UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2021

OR

☐ 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	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $.01 per share	UTHR	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 ☒ No ☐

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 ☐ No ☒

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 ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes ☒ No ☐

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

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

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based on the closing price on June 30, 2021, as reported by the Nasdaq Global Select Market was approximately $7,912,099,590.

The number of shares outstanding of the issuer's common stock, par value $0.01 per share, as of February 17, 2022, was 45,132,102.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for the registrant's 2022 annual meeting of shareholders scheduled to be held on June 27, 2022, are incorporated by reference in Part III of this Form 10-K.

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PART I

Item 1. Business

Overview

We build on the strength of our research and development expertise and a distinctive, entrepreneurial culture that encourages diversity, innovation, creativity, sustainability, and, simply, fun. Since inception, our mission has been to find a cure for pulmonary arterial hypertension (**PAH**) and other life-threatening diseases. Toward this goal we have successfully obtained approval from the U.S. Food and Drug Administration (**FDA**) for five medicines, we are always conducting new clinical trials, and we are working to create an unlimited supply of manufactured organs for transplantation.

We are the first publicly-traded biotech or pharmaceutical company to take the form of a public benefit corporation (**PBC**). Our public benefit purpose is *to provide a brighter future for patients through (a) the development of novel pharmaceutical therapies; and (b) technologies that expand the availability of transplantable organs*. At the same time, we seek to provide our shareholders with superior financial performance and our communities with earth-sensitive energy utilization.

We market and sell four commercial therapies in the United States to treat PAH: Tyvaso® (treprostinil) Inhalation Solution (**Tyvaso**), which includes the Tyvaso Inhalation System; Remodulin® (treprostinil) Injection (**Remodulin**); Orenitram® (treprostinil) Extended-Release Tablets (**Orenitram**); and Adcirca® (tadalafil) Tablets (**Adcirca**). Tyvaso has also been approved to treat pulmonary hypertension associated with interstitial lung disease (**PH-ILD**). In the United States, we also market and sell an oncology product, Unituxin® (dinutuximab) Injection (**Unituxin**), which is approved for treatment of high-risk neuroblastoma, and the Remunity® Pump for Remodulin (**Remunity**). Outside the United States, we generate revenues from the sale of Tyvaso, Remodulin, and Unituxin.

We are actively advancing a pipeline of research and development projects that includes new indications, formulations, and delivery devices for our existing products, as well as new products to treat PAH and other conditions.

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
Tyvaso	Inhaled via ultrasonic nebulizer	PAH and PH-ILD	Commercial sales in the U.S., Argentina, and Israel*	Worldwide
Remodulin	Continuous subcutaneous	PAH	Commercial sales in the U.S., most of Europe**, Argentina, Canada, Chile, Columbia, Israel, Japan, Mexico, Peru, South Korea, and Venezuela	Worldwide
Remodulin	Continuous intravenous	PAH	Commercial sales in the U.S., most of Europe**, Argentina, Canada, Columbia, Israel, Japan, Mexico, Peru, Saudi Arabia, and South Korea	Worldwide
Remunity Pump for Remodulin	Continuous subcutaneous via pre-filled cartridges	PAH	Commercial sales in the U.S.	Worldwide
Orenitram	Oral	PAH	Commercial sales in the U.S.	Worldwide
Unituxin	Intravenous	High-risk neuroblastoma	Commercial sales in the U.S., Canada, and Japan	Worldwide
Adcirca	Oral	PAH	Commercial sales in the U.S.	United States

* Tyvaso is only approved for PAH in Argentina and Israel.

** Remodulin is marketed and sold in most of the major European markets other than the United Kingdom.

Products to Treat Pulmonary Hypertension

The World Health Organization (**WHO**) has classified pulmonary hypertension into five groups. PAH is designated as 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. Pulmonary hypertension associated with lung disease, such as PH-ILD, has been classified as WHO Group 3 pulmonary hypertension. In addition, patients with PAH are classified into classes based on clinical severity, 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.

Our pulmonary hypertension products were initially approved to treat only PAH. In March 2021, one of our products — Tyvaso — was approved to treat PH-ILD in addition to PAH. We are engaged in further research and development for additional indications for Tyvaso. For further details, see *Research and Development* below.

