UNITED THERAPEUTICS Corp
Form 10-K
February 22, 2017

QuickLinks -- Click here to rapidly navigate through this document

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, 2016

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 ý 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. o

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, 2016, as reported by the NASDAQ Global Select Market was approximately $4,094,026,937.

The number of shares outstanding of the issuer's common stock, par value $0.01 per share, as of February 10, 2017, was 44,961,616.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for the registrant's 2017 annual meeting of shareholders scheduled to be held on June 28, 2017, are incorporated by reference in Part III of this Form 10-K.

TABLE OF CONTENTS

PART I

ITEM 1. BUSINESS

Overview

United Therapeutics Corporation is a biotechnology company focused on the development and commercialization of innovative products to address the unmet medical needs of patients with chronic and life-threatening conditions. We market and sell four commercial therapies in the United States to treat pulmonary arterial hypertension (PAH): Remodulin® (treprostinil) Injection; Tyvaso® (treprostinil) Inhalation Solution (Tyvaso); Orenitram® (treprostinil) Extended-Release Tablets (Orenitram); and Adcirca® (tadalafil) Tablets (Adcirca). We also market and sell an oncology product in the United States, Unituxin® (dinutuximab) Injection (Unituxin), which is approved for treatment of high-risk neuroblastoma. Outside the United States, our only significant revenues are derived from the sale of Remodulin, which is approved in Europe and various other countries. We are also engaged in research and development of new indications and delivery devices for our existing products, as well as new products to treat PAH and other conditions. Finally, we are engaged in early-stage research and development of a number of organ transplantation-related technologies.

We generate revenues from sales of our five commercially approved products noted above. Remodulin was approved by the U.S. Food and Drug Administration (FDA) for subcutaneous and intravenous administration in 2002 and 2004, respectively, and has been sold commercially in the United States since 2002. Tyvaso and Adcirca were both approved by the FDA and launched commercially in the United States in 2009. Orenitram was approved by the FDA in 2013 and Unituxin was approved by the FDA in 2015. We commenced sales of Orenitram and Unituxin during the second quarter of 2014 and third quarter of 2015, respectively. We expect sales of our current commercial products will continue to be our primary sources of revenues for the next several years. Our sales and marketing staff supports the availability of our commercial products in the United States, and these efforts are supplemented by our contract distributors. Outside the United States, our contract distributors are primarily responsible for sales and marketing efforts.

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

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

Our Commercial Products

Our commercial product portfolio consists of the following:

Product	Mode of Delivery	Indication	Current Status	Our Territory
Remodulin	Continuous subcutaneous	PAH	Commercial in the U.S., most of Europe*, Argentina, Brazil, Canada, Chile, China, Israel, Japan, Mexico, Peru, Saudi Arabia, South Korea, Taiwan and Venezuela	Worldwide
Remodulin	Continuous intravenous	PAH	Commercial in the U.S., most of Europe*, Argentina, Canada, China, Israel, Japan, Mexico, Peru, Saudi Arabia, South Korea and Switzerland	Worldwide
Tyvaso	Inhaled	PAH	Commercial in the U.S. and Israel	Worldwide
Adcirca	Oral	PAH	Commercial in the U.S.	United States
Orenitram	Oral	PAH	Commercial in the U.S.	Worldwide
Unituxin	Intravenous	High-risk neuroblastoma	Commercial in the U.S.	Worldwide

*

We have obtained approval for subcutaneous and intravenous Remodulin in 24 member countries of the European Economic Area (EEA), as well as other non-EEA countries in Europe, and have received pricing approval in most of these countries.

Products to Treat Cardiopulmonary Diseases

Pulmonary Arterial Hypertension

PAH is a life-threatening disease that affects the blood vessels in the lungs and is characterized by increased pressure in the pulmonary arteries, which are the blood vessels leading 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. This eventually leads to right heart failure and, ultimately, death. PAH is characterized by structural changes in blood vessel walls, aggregation of platelets and alteration of smooth muscle cell function. We believe that PAH affects about 500,000 individuals worldwide. We have seen increases in the number of people diagnosed with the disease, but due to the rarity of the disease and the complexity of diagnosing it, only a small fraction of patients with PAH are being treated.

Current FDA-approved therapies for PAH focus on three distinct molecular pathways: the prostacyclin pathway, the nitric oxide (NO) pathway, and the endothelin (ET) pathway. The classes of drugs that target these three pathways are:

Prostacyclin Analogues and IP Prostacyclin Receptor Agonists. Patients with PAH have been shown to have reduced levels of prostacyclin, a naturally occurring substance that relaxes the pulmonary

blood vessels, prevents platelet aggregation and inhibits the proliferation of smooth muscle cells in the pulmonary vessels. Therefore, drugs that mimic the action of prostacyclin, known as prostacyclin analogues, are established PAH treatments. Another class of therapy, called IP prostacyclin receptor agonists, has recently been developed to address PAH through the prostacyclin pathway. As compared with prostacyclin analogues, which broadly mimic the effect of prostacyclin, IP prostacyclin receptor agonists bind selectively to the IP receptor, one of several prostacyclin receptors.

