occurring substance in the body that causes constriction and structural changes of the pulmonary blood vessels. Therefore, one established therapeutic approach has been to block the action of endothelin with drugs that are known as endothelin receptor antagonists (ETRAs).

PDE-5 Inhibitors. Patients with PAH have also been shown to have reduced levels of the enzyme responsible for producing NO, a naturally occurring substance in the body that causes relaxation of the pulmonary blood vessels. NO produces this effect by increasing intracellular levels of an intermediary known as cyclic guanosine monophosphate (cGMP). Therefore, another established therapeutic approach has been to inhibit the degradation of cGMP, using drugs that are known as PDE-5 inhibitors.

Prostacyclin Analogues. Finally, patients with PAH have been shown to have reduced levels of prostacyclin, a naturally occurring substance that has the effect of relaxing the pulmonary blood vessels, preventing platelet aggregation, and inhibiting the proliferation of smooth muscle cells in the pulmonary vessels. Therefore, drugs that mimic the action of prostacyclin, known as prostacyclin analogues, are also established PAH treatments.

Because any or all of these three pathways may be therapeutic targets in a patient, the described three classes of drugs are used alone or sometimes in combination to treat patients with PAH. We currently market Remodulin and Tyvaso, prostacyclin analogues, and Adcirca, a PDE-5 inhibitor, for the treatment of PAH.

Remodulin

Our lead product for treating PAH is Remodulin (treprostinil) Injection, the main ingredient of which is treprostinil, a prostacyclin analogue. We sell Remodulin to our specialty pharmaceutical distributors in the United States at a discount from an average wholesale price recommended by us, and to our international distributors at a transfer price set by us. We recognized approximately $331.6 million, $269.7 million and $200.9 million in Remodulin revenues, representing 90%, 96% and 95% of our net revenues in 2009, 2008 and 2007, respectively. In May 2002, Remodulin was approved by the FDA as a continuous subcutaneous infusion for the treatment of PAH in patients with New York Heart Association (NYHA) Class II-IV (moderate to severe) symptoms. In November 2004, the FDA expanded its approval to permit continuous intravenous infusion of Remodulin for patients who cannot tolerate subcutaneous infusion. In March 2006, the FDA expanded its approval to include transition of patients to Remodulin from Flolan® (epoprostenol), the first FDA-approved prostacyclin therapy for PAH, to reduce the rate of clinical deterioration. Remodulin is also approved as a continuous subcutaneous infusion treatment for various forms of PAH in 33 countries throughout the world, and as a continuous intravenous infusion treatment for various forms of PAH in Canada, Israel, Mexico, Peru and Argentina. Applications for approval for both subcutaneous and intravenous Remodulin are under review in other countries. We continue to work on expanding Remodulin commercialization to other new territories, including Japan.

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Flolan is delivered continuously through a surgically implanted intravenous catheter connected to an external pump. Flolan is approved for the treatment of patients with certain subsets of late-stage PAH. Generic formulations of Flolan are also available. We believe Remodulin provides patients with a less invasive alternative to Flolan and its equivalents. In contrast to Flolan, Remodulin is stable at room temperature and lasts significantly longer inside the human body. These attributes allow for safer and more convenient drug delivery to patients. Unlike Flolan, Remodulin can be delivered by subcutaneous infusion with a pager-sized miniature pump. Subcutaneous delivery of Remodulin also eliminates the risk of central venous catheter infection and the hospitalization required to begin intravenous infusion. Remodulin's extended presence in the body may also reduce the risk of rebound PAH, and possibly death, if treatment is abruptly interrupted. The stability of Remodulin also allows it to be packaged as an aqueous solution, so patients do not have to mix the drug, as they do with Flolan. Remodulin can be continuously infused for up to 48 hours before refilling the infusion pump, unlike Flolan, which must be mixed and refilled every 24 hours. Treprostinil, the active ingredient in Remodulin, is highly soluble in an aqueous solution, which enables us to manufacture Remodulin in highly concentrated solutions. This allows therapeutic concentrations of Remodulin to be delivered at low flow rates via miniaturized infusion pumps for both subcutaneous and intravenous infusion. Lastly, Remodulin does not require the patient to keep the drug cool during infusion. This eliminates the need for cooling packs or refrigeration to keep it stable, as is required with Flolan due to Flolan's chemical instability at room temperature.