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 therapies approved by the FDA for PAH focus on three distinct molecular pathways: the prostacyclin pathway, the nitric oxide pathway, and the endothelin 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 molecule that relaxes the pulmonary blood vessels, prevents platelet aggregation, and inhibits the proliferation of smooth muscle cells in the pulmonary vessels. Drugs that mimic the action of prostacyclin, known as prostacyclin analogues, are established PAH treatments. Another class of therapy, called IP prostacyclin receptor agonists, also addresses PAH through the prostacyclin pathway. As compared with prostacyclin analogues, which broadly mimic the effect of prostacyclin, IP prostacyclin receptor agonists bind selectively to (and activate) the IP receptor, one of several prostacyclin receptors.
- *Phosphodiesterase Type 5 (**PDE-5**) Inhibitors and Soluble Guanylate Cyclase (**sGC**) Stimulators.* Patients with PAH have also been shown to have reduced levels of the enzyme responsible for producing nitric oxide, a naturally occurring substance in the body that causes relaxation of the pulmonary blood vessels. Nitric oxide 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 nitric oxide. When nitric oxide 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 peptide 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 all formulations of treprostinil, a prostacyclin analogue, and Adcirca is a PDE-5 inhibitor.

PH-ILD is also a rare condition, impacting at least 30,000 patients in the United States. In March 2021, Tyvaso became the first and only FDA-approved therapy to treat PH-ILD. Previously, several other leading therapies had been studied in PH-ILD patients, but did not show benefit, and in some cases may have shown adverse consequences.

Tyvaso

Tyvaso was initially approved by the FDA to treat PAH and launched commercially in the United States in 2009. We sell Tyvaso to specialty pharmaceutical distributors in the United States. We recognized $607.5 million, $483.3 million, and $415.6 million in Tyvaso net product sales, representing 36 percent, 33 percent, and 29 percent of our total revenues for the years ended December 31, 2021, 2020, and 2019, respectively. Tyvaso is approved and commercialized in the United States, Israel, and Argentina.

Tyvaso is administered four times a day by inhaling up to twelve 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 ultrasonic nebulizer and related accessories. 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. Tyvaso is regulated by the FDA as a drug-device combination product, consisting of Tyvaso drug product and the Tyvaso Inhalation System.

Ventavis® (iloprost) is the only other FDA-approved inhaled prostacyclin analogue that is available on the market. 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.

Studies establishing the effectiveness of Tyvaso included predominately PAH patients with functional class III symptoms (patients who may not have symptoms at rest but whose activities are greatly limited by shortness of breath, fatigue, or near fainting). Tyvaso was generally well tolerated in our trials. The most common side effects were transient cough, headache, nausea, dizziness, and flushing.

In February 2020, we reported the results of the *INCREASE* phase 3 registration study of Tyvaso in patients with PH-ILD, including patients with underlying idiopathic pulmonary fibrosis (**IPF**) and combined pulmonary fibrosis and emphysema. The study met all of its primary and secondary endpoints. In January and June 2021, data from the *INCREASE* study were published in the *New England Journal of Medicine* and *The Lancet Respiratory Medicine*, respectively. In March 2021, the FDA approved our efficacy supplement to the Tyvaso NDA, which resulted in revised labeling reflecting the outcome of the *INCREASE* study. As a result, Tyvaso became the first and only therapy approved by the FDA to treat PH-ILD, which we estimate affects at least 30,000 patients in the United States. We are working with an international distributor to seek approval of Tyvaso for PH-ILD in Europe and other territories outside the United States, on the basis of the *INCREASE* study results.

In August 2018, we settled patent litigation with Watson Laboratories, Inc. (**Watson**) related to its abbreviated new drug application (**ANDA**) seeking FDA approval to market a generic version of Tyvaso in the United States. Under the terms of this settlement, Watson may launch its generic version of Tyvaso in the United States beginning in January 2026, although Watson may be permitted to enter the market earlier under certain circumstances. For further detail, see the section below entitled *Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights*.

Remodulin

Remodulin was approved by the FDA for subcutaneous and intravenous administration in 2002 and 2004, respectively, and has been sold commercially in the United States since 2002. We sell Remodulin to specialty pharmaceutical distributors in the United States and to pharmaceutical distributors internationally. We recognized $513.7 million, $516.7 million, and $587.0 million in Remodulin net product sales, representing 31 percent, 35 percent, and 40 percent of our total revenues for the years ended December 31, 2021, 2020, and 2019, respectively. 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 marketed and sold for treatment of PAH throughout most of Europe, Canada, Mexico, and various countries throughout Asia, the Middle East, and South America, as noted in the table above.