Phosphodiesterase Type 5 (PDE-5) Inhibitors and Guanylate Cyclase (sGC) Stimulators. 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 cyclic guanosine monophosphate GMP (cyclic GMP). Therefore, another established therapeutic approach has been to inhibit the degradation of cyclic GMP using drugs known as PDE-5 inhibitors. In addition, sGC is an enzyme found in the endothelial cells and the receptor for NO. When NO binds to sGC, the enzyme enhances production of cyclic GMP. As a result, sGC stimulators are also approved to treat PAH.

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

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

The clinical severity of PAH is classified according to a system originally developed for heart failure by the New York Heart Association and then modified by the World Health Organization (WHO) for patients with PAH, ranging from functional class I (no symptoms) through functional class IV (severe symptoms). Labeled indications for PAH therapies often note that clinical studies for the drug predominantly included patients in one or more functional classes.

PAH is a subset of the condition more broadly known as pulmonary hypertension. The WHO has classified pulmonary hypertension into five groups, with PAH being designated WHO Group 1, which includes multiple etiologies such as idiopathic (meaning the cause is unknown) and heritable PAH, as well as PAH associated with connective tissue diseases. While our PAH therapies' labeling is limited to the treatment of WHO Group 1 PAH, we are engaged in research and development efforts to expand the use of Orenitram to treat pulmonary hypertension in certain categories of WHO Groups 2 and 5, and Tyvaso to treat pulmonary hypertension in certain categories of WHO Group 3. For further details, see *Research and Development* below.

Remodulin

One of our lead products for treating PAH is Remodulin, the active pharmaceutical ingredient of which is a prostacyclin analogue known as treprostinil. We sell Remodulin to specialty pharmaceutical distributors in the United States and to pharmaceutical distributors internationally. We recognized approximately $602.3 million, $572.8 million and $553.7 million in Remodulin net product sales, representing 38 percent, 39 percent and 43 percent of our total revenues for the years ended December 31, 2016, 2015 and 2014, respectively. The FDA approved Remodulin as a continuous subcutaneous infusion therapy in 2002, and as a continuous intravenous infusion therapy in 2004. Remodulin is indicated to treat patients with PAH, to diminish symptoms associated with exercise.

Studies establishing effectiveness included patients with functional class II-IV (moderate to severe) symptoms.

Outside of the United States, Remodulin is approved for the treatment of PAH in 39 countries by continuous subcutaneous administration and in 35 countries by continuous intravenous administration, and is sold commercially in most of these countries. Applications for approval of both subcutaneous and intravenous Remodulin are under review in other countries.

We believe Remodulin has many qualities that make it an appealing alternative to competitive therapies. Remodulin is stable at room temperature, so it does not need to be cooled during infusion and patients do not need to use cooling packs or refrigeration to keep it stable. Treprostinil is highly soluble and highly potent, which enables us to manufacture Remodulin in concentrated solutions. This allows therapeutic concentrations of Remodulin to be delivered at very low flow rates via miniaturized infusion pumps for both subcutaneous and intravenous infusion. Remodulin can be continuously infused for up to 48 hours intravenously or 72 hours subcutaneously before refilling the external infusion pump, and is packaged as an aqueous solution so patients do not have to reconstitute the drug before refilling their pumps. This profile contrasts favorably with the other continuously infused prostacyclins in the market Flolan®, Veletri® and generic epoprostenol.

Flolan and generic epoprostenol are not stable at room temperature (and therefore require refrigeration or the use of cooling packs), but Veletri may be stable at room temperature depending on its concentration. Flolan, generic epoprostenol, and Veletri have shorter half-lives than Remodulin, requiring mixing prior to pump refills. None of these competitive products may be administered via subcutaneous infusion, and therefore may only be delivered intravenously.

We have settled patent litigation with three generic drug companies that filed abbreviated new drug applications (ANDAs) with the FDA to market generic versions of Remodulin in the United States. The first such settlement permits Sandoz Inc. (Sandoz) to launch its generic version of Remodulin in the United States in June 2018 (or earlier in certain circumstances). The second and third settlements permit Teva Pharmaceuticals USA, Inc. (Teva) and Par Sterile Products, LLC (Par) to launch their generic versions of Remodulin in the United States in December 2018 (or earlier in certain circumstances). For further detail, see the section below entitled *Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity Generic Competition*.

There are serious adverse events associated with Remodulin. For example, when infused subcutaneously, Remodulin causes varying degrees of infusion site pain and reaction (redness and swelling) in most patients. Patients who cannot tolerate the infusion site pain related to the use of subcutaneous Remodulin may instead use intravenous Remodulin. Intravenous Remodulin is delivered continuously through a surgically implanted central venous catheter, similar to Flolan, Veletri and generic epoprostenol. Patients who receive therapy through implanted venous catheters have a risk of developing blood stream infections and a serious systemic infection known as sepsis. Other common side effects associated with both subcutaneous and intravenous Remodulin include headache, diarrhea, nausea, jaw pain, vasodilation and edema.

Tyvaso

We commenced commercial sales of Tyvaso, our inhaled treprostinil product, in the United States in 2009. We sell Tyvaso to the same specialty pharmaceutical distributors in the United States that distribute Remodulin. For the years ended December 31, 2016, 2015 and 2014, we recognized approximately $404.6 million, $470.1 million and $463.1 million in Tyvaso net product sales, representing 25 percent, 32 percent and 36 percent, respectively, of our total revenues.