In June 2008, the FDA approved a generic version of Flolan, developed by GeneraMedix, Inc. (GeneraMedix), that is stable at room temperature, but still shares all of Flolan's other attributes including, but not limited to, risk of central venous catheter infection, required hospitalization at the start of treatment, shorter half-life increasing risk of rebound PAH, mixing, greater frequency of pump refills and larger pump size. In February 2009, GeneraMedix licensed the commercial rights for its generic Flolan to Actelion Pharmaceuticals Ltd (Actelion). Actelion also markets Tracleer® and Ventavis® for the treatment of PAH.

There are noteworthy adverse events associated with Remodulin. When infused subcutaneously, Remodulin causes varying degrees of infusion site pain and reaction (redness and swelling) in most patients. Patients who cannot tolerate the site pain related to use of subcutaneous Remodulin may instead use intravenous Remodulin. Intravenous Remodulin is delivered continuously by an external pump through a surgically implanted central venous catheter, similar to Flolan. When delivered intravenously, Remodulin bears the risk of a serious bloodstream infection known as sepsis, as does Flolan.

In January 2007, the results of a prospective, open-label study demonstrated that stable patients with PAH can be safely transitioned from Flolan to intravenous Remodulin using a rapid switch protocol.

FDA Approval of Subcutaneous and Intravenous Remodulin

We filed a New Drug Application with the FDA for Remodulin in late 2000. In May 2002, the FDA approved Remodulin as a continuous subcutaneous infusion for the treatment of PAH in patients with NYHA class II-IV symptoms to diminish symptoms associated with exercise. Remodulin is approved for all types of PAH and is the only PAH prostacyclin analogue therapy approved for patients with NYHA class II-IV symptoms.

In July 2003, we opened an Investigational New Drug Application (IND) for the development of Remodulin by intravenous delivery for the treatment of PAH. A late 2003 study performed in healthy volunteers established that intravenous and subcutaneous Remodulin were bioequivalent (meaning that the two routes of infusion result in comparable levels of treprostinil in the blood).

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In January 2004, we filed a Supplemental New Drug Application with the FDA to request approval for intravenous Remodulin for the treatment of PAH. In November 2004, based on data establishing intravenous Remodulin's bioequivalence with the previously approved subcutaneous Remodulin, the FDA approved intravenous Remodulin for those not able to tolerate subcutaneous infusion.

International Regulatory Review of Subcutaneous and Intravenous Remodulin

Remodulin for subcutaneous use is approved in countries throughout the world. We used the mutual recognition process, described more fully in *Governmental Regulation*, to obtain approval of subcutaneous Remodulin in most countries in the EU. The mutual recognition process for subcutaneous Remodulin was completed in August 2005, with positive decisions received from most EU member countries. We withdrew our applications in the Republic of Ireland (Ireland), Spain and the United Kingdom (UK) following a request for additional documentation from these countries. A license variation for intravenous Remodulin will be resubmitted once our compulsory five-year renewal application for subcutaneous Remodulin is approved, which we believe will occur in the first half of 2010. At that time, we will submit the intravenous Remodulin license variation to our host nation, France.

Under the named-patient system, we are permitted to import Remodulin into EU member countries for sale to hospitals for use in treating specifically identified patients. We will continue to sell (but not market) Remodulin under the named-patient system in certain EU member countries where Remodulin is not approved. In December 2009, we notified the hospitals and physicians in the UK and Ireland that we will not be providing Remodulin therapy for new PAH patients after March 31, 2010. We will continue to support and provide Remodulin to PAH patients who start Remodulin therapy prior to March 31, 2010, for as long as it is required for each patient. Antigen International Ltd. (part of Goldshield Group Ltd.), our Remodulin distributor in the UK and Ireland, is disputing our decision and has filed an arbitration request. We are currently in the preliminary stages of the arbitration process.