We believe that 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 under certain circumstances 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 before refilling the external infusion pump. This profile contrasts favorably with non-treprostinil based, continuously infused prostacyclin therapies on 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 also face competition from manufacturers of generic versions of Remodulin in the United States and abroad. See the section below entitled *Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights*.

Patients must use external pumps manufactured by third parties to deliver Remodulin. Smiths Medical, Inc. (**Smiths Medical**) manufactures the pumps used by most patients in the United States to administer Remodulin, including the CADD-MS® 3 (**MS-3**) pump used to deliver subcutaneous Remodulin, and the CADD-Legacy® pump to deliver intravenous Remodulin. In 2015, Smiths Medical notified us that it was planning to discontinue the manufacture of the MS-3 pumps and associated cartridges. We entered into an agreement with Smiths Medical for us to fund the manufacture of a further supply of MS-3 pumps and cartridges for use with branded Remodulin only. We recently launched sales of a next-generation subcutaneous pump called the Remunity Pump, and are developing additional next-generation subcutaneous and intravenous delivery systems as noted below under *Research and Development*.

There are serious side effects 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. As noted below under *Research and Development*, we are working on a prodrug version of Remodulin called RemoPro™ to reduce the infusion site pain associated with subcutaneous administration of treprostinil.

Remunity Pump

In February 2021, we launched limited commercial sales of the Remunity Pump, which is a pre-filled, semi-disposable system for subcutaneous delivery of treprostinil, developed in collaboration with DEKA Research & Development Corp (**DEKA**) under an exclusive development and license agreement. The Remunity Pump consists of a small, lightweight, durable pump and controller designed to have a service life of at least three years. The Remunity Pump uses disposable cartridges filled with Remodulin, which can be connected to the pump with less patient manipulation than is typically involved in filling other currently-available subcutaneous pumps. In November 2019, we entered into a supply agreement with an affiliate of DEKA to manufacture and supply the Remunity Pump to us. Under the terms of the agreement, we reimburse all of DEKA's and its affiliates' costs to manufacture the Remunity Pump.

The Remunity Pump is being offered to patients primarily by contracted specialty pharmacies, which deliver Remunity Pump disposable cartridges pre-filled exclusively with Remodulin. As noted below under *Research and Development*, we are working on a new version of the Remunity Pump that enables us to pre-fill cartridges as part of the manufacturing process. This version is expected to have an extended shelf life and simplified supply chain, and will allow patients to keep more drug product on hand.

Based on initial feedback from Remunity patients shortly after launch, we learned that the pump's alarms can in some cases be overly sensitive. These alarm issues do not raise safety concerns, but to ensure a continued positive experience with the pump, we recently paused the introduction of new patients to Remunity while we work with DEKA to optimize the alarm profile. We are conducting final testing of the pump's alarms before we continue with our broader launch.

Orenitram

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. In 2013, the FDA approved Orenitram for treatment of PAH patients to improve exercise capacity. The primary study that supported efficacy of Orenitram was a 12-week monotherapy study in which PAH patients were not on any approved background PAH therapy. In August 2018, we announced that our clinical study of Orenitram called *FREEDOM-EV* had met its primary endpoint of delayed time to first clinical worsening event. In particular, the preliminary results showed that Orenitram, when taken with an oral PAH background therapy, decreased the risk of a clinical worsening event versus placebo by 25 percent (p=0.0391), driven by a 61 percent decrease in the risk of disease progression for patients taking Orenitram, when compared to placebo (p=0.0002). In October 2019, the FDA approved a supplement to our new drug application (**NDA**) to update the Orenitram label to reflect the *FREEDOM-EV* results. As a result, Orenitram is now indicated to delay disease progression and improve exercise capacity. Mortality rates were similar between Orenitram and placebo groups at the end of randomized treatment. However, in participants for whom data are available (89 percent), Orenitram was associated with a 37 percent decreased risk of mortality compared with placebo at study closure (p=0.0324). These mortality data are not reflected in the FDA-approved label because they include data accrued in the open-label extension study.