Tyvaso is administered four times a day by inhaling up to nine breaths during each treatment session, which takes approximately three minutes. Tyvaso is required to be administered using our

proprietary Tyvaso Inhalation System, which consists of an ultra-sonic nebulizer that provides a dose of Tyvaso on a breath-by-breath basis. A single ampule containing Tyvaso is emptied into the Tyvaso Inhalation System once per day, so the Tyvaso Inhalation System only needs to be cleaned once daily.

Ventavis® (iloprost) is the only other FDA-approved inhaled prostacyclin analogue. Patients need to inhale Ventavis six to nine times per day via a nebulizer. According to its package insert, each Ventavis inhalation consists of four to ten minutes of continuous inhalation via the nebulizer. We completed an open-label study in the United States to investigate the clinical effects of switching patients from Ventavis to Tyvaso. Patients in this study saved an average of approximately 1.4 hours per day when administering Tyvaso compared to Ventavis.

In 2009, the FDA approved Tyvaso for the treatment of PAH patients to improve exercise capacity using the Tyvaso Inhalation System. Studies establishing effectiveness included predominately patients with functional class III symptoms (may not have symptoms at rest but activities are greatly limited by shortness of breath, fatigue, or near fainting). Tyvaso was generally well tolerated in our trials. The most common adverse events were transient cough, headache, nausea, dizziness and flushing. Tyvaso is also approved in Israel, where we commenced commercial sales during the second quarter of 2015.

We filed a Marketing Authorization Application (MAA) in December 2008 for Tyvaso with the European Medicines Agency (EMA) using the centralized filing process, but withdrew our MAA from consideration by the EMA due to the EMA's major objection related to findings of non-compliance with good clinical practices at two clinical sites. We are evaluating the resubmission of Tyvaso for EMA approval based on experience with the drug since it was approved by the FDA.

Orenitram

Orenitram is an extended-release, oral tablet form of treprostinil, which we launched commercially in the United States during the second quarter of 2014. Orenitram is the only FDA approved, orally administered prostacyclin analogue, and is the only oral PAH prostacyclin class therapy approved in the United States that is titratable to a maximum tolerated dose, without a dose ceiling. We sell Orenitram to the same specialty pharmaceutical distributors in the United States that distribute Remodulin and Tyvaso. For the years ended December 31, 2016, 2015 and 2014, we recognized approximately $157.2 million, $118.4 million and $41.2 million in Orenitram net product sales, representing ten percent, eight percent and three percent, respectively, of our total revenues. Orenitram was approved by the FDA in December 2013 for treatment of PAH patients to improve exercise capacity. The primary study that established efficacy included predominately patients with functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). The most common side effects observed in our clinical studies were headache, nausea and diarrhea. We have not submitted Orenitram for approval in major markets outside the United States.

Adcirca

We began selling Adcirca in 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 Eli Lilly and Company (Lilly) for the treatment of erectile dysfunction. We acquired the commercial rights to Adcirca for the treatment of PAH in the United States from Lilly in 2008. We sell Adcirca at prices established by Lilly, which are at parity with Cialis pricing. For the years ended December 31, 2016, 2015 and 2014, we recognized approximately $372.2 million, $278.8 million and $221.5 million in Adcirca net product sales, representing 23 percent, 19 percent and 17 percent, respectively, of our total revenues.

In 2009, the FDA approved Adcirca with a recommended dose of 40 mg, making it the only once-daily PDE-5 inhibitor for the treatment of PAH. Adcirca is indicated to improve exercise ability in

patients with PAH. Studies establishing effectiveness included predominately patients with functional class II-III symptoms. Headaches were the most commonly reported side effect.

Prior to the approval of Adcirca, Revatio®, which is marketed by Pfizer Inc. (Pfizer), was the only PDE-5 inhibitor approved for the treatment of PAH. Sildenafil citrate, the active ingredient in Revatio, is also the active ingredient in Viagra®, which is marketed by Pfizer for the treatment of erectile dysfunction. In 2012, several companies launched generic formulations of sildenafil citrate. Revatio and generic sildenafil citrate are dosed three times daily.

In September 2014, Gilead Sciences, Inc. (Gilead) announced the results of a study of ambrisentan (an ETRA) and tadalafil in PAH patients as a first-line combination treatment, compared to treating PAH patients with only ambrisentan or tadalafil. In the study, first-line treatment with both therapies reduced the risk of clinical failure (a composite endpoint that incorporates clinical worsening events death, hospitalization and disease worsening and a component of unsatisfactory long-term clinical response) compared to a monotherapy treatment by 50 percent. Based on these results, in October 2015, the FDA approved an update to the NDA for Letairis® (ambrisentan), permitting the use of Letairis in combination with tadalafil for PAH to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Products to Treat Cancer

Unituxin

In March 2015, the FDA approved our Biologics License Application (BLA) for Unituxin, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of patients with high-risk neuroblastoma (a rare form of pediatric cancer) who achieve at least a partial response to prior first-line multiagent, multimodality therapy. Unituxin is a chimeric, composed of a combination of mouse and human DNA, monoclonal antibody that induces antibody-dependent cell-mediated cytotoxicity, a mechanism of cell-mediated immunity whereby the immune system actively targets a cell that has been bound by specific antibodies. Unituxin therapy is associated with severe side effects, including infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

We commenced U.S. sales of Unituxin in the third quarter of 2015. For the years ended December 31, 2016 and 2015, we recognized approximately $62.5 million and $20.5 million in Unituxin net product sales, representing four percent and one percent, respectively, of our total revenues.