Tyvaso

We commenced commercial sales of Tyvaso in September 2009. We sell Tyvaso at a discount from an average wholesale price recommended by us to the same specialty pharmaceutical distributors in the United States that distribute Remodulin. In 2009, we recognized approximately $20.3 million in Tyvaso revenues, representing 5% of our net revenues. We did not recognize any revenues from Tyvaso in 2008 and 2007.

Currently, the only other FDA approved inhaled prostacyclin analogue is Ventavis. Ventavis is marketed by Actelion in the United States and by Bayer Schering Pharma AG in Europe. The active ingredient in Ventavis, iloprost, has a half-life of approximately 20 to 30 minutes and can cause a decrease in systemic blood pressure if the drug is administered at too high a dose. As a result, Ventavis is inhaled via a nebulizer six to nine times per day at a low dose. Per its label, each Ventavis inhalation consists of 4 to 10 minutes of continuous inhalation via the nebulizer. Tyvaso has a longer half-life and greater selectivity to the lungs than Ventavis. Thus, patients only need to take Tyvaso four times a day, inhaling nine breaths during each two-to-three-minute treatment session. We are conducting an open-label study in the United States to investigate the clinical effects of switching patients from Ventavis to Tyvaso. Data is being prepared and has been accepted for presentation at the American Thoracic Society scientific symposia in May 2010.

Tyvaso has been generally well tolerated in our trials, and adverse events appeared to be similar to those previously reported for treprostinil or due to administration by inhalation. The most common adverse events seen in the trial were transient cough, headache, nausea, dizziness and flushing.

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Tyvaso Inhalation System

The Tyvaso Inhalation System, an ultra-sonic nebulizer and related accessories, was exclusively used for administration of Tyvaso in the TRIUMPH-1 trial. The Tyvaso Inhalation System is manufactured by NEBU-TEC International Med Products Eike Kern GmbH (NEBU-TEC), a German company. The Tyvaso Inhalation System is CE-marked in Europe, which means that the device conforms to EU health and safety requirements. In December 2008, we entered into an Agreement of Sale and Transfer with NEBU-TEC under which NEBU-TEC would sell to us its Tyvaso Inhalation System business and all associated assets and rights upon FDA approval of Tyvaso and the use of the Tyvaso Inhalation System with Tyvaso. As specified in the agreement, the closing and the transfer of all the associated assets and rights occurred in September 2009. Our agreement with NEBU-TEC also gives us the right to purchase their next generation nebulizer, the SIM-Neb. For additional details on the terms of our agreement with NEBU-TEC, see *NEBU-TEC Agreement of Sale and Transfer* below.

FDA Approval of Tyvaso

In June 2008, we submitted a New Drug Application (NDA) to obtain FDA approval to market Tyvaso for the treatment of PAH in the United States. On July 30, 2009, the FDA approved Tyvaso for the treatment of PAH using the Tyvaso Inhalation System. Tyvaso is indicated to increase walk distance in patients with NYHA Class III symptoms of PAH, which includes multiple etiologies such as idiopathic and familial PAH, as well as PAH associated with scleroderma and congenital heart disease.

In connection with the Tyvaso approval, we have agreed to a post-marketing requirement (PMR) and certain post-marketing commitments (PMCs). PMRs and PMCs are studies that sponsors conduct after FDA approval to gather additional information about a product's safety, efficacy, or optimal use. PMRs are required studies; whereas, a sponsor voluntarily commits to conduct PMCs. We are required to provide the FDA annual updates on our PMR and PMCs. Failure to complete the studies or adhere to the timelines set by the FDA for the PMR could result in penalties, including fines or withdrawal of Tyvaso from the market, unless we are able to demonstrate good cause for not completing the studies or adhering to our timelines.