Secondary endpoints in the *FREEDOM-EV* study included changes from baseline in six-minute walk distance (**6MWD**), Borg dyspnea score (shortness of breath test), functional class, NT-proBNP levels, and combined 6MWD and Borg dyspnea score. Secondary endpoint data, which are not included in the updated FDA-approved labeling, are summarized below:

- *Change in 6MWD*: The median 6MWD trended toward improvement at week 24 (Hodges-Lehmann treatment estimate: seven meters). Median 6MWD improved with Orenitram at weeks 36 (13 meters) and 48 (21 meters) compared to placebo.
- *Change in Borg dyspnea score and WHO functional class*: When classified categorically as "improved," "no change," or "deteriorated," participants in the Orenitram group exhibited a significantly positive shift in Borg dyspnea score and WHO functional class compared to placebo at weeks 24, 36, and 48.
- *Change in NT-proBNP levels*: NT-proBNP levels were significantly improved with Orenitram at weeks 24 and 36. Per the study protocol, NT-proBNP was not assessed at week 48.
- *Change in combined 6MWD and Borg dyspnea score*: Combined 6MWD and Borg dyspnea score was significantly improved with Orenitram when assessed at week 24 compared to placebo.

In 2020, we published the results of a retrospective study in which selexipag was associated with 67 percent higher PAH-associated healthcare costs on average, during the first six months of therapy, compared to Orenitram. Selexipag and Orenitram are the only FDA-approved oral prostacyclin-class therapies.

We sell Orenitram to the same specialty pharmaceutical distributors in the United States that distribute Tyvaso and Remodulin. We recognized $306.1 million, $293.1 million, and $225.3 million in Orenitram net product sales, representing 18 percent, 20 percent, and 16 percent of our total revenues for the years ended December 31, 2021, 2020, and 2019, respectively. The studies that established efficacy included predominately patients with functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66 percent) or PAH associated with connective tissue disease (26 percent). The most common side effects

observed in our clinical studies were headache, nausea, and diarrhea. Orenitram is currently only approved in the United States. Our distributors are pursuing approval of Orenitram in certain countries outside the United States.

In February 2018, we settled patent litigation with Actavis Laboratories FL, Inc. (**Actavis**) related to its ANDA seeking FDA approval to market a generic version of Orenitram in the United States. Under the terms of this settlement, Actavis may launch its generic version of Orenitram in the United States beginning in June 2027, although Actavis may be permitted to enter the market earlier under certain circumstances. We are also engaged in patent litigation with another generic company, ANI Pharmaceuticals, Inc., regarding its ANDA seeking to market a generic version of Orenitram in the United States. For further detail, see the section below entitled *Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights*.

Adcirca

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 treatment of erectile dysfunction. We acquired the commercial rights to Adcirca for 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. We recognized $55.9 million, $67.3 million, and $107.2 million in Adcirca net product sales, representing three percent, four percent, and seven percent of our total revenues for the years ended December 31, 2021, 2020, and 2019, respectively.

In 2009, the FDA approved Adcirca with a recommended dose of 40 mg, making it the only once-daily PDE-5 inhibitor for 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.

In August 2018, Mylan N.V. announced the launch of its generic version of Adcirca, which resulted in a material adverse impact on Adcirca net product sales. Additional companies launched generic versions of Adcirca in February 2019. In June 2020, we amended our Adcirca license agreement to extend its term through December 31, 2023. For further detail, see the section below entitled *Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights.*

Product 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, interleukin-2, and 13-cis-retinoic acid, for 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 monoclonal antibody composed of a combination of mouse and human DNA 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. In November 2018, we received approval from Health Canada to market Unituxin, and we launched commercial sales of the product in Canada in late 2019. In June 2021, our Japanese distributor obtained approval to market Unituxin in Japan, and launched sales shortly thereafter.

We recognized $202.3 million, $122.9 million, and $113.7 million in Unituxin net product sales, representing 12 percent, eight percent, and eight percent of our total revenues for the years ended December 31, 2021, 2020, and 2019, respectively.