Research and Development

We focus most of our research and development efforts on the following pipeline programs:

Product	Mode of Delivery	Indication	Current Status STUDY NAME CAPS	Target FDA Approval Date	Our Territory	Target U.S. Patient Population Size
RemoSynch (Implantable System for Remodulin)	Continuous intravenous via implantable pump	PAH	Medtronic PMA pending (FDA action anticipated April 2017). UT NDA pending (FDA action anticipated June 2017).	2017	United States, United Kingdom, Canada, France, Germany, Italy and Japan	6,000
RemUnity (treprostinil)	Continuous subcutaneous via pre-filled, semi-disposable pump	PAH	Pre-NDA	2018	Worldwide	6,000
Dinutuximab	Injection or infusion	Multiple GD2 expressing cancers	Phase II/III	2019-2023 for accelerated approval and other regulatory pathways	Worldwide	12,000
OreniPlus (Orenitram in combination with approved background therapy)	Oral	PAH (decrease morbidity and mortality)	Phase IV *FREEDOM-EV*	2019	Worldwide	15,000
Tysuberprost (esuberaprost in combination with Tyvaso)	Oral (esuberaprost) Inhaled (Tyvaso)	PAH (decrease morbidity and mortality)	Phase III *BEAT*	2019	North America, Europe, Mexico, South America, Egypt, India, South Africa and Australia	10,000
Tyvaso-ILD (treprostinil)	Inhaled	Pulmonary hypertension associated with idiopathic pulmonary fibrosis (WHO Group 3)	Phase III *INCREASE*	2020	Worldwide	27,500
Aurora-GT (eNOS gene therapy)	Intravenous injection	PAH	Phase II/III *SAPPHIRE*	2020*	United States**	10,000
OreniLeft (treprostinil)	Oral	Pulmonary hypertension associated with left ventricular diastolic dysfunction (WHO Group 2)	Phase III *SOUTHPAW*	2021	Worldwide	50,000

OreniCell (treprostinil)	Oral	Reduce morbidity and mortality in patients with pulmonary hypertension associated with sickle cell disease (WHO Group 5)	Phase II/III *IRONS*	2022	Worldwide	25,000
Manufactured Organs	Transplant	End-stage organ failure	Pre-clinical	2023	Worldwide	> 30,000

*
Reflects anticipated Canadian approval date. FDA filing and approval will follow Canadian approval.

**
Canadian rights are held by an affiliated Canadian entity, of which we hold a majority financial stake.

RemoSynch (Implantable System for Remodulin)

We are working with Medtronic, Inc. (Medtronic) on a program to develop Medtronic's proprietary intravascular infusion catheter to be used with its SynchroMed® II implantable infusion pump and related infusion system components (together referred to as the Implantable System for Remodulin, or RemoSynch) in order to deliver Remodulin for the treatment of PAH. The SynchroMed

II device is already approved for delivery of medication to treat neuropathic pain. With our funding, Medtronic completed the DelIVery clinical trial, which studied the safety of the Implantable System for Remodulin. The primary objective was to demonstrate a rate of catheter-related complications below 2.5 per 1,000 patient-days while using the Implantable System for Remodulin. In September 2013, Medtronic informed us that this primary objective was met. If the Implantable System for Remodulin is approved, the technology has the potential to reduce many of the patient burdens and other complications associated with the use of external pumps to administer prostacyclin analogues. In order to launch RemoSynch in the United States, Medtronic and we are pursuing parallel regulatory filings relating to the device and the drug, respectively. Medtronic's PMA relating to the device is pending review, with FDA action anticipated in April 2017. We have resubmitted our NDA requesting FDA approval to allow the use of Remodulin with the Implantable System for Remodulin, and anticipate FDA action in June 2017.

Medtronic is entirely responsible for regulatory approvals and all manufacturing and quality systems related to its infusion pump and related components. Medtronic has received a consent decree citing violations of the quality system regulation for medical devices and requiring it to stop manufacturing, designing and distributing SynchroMed II implantable infusion pump systems, except in limited circumstances, until the FDA determines that Medtronic has met all the provisions listed in the consent decree. It is unclear how this consent decree will impact our ability to obtain FDA approval for RemoSynch, or its commercial prospects if approved.

RemUnity

In December 2014, we entered into an exclusive agreement with DEKA Research & Development Corp. (DEKA) to develop a pre-filled, semi-disposable pump system for subcutaneous delivery of treprostinil, which we call the RemUnity system. Under the terms of the agreement, we are funding the development costs related to the RemUnity system and will pay product fees and a single-digit royalty to DEKA based on commercial sales of the system and the treprostinil drug product sold for use with the system. Currently, we are engaged in engineering, design and development efforts to optimize the RemUnity pump to deliver treprostinil in pre-filled reservoirs, and intend to complete human factor studies in healthy volunteers and functionality testing in patients before submitting an application to the FDA to approve the pre-filled RemUnity pump.