In accordance with the PMR, we will conduct a long-term observational study in the U.S. that will include 1,000 patient-years of follow-up in Tyvaso-treated patients, and 1,000 patient-years of follow-up in matched control patients receiving other PAH treatments to evaluate the potential association between Tyvaso and oropharyngeal and pulmonary toxicity. We have submitted a draft protocol of the PMR to the FDA for review, and have committed to submitting the results by December 15, 2013.

The PMC requires us to modify the Tyvaso Inhalation System and perform a usability analysis followed by a human factors study, and we will conduct a study in healthy volunteers to collect data to verify expected dosing with the modified device. We have submitted draft protocols for these PMCs to the FDA for review, and we have committed to submitting a supplement to our Tyvaso NDA describing the results no later than October 31, 2010. The human factors study will commence in March 2010; therefore, we believe we are on track to meet the timeline for final report submission.

International Regulatory Review of Tyvaso

In April 2004, the EMA designated Tyvaso an orphan medicinal product for the treatment of both PAH and chronic thromboembolic pulmonary hypertension. We filed an MAA in December 2008 for Tyvaso and the Tyvaso Inhalation System with the EMA using the centralized filing process. See *Governmental Regulation* below for further discussion on the centralized filing process for the EU. In February 2010, we withdrew our MAA from consideration by the EMA due to the EMA's major objection related to findings of non-compliance with good clinical practice (GCP) at two clinical sites. The EMA stated that these findings would preclude a recommendation for approval of Tyvaso in the

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EU. The EMA had no major objections at the time of withdrawal related to the safety or efficacy of Tyvaso.

UT-15C Sustained Release (Oral Treprostinil)

Pulmonary Arterial Hypertension

We are developing a novel salt form of treprostinil, treprostinil diethanolamine for oral administration. We use technology licensed from Supernus Pharmaceuticals, Inc. (Supernus), to provide for sustained release of treprostinil in tablets. The tablet coating technology allows for treprostinil to be released into the body through an extremely small hole that is laser-drilled into the coating of each tablet. This technology releases treprostinil at a relatively even rate in the gastrointestinal tract. In 2005, a Phase I study of healthy volunteers demonstrated that the formulation and coating provided sustained blood concentrations of treprostinil for 8 to 10 hours following a single oral dose. This duration may allow for twice daily dosing. In July 2005, the EMA announced that oral treprostinil had been designated an orphan medicinal product for the treatment of PAH.

In October 2006, we commenced two Phase III multi-national, placebo-controlled clinical trials of oral treprostinil in patients with PAH to study both safety and efficacy. The FREEDOM-C trial was a 16-week study of patients on approved background therapy using a PDE-5 inhibitor, such as Revatio, or an ERA, such as Tracleer, or a combination of both. The FREEDOM-M trial is a 12-week study of patients who are not on any background therapy. These trials have been conducted at a total of approximately 60 centers throughout the United States and the rest of the world.

We commenced both trials using a 1 mg tablet, but during the open-label extension trial (and associated pharmacokinetic substudy) we discovered that treprostinil concentrations were higher in PAH patients than in healthy individuals due to the difference in overall absorption, metabolism and excretion of the drug between these two populations. These differences led to a number of discontinuations by patients randomized to receive drug due to tolerability-related side effects, including nausea, jaw-pain and headaches. As a result, we introduced a 0.5 mg tablet in July 2007 and a 0.25 mg tablet in April 2008 to enable more gradual dose titration (increase).

In November 2008, we announced that the FREEDOM-C trial did not meet statistical significance for its primary endpoint.

Analysis suggests that the inability to dose titrate was a limiting factor that suppressed the overall treatment effect. Of the 174 patients who received active drug, 25 patients discontinued due to an adverse event and 33 patients completed the trial, but were unable to titrate their doses above 1 mg twice daily. Accordingly, 58 (33%) of the patients in the active treatment group were only able to maintain a suboptimal dose of 1 mg or less twice daily. Adverse events that led to discontinuation or inability to dose-escalate included headache, nausea and vomiting. Discontinuations were most common in patients who only had access to the 1 mg tablets during the study, which was the only tablet size available when the trial began. There were no discontinuations among patients who had access to 0.25 mg tablets.