Research and Development

We focus most of our research and development efforts on the following pipeline programs. We also engage in a variety of additional research and development efforts, including technologies designed to increase the supply of transplantable organs and tissues and improve outcomes for transplant recipients through regenerative medicine, 3-D organ bioprinting, xenotransplantation, and *ex-vivo* lung perfusion. Please note that our expectations regarding our research and development programs are subject to the risks described below under *Management's Discussion and Analysis—Impact of COVID-19 on our Business,* and *Risk Factors—Risks Related to our Products—We face risks and uncertainties related to the COVID-19 pandemic, which could significantly disrupt our operations and/or business for an unknown period of time.*

Select Pipeline Programs

Product	Mode of Delivery	Indication	Current Status STUDY NAME	Our Territory
Tyvaso DPI™ (treprostinil)	Inhaled dry powder via pre-filled, single-use cartridges	PAH and PH-ILD	Phase 3 *BREEZE* and pivotal pharmacokinetic studies completed; NDA pending with FDA, with decision anticipated by May 2022	Worldwide
Tyvaso (treprostinil)	Inhaled	PH-COPD	Phase 3 *PERFECT* study	Worldwide
RemoPro™ (subcutaneous Remodulin prodrug)	Continuous subcutaneous	PAH	Phase 1	Worldwide
Tyvaso (treprostinil)	Inhaled	IPF	Phase 3 *TETON* studies	Worldwide
Ralinepag (IP receptor agonist)	Oral	PAH	Phase 3 *ADVANCE* studies	Worldwide, subject to out-licenses granted in certain Asian territories
Aurora-GT™ (gene therapy)	Intravenous	PAH	*SAPPHIRE* study (registration phase in Canada)	United States

Remunity Pump and RemoPro

As noted above under *Products to Treat Pulmonary Arterial Hypertension—Remunity Pump*, in February 2021, we launched commercial sales of the Remunity Pump, which is a pre-filled, semi-disposable system for subcutaneous delivery of treprostinil, developed in collaboration with DEKA under an exclusive development and license agreement. The Remunity Pump consists of a small, lightweight, durable pump and separate controller. The Remunity Pump uses disposable cartridges filled with Remodulin, which can be connected to the pump with less patient manipulation than is typically involved in filling other currently-available subcutaneous pumps. In November 2019, we entered into a supply agreement with an affiliate of DEKA to manufacture and supply the Remunity Pump to us. Under the terms of the agreement, we reimburse all of DEKA's and its affiliates' costs to manufacture the Remunity Pump.

The Remunity Pump is being offered to patients primarily by contracted specialty pharmacies, which deliver Remunity Pump disposable cartridges pre-filled exclusively with Remodulin. We are also developing a version of the system that will include disposable components that are pre-filled as part of the manufacturing process. This version is expected to have an extended shelf life and simplified supply chain, and will allow patients to keep more drug product on hand.

We are conducting a series of phase 1 studies to develop a new prodrug of treprostinil called RemoPro, which is intended to enable subcutaneous delivery of treprostinil therapy without the site pain currently associated with subcutaneous Remodulin. As a prodrug, RemoPro is designed to be inactive in the subcutaneous tissue, which should decrease or eliminate site pain, and to metabolize into treprostinil once it is absorbed into the blood.

Finally, we are collaborating with two medical device manufacturers to develop additional next-generation pump systems for Remodulin.

Tyvaso — *PERFECT* and *TETON* studies

We are enrolling a phase 3 registration study called *PERFECT*, which is a study of Tyvaso in patients with WHO Group 3 pulmonary hypertension associated with chronic obstructive pulmonary disease (**PH-COPD**). There are presently no FDA-approved therapies indicated for treatment of PH-COPD, which we estimate affects 100,000 patients in the United States.

We are also enrolling a phase 3 study called *TETON 1*, which is a study of Tyvaso in patients with IPF. The primary endpoint of this study, which will be conducted entirely in the United States, is the change in absolute forced vital capacity (**FVC**) from baseline to week 52. The *TETON 1* study was prompted by data from the *INCREASE* study, which demonstrated improvements in certain key parameters of lung function in pulmonary hypertension patients with fibrotic lung disease (improved absolute FVC and reduced exacerbations of underlying lung disease). Specifically, in the *INCREASE* study, treatment with Tyvaso resulted in significant improvements in percent predicted FVC at weeks 8 and 16, with subjects having underlying etiologies of idiopathic interstitial pneumonias (week 8: 2.0%, p=0.0373 and week 16: 2.9%; p=0.0096) and IPF (week 8: 2.5%; p=0.0380 and week 16: 3.5%; p=0.0147) showing the greatest improvement. Consistent positive effects were also observed in patients with chronic hypersensitivity pneumonitis and environmental/occupational lung disease. These data points, combined with substantial preclinical evidence of antifibrotic activity of treprostinil, suggest that Tyvaso may offer a treatment option for patients with fibrotic lung disease. In December 2020, the FDA granted orphan designation for treprostinil to treat IPF. We are also in the process of commencing *TETON 2*, which is an additional phase 3 study of Tyvaso in IPF that is similar to *TETON 1*, but will be conducted outside the United States.