Tyvaso and Tyvaso-ILD

We are developing further enhancements intended to make the Tyvaso Inhalation System easier to use and have submitted a supplement for the new device, with FDA action anticipated in late 2017. In addition, we have commenced a phase III registration study called INCREASE, which is a study of Tyvaso in patients with WHO Group 3 pulmonary hypertension associated with interstitial lung disease (specifically associated with idiopathic pulmonary fibrosis or emphysema), which we refer to as Tyvaso-ILD. There are presently no FDA approved therapies indicated for treatment of WHO Group 3 pulmonary hypertension.

Orenitram, OreniPlus, OreniLeft and OreniCell

In December 2013, the FDA approved Orenitram for the treatment of PAH in WHO Group 1 patients to improve exercise capacity. The primary study that supported efficacy of Orenitram was a 12-week monotherapy study (FREEDOM-M) in which PAH patients were not on any approved background PAH therapy.

We believe that in order for Orenitram to reach its full commercial potential, we need to complete further studies to support an amendment to Orenitram's label to indicate that Orenitram delays morbidity and mortality (also known as "time to clinical worsening") in PAH patients who are on an approved oral background therapy. We refer to this program to improve Orenitram's label as OreniPlus. As such, we are conducting a phase IV registration study called FREEDOM-EV, which is intended to support such a label amendment if successful.

We are also planning studies of Orenitram in patients with WHO Group 2 pulmonary hypertension (specifically associated with left ventricular diastolic dysfunction), which we refer to as OreniLeft, and WHO Group 5 pulmonary hypertension (specifically associated with sickle cell disease), which we refer to as OreniCell. There are presently no FDA approved therapies indicated for treatment of WHO Group 2 or 5 pulmonary hypertension.

Tysuberprost

In July 2012, we completed a phase I safety trial of esuberaprost, a single-isomer orally bioavailable prostacyclin analogue, and the data suggested that dosing esuberaprost four times a day was safe. We believe that esuberaprost and treprostinil have differing prostacyclin receptor-binding profiles and thus could provide benefits to certain groups of patients with differing sets of safety and efficacy profiles. We also believe that inhaled treprostinil and oral esuberaprost have complimentary pharmacokinetic and pharmacodynamic profiles, which indicate that they should provide greater efficacy in combination. As a result, we are conducting a phase III registration study called BEAT (***BE***raprost 314d ***A***dd-on to ***T***yvaso) to evaluate the clinical benefit and safety of esuberaprost in combination with Tyvaso for patients with PAH who show signs of deterioration on inhaled treprostinil or have a less than optimal response to inhaled treprostinil treatment. We refer to the resulting combination of esuberaprost and Tyvaso therapies as Tysuberprost.

Unituxin

Under our BLA approval for Unituxin, the FDA has imposed certain post-marketing requirements and post-marketing commitments on us. We are conducting additional clinical and non-clinical studies to satisfy these requirements and commitments. While we believe we will be able to complete these studies, any failure to satisfy these requirements or commitments could result in penalties, including fines or withdrawal of Unituxin from the market, unless we are able to demonstrate good cause for the failure.

In addition, we are planning studies of Unituxin in adult patients with other forms of GD2-expressing cancers. These research and development efforts into new indications for Unituxin have been substantially outsourced to a contract research organization called Precision Oncology, LLC.

Finally, we are working on the development of a fully humanized (non-chimeric) version of dinutuximab, the active ingredient in Unituxin. We intend this new version to reduce some of the side effects associated with Unituxin, which is a chimeric form of the drug composed of a combination of mouse and human DNA.

Aurora-GT

We are planning a phase II/III study of a gene therapy product called Aurora-GT, in which a PAH patient's own endothelial progenitor cells are isolated, transfected with the gene for human endothelial NO-synthase (eNOS), expanded ex-vivo and then delivered to the same patient. This product is intended to rebuild the blood vessels in the lungs that are destroyed by PAH.

Organ Transplantation

We are engaged in research and development of a variety of technologies designed to increase the supply of transplantable organs and tissues and improve outcomes for transplant recipients. These programs include preclinical research and development of alternative tissue sources through tissue and organ xenotransplantation, as well as regenerative medicine to create engineered organs and organ tissues. Although our primary focus is on engineered lungs, we are also developing technology for other engineered organs, such as kidneys and hearts. Through our wholly-owned subsidiary, Lung

Biotechnology PBC, we are also developing technologies to improve outcomes for lung transplant recipients and to increase the supply of donor lungs through ex-vivo lung perfusion.

Research and Development Expenditures

We have incurred substantial expenses for our research and development activities and expect to continue to do so in connection with the programs described above. For details regarding our research and development expenses, see *Part II Item 7 Management's Discussion and Analysis of Financial Condition and Results of Operations Overview Research and Development.*

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) increase understanding of 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. Our sales and marketing teams consisted of approximately 130 employees as of December 31, 2016. During the second half of 2016, we consolidated and restructured our domestic sales force into a unified team that sells all of our PAH products, in order to better educate physicians about how our products can be used to create a "continuum of care" for treating patients across all stages of the disease. Previously, our sales and marketing personnel were divided into two teams that sold different PAH products.