Analysis of other secondary efficacy measures demonstrated statistically significant improvements compared to placebo.

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Enrollment in FREEDOM-M was initially closed on October 31, 2008, with 171 patients enrolled in the trial. We believe that the results of the FREEDOM-C clinical trial, particularly as they relate to treatment effect and dosing, support our continued development of oral treprostinil. Accordingly, based on our observations from the FREEDOM-C clinical trial relating to patient tolerability and tablet strength, we submitted a protocol amendment to the FDA in February 2009 to add patients to the ongoing FREEDOM-M trial. These additional patients will be provided a lower-strength tablet (0.25 mg) when they begin the trial and their doses will be titrated in 0.25 mg increments, which we believe will improve tolerability. In addition, our amendment to the FREEDOM-M protocol specifies that the primary statistical analysis of the trial will include only those patients who started the trial using the 0.25 mg tablet. By amending the protocol for the FREEDOM-M trial we hope to achieve the following objectives: (1) to assess more accurately the effectiveness of oral treprostinil; (2) to improve patient tolerability of oral treprostinil so that an effective maintenance dose can be attained; and (3) to reduce the rate of premature discontinuation due to adverse events. We believe the results of the protocol amendment will reflect the benefits of a favorable dosing regimen for oral treprostinil. In April 2009, we began enrolling patients in FREEDOM-M under the amended protocol.

We commenced a second Phase III clinical trial, FREEDOM-C2, to continue studying dosage and efficacy of oral treprostinil in PAH patients on an approved background therapy. Enrollment in FREEDOM-C2 began in June 2009. Currently, we do not anticipate filing an NDA for oral treprostinil before 2012.

There are currently no approved oral prostacyclin therapies available to patients in the United States or Europe. If we are successful in developing oral treprostinil, then patients and physicians may use prostacyclin earlier in the PAH disease continuum.

Scleroderma

We also initiated a Phase II study to investigate the effectiveness of oral treprostinil in reducing the frequency and severity of ulcers located on the fingers and toes of scleroderma patients. Enrollment of this 150- patient Phase II trial remains ongoing.

Adcirca

We began commercial sales of Adcirca in July 2009. Adcirca is a PDE-5 inhibitor, the active pharmaceutical ingredient of which is tadalafil. Tadalafil is also the active pharmaceutical ingredient in Cialis®, which is marketed by Lilly for the treatment of erectile dysfunction. We acquired the commercial rights to Adcirca for the treatment of PAH in the U.S. from Lilly in November 2008. We sell Adcirca at a discount from an average wholesale price to pharmaceutical wholesalers. In 2009, we recognized approximately $5.8 million in Adcirca revenues, representing 2% of our net revenues. We did not recognize any revenues from Adcirca in 2008 and 2007.

Patients with PAH have been shown to have reduced levels of the enzyme responsible for producing NO, a naturally occurring substance in the body that has the effect of relaxing vascular smooth muscle cell. Impaired blood vessel relaxation in penile tissue is also a cause of erectile dysfunction. NO works to relax pulmonary blood vessels by increasing intracellular levels of an intermediary known as cyclic GMP. Because cyclic GMP is degraded by PDE-5, an established therapeutic approach in the treatment of PAH is to use PDE-5 inhibitors to increase levels of cGMP in blood vessels and improve cardiopulmonary function in PAH patients.

Prior to the approval of Adcirca, Revatio, which is marketed by Pfizer, was the only approved PDE-5 inhibitor for the treatment of PAH. Sildenafil, the active ingredient in Revatio, is also the active ingredient in Viagra®, which is marketed by Pfizer for the treatment of erectile dysfunction. Revatio is dosed three times daily; whereas, patients take Adcirca once daily.

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FDA Approval of Adcirca

In May 2009, the FDA approved Adcirca, with a recommended dose of 40 mg, making it the first once-daily PDE-5 inhibitor for the treatment of PAH. Adcirca is indicated to improve exercise ability in World Health Organization Group I PAH patients, which encompasses patients with multiple forms of PAH including etiologies such as idiopathic and familial PAH as well as PAH associated with collagen vascular disease and congenital heart disease.

Commercial Rights to Adcirca

In December 2008, we completed the transactions contemplated by several agreements we entered into with Lilly and one of its subsidiaries in November 2008, including a license agreement, a manufacturing and supply agreement and a stock purchase agreement. Pursuant to the license agreement, Lilly granted us an exclusive license for the right to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico. Pursuant to the manufacturing and supply agreement, Lilly agreed to manufacture Adcirca and distribute it on our behalf via its wholesaler network, in the same manner that it distributes its own pharmaceutical products. In December 2008, upon closing, we made a one-time, non-refundable, non-creditable payment of $125.0 million under the manufacturing and supply agreement and a one-time payment of $25.0 million under the license agreement. Pursuant to the stock purchase agreement, Lilly purchased 6,301,674 shares of our common stock (adjusted for our September 2009 two-for-one stock split) for an aggregate purchase price of $150.0 million. We issued those shares from treasury. See *Strategic Licenses and Relationships* below for more details on these agreements.

Beraprost-MR

In June 2000, we entered into an agreement with Toray Industries, Inc. (Toray) for the exclusive right to develop and market a sustained release formulation of beraprost (beraprost-SR) in the United States and Canada for the treatment of cardiovascular indications. Beraprost is a chemically stable, orally bioavailable prostacyclin analogue. Like natural prostacyclin and Remodulin, beraprost is believed to dilate blood vessels, prevent platelet aggregation and prevent proliferation of smooth muscle cells surrounding blood vessels.

In March 2007, Lung Rx entered into an amended agreement with Toray to assume and amend the rights and obligations of our June 2000 agreement with Toray concerning the commercialization of a modified release formulation of beraprost (beraprost-MR). The amended agreement grants us additional exclusive rights to commercialize beraprost-MR in Europe and broadens the treatment indication to include vascular disease (excluding renal disease), among other revisions.

The drug substance beraprost consists of equal amounts of four optical isomers, one of which is primarily responsible for the pharmacologic activity of the drug. As we continue clinical development, we plan to proceed with a modified release drug product containing only the most pharmacologically active isomer. As a result, future clinical trials will use the single active isomer.

In October 2007, Toray announced that beraprost-MR received regulatory approval in Japan for use in the treatment of PAH. In July 2008, beraprost-MR was designated an orphan medicinal product by the EMA.

Aviptadil

In February 2010, Lung Rx entered into an agreement with Mondobiotech Holding AG (Mondobiotech) for the exclusive right to develop and market aviptadil, a synthetically produced version of the naturally occurring hormone Vasoactive Intestinal Peptide (VIP), a peptide produced in the digestive system, for the treatment of PAH and other pulmonary diseases. A Phase II study of

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Aviptadil in PAH was recently completed by Mondobiotech and the EMA has designated aviptadil an orphan medicinal product for the treatment of acute lung injury and sarcoidosis.

Products to Treat Cancer

3F8 and 8H9 Antibodies

In December 2007, we entered into two agreements with Memorial Sloan-Kettering Cancer Center (MSKCC) to license certain exclusive rights to two investigational monoclonal antibodies, 3F8 and 8H9, for the treatment of neuroblastoma and metastatic brain cancer. The monoclonal antibody 3F8 is a mouse IgG3 MAb, which is currently used in an investigational setting for the treatment of neuroblastoma, a rare cancer of the sympathetic nervous system mainly affecting children. It is the most common extracranial solid cancer in children and the most common cancer in infants. More than 400 patients have been treated with the 3F8 antibody since 1986 under investigator-initiated Investigational New Drug Applications. There are fewer than 1,000 new cases of neuroblastoma diagnosed each year. In August 2009, we began enrolling patients in a Phase II clinical trial of 3F8 for primary refractory neuroblastoma.