Distribution of Commercial Products

United States Distribution of Remodulin, Tyvaso, Orenitram, and Unituxin

We distribute Remodulin, Tyvaso and Orenitram throughout the United States through two contracted specialty pharmaceutical distributors: Accredo Health Group, Inc. (Accredo) and CVS Caremark (Caremark). These distributors are required to maintain certain minimum inventory levels in order to ensure an uninterrupted supply to patients who are prescribed our therapies. We compensate Accredo and Caremark on a fee-for-service basis for certain ancillary services in connection with the distribution of these products. If any of our distribution agreements expire or terminate, we may, under certain circumstances, be required to repurchase any unsold Remodulin, Tyvaso or Orenitram inventory held by our distributors.

These specialty pharmaceutical distributors are responsible for assisting patients with obtaining reimbursement for the cost of our treprostinil-based products and providing other support services. Under our distribution agreements, we sell each of our treprostinil-based products to these distributors at a transfer price that we establish. We have also established patient assistance programs in the United States, which provide our treprostinil-based products to eligible uninsured or under-insured patients at no charge. Accredo and Caremark assist us with the administration of these programs.

In the second quarter of 2015, we entered into an exclusive distribution agreement with ASD Specialty Healthcare, Inc. (ASD), an affiliate of AmerisourceBergen Corporation, to distribute Unituxin in the United States. Under this agreement, we sell Unituxin to ASD at a transfer price that we establish, and we pay ASD fees for services provided in connection with the distribution and support of Unituxin.

To the extent we increase the price of any of these products, increases are in the single-digit percentages per year.

United States Distribution of Adcirca

Under our manufacturing and supply agreement with Lilly (see *Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity* below for more details), Lilly manufactures Adcirca and

distributes on our behalf through Lilly's wholesaler network, which includes Accredo and Caremark, in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title to Adcirca upon completion of its manufacture by Lilly. Adcirca is shipped to customers in accordance with purchase orders received by Lilly. When customers take delivery of Adcirca, Lilly sends an invoice and collects the amount due from the customer subject to customary discounts and rebates, if any. Although Lilly provides these services on our behalf, we maintain the risk of loss as it pertains to inventory, product returns and non-payment of invoices. The manufacturing and supply agreement will continue in effect until expiration or termination of the license agreement. Lilly retains authority under the license agreement for all regulatory activities with respect to Adcirca, as well as its retail pricing, which has been and is expected to remain at price parity with Cialis. Since receiving FDA approval of Adcirca, Lilly has generally increased the net wholesale price of Adcirca two or three times each year by approximately nine to ten percent each time. We have also established a patient assistance program in the United States, which provides Adcirca to eligible uninsured or under-insured patients at no charge.

International Distribution of Remodulin

We currently sell Remodulin outside the United States to various distributors, each of which has exclusive distribution rights in one or more countries within Europe, Israel and the Middle East, Asia and South and Central America. We also distribute Remodulin in Canada through a specialty pharmaceutical wholesaler. In some of the European markets where we are not licensed to market Remodulin, such as Spain and the United Kingdom, we sell (but do not market) Remodulin on a named-patient basis in which therapies are approved for individual patients by a national medical review board, hospital or health plan on a case-by-case basis.

Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity

Our success depends in part on our ability to obtain and maintain patent protection for our products, preserve trade secrets, prevent third parties from infringing upon our proprietary rights and operate without infringing upon the proprietary rights of others in the United States and worldwide. Many of these proprietary rights stem from licenses and other strategic relationships with third parties. In addition to intellectual property rights, U.S. and international regulatory authorities often provide periods of market exclusivity for manufacturers of biopharmaceutical products.

Patents provide the owner with a right to exclude others from practicing an invention. Patents may cover the active ingredients, uses, formulations, doses, administrations, delivery mechanisms, manufacturing processes and other aspects of a product. The period of patent protection for any given product generally depends on the expiration date of various patents and may differ from country to country according to the type of patents, the scope of coverage and the remedies for infringement available in a country. Most of our commercial products and investigational products are protected by patents that expire on varying dates.

Significant legal questions exist concerning the extent and scope of patent protection for biopharmaceutical products and processes in the United States and elsewhere. Accordingly, there is no certainty that patent applications owned or licensed by us will be issued as patents, or that our issued patents will afford meaningful protection against competitors. Once issued, patents are subject to challenge through both administrative and judicial proceedings in the United States and other countries. Such proceedings include re-examinations, *inter partes* reviews, post-grant reviews and interference proceedings before the U.S. Patent and Trademark Office, as well as opposition proceedings before the European Patent Office. Litigation may be required to enforce, defend or obtain our patent and other intellectual property rights. Any administrative proceeding or litigation could require a significant commitment of our resources and, depending on outcome, could adversely affect the scope, validity or enforceability of certain of our patent or other proprietary rights.

Remodulin, Tyvaso and Orenitram Proprietary Rights

We have a number of issued patents and pending patent applications covering the stable prostacyclin analogue known as treprostinil, which is the active pharmaceutical ingredient in Remodulin, Tyvaso and Orenitram.