The monoclonal antibody 8H9 is a mouse IgG1 MAb that is highly reactive with a range of human solid tumors, including human brain cancers. The 8H9 antibody is in early investigational development for metastases that develop in the brain from the spread of cancers from other tissues in the body. Metastatic brain cancers are ten times more common than cancers that originate in the brain, and prognosis is very poor. In the United States, more than 100,000 cases of metastatic brain cancer are diagnosed each year.

OvaRex

In April 2002, we entered into a license agreement with AltaRex Corp., which later became AltaRex Medical Corp., a wholly-owned subsidiary of ViRexx Medical Corp. (AltaRex). Our license agreement with AltaRex provided us with certain exclusive rights to a platform of five investigational immunotherapeutic monoclonal antibodies. The lead product, OvaRex® MAb for the treatment of advanced ovarian cancer, had completed Phase II studies when we entered into the license agreement.

In December 2007, we announced the completion of our two pivotal trials of OvaRex. Analysis of the results demonstrated that the studies failed to reach statistical significance. Based on the trial results, we decided to terminate our license agreement with AltaRex and cease further development activities with the molecules licensed thereunder.

Products to Treat Infectious Diseases Glycobiology Antiviral Agents

We have a license agreement with the Glycobiology Institute at the University of Oxford for the exclusive worldwide rights to certain patents relating to novel antiviral compounds. These glycobiology antiviral compounds are small molecules that may be effective as oral therapies for the treatment of hepatitis B and C infections, as well as dengue fever and certain influenza viruses. Currently, many of these compounds are undergoing laboratory testing, and new compounds are also being synthesized.

Products to Treat Diseases in Other Platforms

In February 2010, Lung Rx entered into a Development Agreement with ImmuneWorks, Inc. (ImmuneWorks) to develop ImmuneWorks' lead compound, IW001, a purified bovine (derived from cows) Type V Collagen oral solution for the treatment of Idiopathic Pulmonary Fibrosis (IPF), a progressive lung disease characterized by abnormal and excessive deposition of fibrotic tissue in the lung, and Primary Graft Dysfunction (PGD), a type of organ rejection in patients receiving lung transplant. We expect to commence human clinical testing of IW001 in 2010. In addition to funding the

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development program, we have been granted an option to acquire all of the issued and outstanding capital stock of ImmuneWorks. In November 2009, the FDA granted IW001 orphan drug exclusivity.

Products to Provide Telemedicine Services for Cardiac Arrhythmias and Ischemic Heart Disease

CardioPAL SAVI and Decipher Recorders

We provide telemedicine monitoring services to detect cardiac arrhythmias and ischemic heart disease through our wholly-owned subsidiary Medicomp, Inc. (Medicomp), which we acquired in December 2000. Cardiac arrhythmias and ischemic heart disease affect an estimated 20 million Americans, and possibly ten times that number worldwide. If left undetected and untreated, these conditions can result in heart attacks and death. Medicomp provides cardiac Holter monitoring (a 24-hour continuous test of heart rhythms), event monitoring (a test that typically extends to 30 days and looks for more elusive, intermittent arrhythmias) and other cardiac monitoring services remotely via telephone and the internet for hospitals, clinicians and other providers. Medicomp's services are delivered through its proprietary, miniaturized, digital Decipher Holter recorder/analyzer and its CardioPAL family of event monitors.

In March 2005, Medicomp received FDA market clearance for a p-wave analysis in addition to its artificial intelligence algorithm that runs on all of its newly manufactured CardioPAL devices. The p-wave is a diminutive but important portion of the electrocardiograph, the analysis of which helps determine if an arrhythmia was generated from the top chambers of the heart, the atria, or from the bottom chambers of the heart, the ventricles. This level of analysis leads to more reliable, automatic detection of arrhythmias, like atrial fibrillation. In October 2009, we received FDA approval for a wireless version of our CardioPAL SAVI event monitor, which we launched in 2010.

Holter and event services and systems are marketed to physicians, hospitals, and managed care providers directly by Medicomp's sales force. We recognized revenues of approximately $11.0 million, $9.5 million and $7.7 million from the sales of telemedicine products and services in 2009, 2008 and 2007, respectively.

Sales and Marketing

Our marketing strategy for our Commercial Products is to use our sales and marketing teams to reach out to the prescriber community to: (1) increase PAH awareness; (2) understand the progressive nature of PAH; and (3) increase awareness of our Commercial Products and how they fit into the various stages of disease progression and treatment. The sales and marketing team consisted of approximately 70 employees as of December 31, 2009. We anticipate growth in our sales force in the near-term as we position our business for further expansion. We divide our domestic sales force into two teams. One sales team is primarily responsible for medical practice accounts that are historically large Remodulin prescribers. The other sales team is primarily responsible for medical practice accounts that have not historically been large prescribers of Remodulin. The efforts of our sales and marketing teams are supplemented by our specialty pharmaceutical distributors. For additional information about our agreements with our distributors, see *Domestic Distribution of Commercial Products*. Our distributors are experienced in all aspects of using and administering chronic therapies, as well as patient care, the sale and distribution of these medicines and reimbursement from insurance companies and other payers. Outside of the United States, we have entered into exclusive distribution agreements covering most of Europe, South America, Israel, and parts of Asia. Sales in Canada are currently conducted under the management of our wholly-owned subsidiary, Unither Biotech Inc., through a national specialty pharmaceutical wholesaler. We are working with our current distributors to expand Remodulin sales into other countries in which they have distribution rights.

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Domestic Distribution of Commercial Products

Remodulin and Tyvaso

We have entered into separate, non-exclusive distribution agreements with CuraScript, Inc. (CuraScript), Accredo Health Group, Inc. (Accredo), and CVS Caremark (Caremark), our specialty pharmaceutical distributors in the United States, to market, promote and distribute both Remodulin and Tyvaso. Our Remodulin distribution agreements with Accredo and Caremark include automatic term renewals for additional one-year periods subject to notice of termination. Our Remodulin distribution agreement with Curascript contains two-year term renewal periods. We entered into our distribution agreements for Tyvaso in August 2009. Our Tyvaso distribution agreements have one-year terms and renew automatically for additional one-year periods, unless terminated earlier. We update our distribution agreements from time to time to reflect changes in the regulatory environment. Such changes have not had a significant impact on our operations or our relationships with our distributors, and tend to occur in the ordinary course of business. We compensate our distributors on a fee-for-service basis as set forth in our distribution agreements. If any of our distribution agreements expire or terminate, we may, under certain circumstances, be required to repurchase any unsold Remodulin or Tyvaso inventory held by our distributors. None of our current agreements grants our distributors the distribution rights for oral treprostinil in the United States.

Our specialty pharmaceutical distributors are responsible for assisting patients with obtaining reimbursement for the cost of Remodulin and Tyvaso and providing other support services. Under our distribution agreements, we sell Remodulin and Tyvaso to our distributors at a discount from an average wholesale price recommended by us. We have also established a patient assistance program in the United States, which provides eligible uninsured or underinsured patients with Remodulin and Tyvaso at no charge for a certain period of time.

In January 2010, we notified Accredo, CuraScript and Caremark of our intention to increase the price of Remodulin for all concentrations by 9.6 percent effective March 25, 2010. This is only the second time since the launch of Remodulin that we have initiated an across-the-board increase in its price. The last such increase was in mid-2006 and we increased the price by 3.4 percent. Our Remodulin distribution agreements do not allow our distributors to preorder inventory prior to a price increase. We are currently analyzing the impact of this price increase on our business.

Adcirca

We sell Adcirca at a discount from an average wholesale price to pharmaceutical wholesalers. Under our manufacturing and supply agreement with Lilly, (see *Strategic Licenses and Relationships* below for more details), Lilly has agreed to manufacture Adcirca and distribute it via its wholesaler network, which includes our specialty pharmaceutical distributors, in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title