In January 1997, we acquired patents covering the use of treprostinil for PAH from GlaxoSmithKline PLC (formerly Glaxo Wellcome, Inc.) (Glaxo) in exchange for certain payments including a royalty on sales of any product containing treprostinil. All of these patents expired in October 2014, as did our royalty payment obligation to Glaxo.

In October 1997, we filed patent applications for a new synthesis method for treprostinil in the United States, Europe and various other countries. These applications resulted in the grant of three patents in the United States, all of which expire in October 2017, as well as patents granted in a number of other countries which expire in October 2018.

We continue to conduct research into new methods to synthesize treprostinil and have filed a number of additional patent applications relating to manufacturing treprostinil, several of which have already been granted in the United States. One such patent was granted, expiring in 2028, and is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book (see *Orange Book* below), for Remodulin, Tyvaso and Orenitram.

In addition to the treprostinil patents noted above, we have other patents specific to our individual treprostinil-based products, including the following:

Remodulin. We have been granted three U.S. patents covering an improved diluent for Remodulin, which expire in 2028 and 2029. We have another patent covering intravenous administration of Remodulin with certain diluents, which expires in 2024. All four of these patents are listed in the Orange Book.

Tyvaso. We have been granted two U.S. patents, as well as patents in other countries, for Tyvaso that cover methods of treating PAH by inhaled delivery. These patents will expire in the United States in 2018 and in various countries throughout the world in 2020. We recently were granted two additional patents directed to a method of treating pulmonary hypertension and a kit for treating pulmonary hypertension. These two new patents expire in 2028 and are listed in the Orange Book. Counterparts to these patents are issued in several other countries.

Orenitram. Our patents for Orenitram cover methods of use for treating PAH, orally administered formulations, controlled moisture storage and manufacturing methods, as well as those covering controlled release formulations licensed to us by Supernus Pharmaceuticals Inc. (Supernus). These patents will expire in the United States between 2024 and 2031 and in various countries throughout the world between 2024 and 2030.

We have additional pending U.S. and international patent applications relating to Remodulin, Tyvaso and Orenitram.

Orange Book

In seeking approval of a drug through an NDA or upon issuance of new patents following approval of an NDA, applicants are required to submit to the FDA each patent that has claims covering the applicant's product or a method of using the product. Each of the patents submitted is then published in the Orange Book. See *Governmental Regulation Patent Term and Regulatory Exclusivity* below for further details. Remodulin currently has six unexpired Orange Book-listed patents with expiration dates ranging from 2017 to 2029. Tyvaso currently has six unexpired Orange Book listed patents with expiration dates ranging from 2017 to 2028. Orenitram currently has twelve unexpired Orange Book

listed patents with expiration dates ranging from 2017 to 2031. Additional patent applications are pending, and if granted, may be eligible for listing in the Orange Book.

Regulatory Exclusivity

Remodulin's regulatory exclusivity in the U.S. and Europe has expired. In June 2010, the FDA granted orphan drug designation for Tyvaso, which resulted in an orphan exclusivity period that expired in July 2016. In April 2004, the EMA designated Tyvaso an orphan medicinal product for the treatment of both PAH and chronic thromboembolic pulmonary hypertension, which would confer a ten-year exclusivity period commencing if and when we obtain marketing approval. As a result of FDA approval of our NDA for Orenitram as a new dosage form, Orenitram had three years of market exclusivity for PAH, which expired in December 2016. A request for orphan drug designation for Orenitram was denied by the FDA.

Supernus License

In 2006, we entered into an exclusive license agreement with Supernus to use certain of its technologies in manufacturing Orenitram. Under the agreement, we paid Supernus certain amounts upon the achievement of specified milestones based on the development and commercial launch of Orenitram for PAH, and we would be obligated to make additional milestone payments if we develop Orenitram for a second indication. In addition, the agreement provides that we will pay a single-digit percentage royalty based on net worldwide sales. This royalty will be paid for approximately twelve years commencing with the first product sale, which occurred in the second quarter of 2014.

Generic Competition

We settled litigation with Sandoz, Teva and Par relating to their ANDAs seeking FDA approval to market generic versions of Remodulin before the expiration of certain of our U.S. patents. Under the terms of our settlement agreements, Sandoz will be permitted to market its generic version of Remodulin in the United States beginning in June 2018, and both Teva and Par will be permitted to market their generic versions of Remodulin in the United States in December 2018, although each of these companies may be permitted to enter the market earlier under certain circumstances.

We are engaged in litigation with Watson Laboratories, Inc. (Watson), based on its ANDA to market a generic version of Tyvaso before the expiration of certain of our U.S. patents at various dates from November 2018 through December 2028. We also are engaged in litigation with Actavis Laboratories FL, Inc. (Actavis), contesting its ANDA to market a generic version of the 0.25 mg, 1.0 mg and 2.5 mg strengths of Orenitram before the expiration of certain of our U.S. patents at various dates from 2024 through 2031.

Finally, SteadyMed Ltd. (SteadyMed) has filed a petition for *inter partes* review seeking to invalidate the claims of one of our patents that expires in December 2028 and relates to treprostinil (U.S. Patent No. 8,497,393, which we refer to as the '393 Patent), which is the active ingredient in Remodulin, Tyvaso and Orenitram. In April 2016, the Patent Trial and Appeal Board (PTAB) of the U.S. Patent and Trademark Office instituted an *inter partes* review of the '393 Patent on the basis of SteadyMed's petition. The PTAB preliminarily agreed with SteadyMed's arguments concerning invalidity, and initially found that there is a reasonable likelihood that SteadyMed would prevail in challenging the '393 patent. Oral argument was held before the PTAB in November 2016. We are currently awaiting the PTAB's final decision, which we expect in or before April 2017. SteadyMed announced that it is developing a product called Trevyent®, which is a single-use, pre-filled pump intended to deliver a two-day supply of treprostinil subcutaneously using SteadyMed's PatchPump® technology. In January 2016, SteadyMed announced that Trevyent had been granted orphan drug

designation by the FDA for the treatment of PAH. SteadyMed has announced plans to file an NDA for Trevyent during the second quarter of 2017, and launch the product in 2018.

For further details regarding the Watson, Actavis and SteadyMed matters, please see Note 19 *Litigation*, to our consolidated financial statements.

As a result of our settlements with Sandoz, Teva and Par, we expect to see generic competition for Remodulin from these companies in the United States beginning in June 2018 (Sandoz) and December 2018 (Teva and Par) (or earlier under certain circumstances). This increased competition could reduce our net product sales and profits. In addition, while we intend to vigorously enforce our intellectual property rights relating to our products, there can be no assurance that we will prevail in defending our patent rights, or that additional challenges from other ANDA filers or other challengers will not surface with respect to our products. Our patents could be invalidated, found unenforceable or found not to cover one or more generic forms of Remodulin, Tyvaso or Orenitram. If any ANDA filer were to receive approval to sell a generic version of Remodulin, Tyvaso or Orenitram and/or prevail in any patent litigation, the affected product(s) would become subject to increased competition, which could reduce our net product sales and profits.

Certain patents for Revatio, a PDE-5 inhibitor marketed by Pfizer for treatment of PAH, expired in 2012, leading several manufacturers to launch generic formulations of sildenafil citrate, the active ingredient in Revatio. Generic sildenafil's lower price relative to Adcirca could lead to pressure from payers to use generic products within the same class of therapy initially, which could erode Adcirca's market share and limit its potential sales. Although we believe Adcirca's once-daily dosing regimen provides a significant competitive advantage over generic sildenafil's multiple dosing regimen, government payers and private insurance companies may favor the use of less expensive generic sildenafil over Adcirca. Thus far, we have not observed any measurable impact of generic sildenafil on sales of Adcirca; however, circumstances could change over time and our revenues could be adversely impacted. The U.S. patent for Adcirca for the treatment of pulmonary hypertension will expire in November 2017, after which time we expect to see generic competition for Adcirca that could have a material adverse impact on our Adcirca revenues.

Patent expiration and generic competition for any of our commercial PAH products could have a significant, adverse impact on our revenues and profits, and is inherently difficult to predict. For additional discussion, refer to the risk factor entitled, *Our intellectual property rights may not effectively deter competitors from developing competing products that, if successful, could have a material adverse effect on our revenues and profit*s, contained in *Item 1A Risk Factors* included in this Report.

Lilly Agreements Related to Adcirca

In 2008, we entered into several agreements with Lilly regarding Adcirca, including a license agreement and a manufacturing and supply agreement.

License Agreement

Under the terms of 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. We agreed to pay Lilly royalties equal to five percent of our net product sales of Adcirca, as a pass through of Lilly's third-party royalty obligations, for so long as Lilly is required to make such payments.

Lilly retained the exclusive rights to develop, manufacture and commercialize pharmaceutical products containing tadalafil, the active pharmaceutical ingredient in Adcirca, for the treatment of pulmonary hypertension outside of the United States and for the treatment of other diseases worldwide. Lilly retained authority for all regulatory activities with respect to Adcirca and for setting

the wholesale price of Adcirca, which has been and is expected to continue to be at price parity with Cialis.

The license agreement will continue in effect until the later of: (1) expiration, lapse, cancellation, abandonment or invalidation of the last claim to expire within a Lilly patent covering the commercialization of Adcirca for the treatment of pulmonary hypertension in the United States; or (2) expiration of any government-conferred exclusivity rights to use Adcirca for the treatment of pulmonary hypertension in the United States. The U.S. patent for Adcirca for the treatment of pulmonary hypertension will expire in November 2017. Lilly has two additional patents expiring in 2020 covering Adcirca and claiming pharmaceutical compositions and free drug particulate forms. The PTAB issued a final decision finding these patents invalid as the result of an *inter partes* review proceeding initiated by Actelion Pharmaceuticals Ltd (Actelion). Lilly's appeal of the PTAB's decision is pending before the United States Court of Appeals for the Federal Circuit. As a result, it is unclear whether our license agreement will expire in November 2017. In any event, we are likely to face generic competition following the expiration of the November 2017 patent, as the FDA has already tentatively approved ANDAs filed by several generic companies to market generic versions of Adcirca following the expiration of the November 2017 patent.

We have the right to terminate the license agreement upon six months written notice to Lilly. Lilly has the right to terminate in the event of a change of control of our company. Either party may terminate upon a material breach by the other party of the license agreement or the manufacturing and supply agreement, described above.

Manufacturing and Supply Agreement