If Tyvaso DPI is approved and the *PERFECT* and *TETON* studies are successful, we also plan to seek FDA approval to expand the Tyvaso-ILD label to include PH-COPD and IPF, respectively.

Tyvaso DPI

We have developed a dry powder formulation of inhaled treprostinil called Tyvaso DPI, under an in-license from MannKind Corporation (**MannKind**). Tyvaso DPI incorporates the dry powder formulation technology and Dreamboat® inhalation device technology used in MannKind's Afrezza® (insulin human) Inhalation Powder product, which was approved by the FDA in 2014. If the FDA approves Tyvaso DPI, we believe that this new inhaled treprostinil therapy will provide substantial lifestyle benefits to PAH and PH-ILD patients, as compared with nebulized Tyvaso Inhalation Solution therapy, because it will be: (1) less time consuming to administer and easier to maintain, as the device and drug will be provided in pre-filled, single use, disposable cassettes, eliminating the need for cleaning and filling; and (2) mobile and more convenient, as the compact design of the Dreamboat device and drug cassettes used with Tyvaso DPI enables the device to easily fit into the patient's pocket and the device does not require electricity to function.

We completed two clinical studies of Tyvaso DPI. One was a study in healthy volunteers, comparing the pharmacokinetics of Tyvaso DPI to Tyvaso Inhalation Solution. We completed the study in October 2020 and announced in January 2021 that the study demonstrated comparable systemic treprostinil exposure between Tyvaso DPI and Tyvaso Inhalation Solution. In December 2020, we completed a clinical study called *BREEZE*, which evaluated the safety and pharmacokinetics of switching PAH patients from Tyvaso Inhalation Solution to Tyvaso DPI. The *BREEZE* study demonstrated safety and tolerability of Tyvaso DPI in subjects with PAH transitioning from Tyvaso Inhalation Solution, and comparable systemic treprostinil exposure between Tyvaso DPI and Tyvaso Inhalation Solution. In April 2021, we submitted an NDA to the FDA seeking approval for Tyvaso DPI to treat both PAH and PH-ILD.

On October 15, 2021, the FDA provided us a complete response letter (**CRL**) in which it declined to approve the Tyvaso DPI NDA. In its complete response, the FDA cited a single deficiency preventing approval of Tyvaso DPI, related to an open inspection issue at a third-party analytical testing facility for treprostinil drug substance. The CRL noted, but did not cite as a deficiency, that the FDA had not yet completed its review of a Citizen Petition submitted to the FDA in July 2021 concerning the safety of an excipient in Tyvaso DPI. In December 2021, we resubmitted our NDA to the FDA, addressing the single deficiency cited in the CRL. In January 2022, the FDA accepted our resubmitted NDA for review, and designated our NDA as a class 1 resubmission with an expected two-month review period ending in February 2022. In February 2022, the FDA requested additional information concerning the pulmonary safety of Tyvaso DPI. We responded to the FDA's request, and the FDA indicated that our response constitutes a major amendment to the Tyvaso DPI NDA, which extends the FDA's anticipated deadline to review the pending NDA to May 2022.

In August 2021 we entered into a commercial supply agreement with MannKind (the **Supply Agreement**), which was later amended in October 2021. Pursuant to the Supply Agreement, MannKind is responsible for manufacturing and supplying Tyvaso DPI to us on a cost-plus basis. Unless earlier terminated, the initial term of the Supply Agreement continues until December 31, 2031 and will thereafter be renewed automatically for additional, successive two-year terms unless we give 24 months' written notice of non-renewal, or MannKind gives 48 months' written notice of non-renewal, prior to the end of the initial term or any additional renewal term. Each party has customary termination rights, including termination for the other party's material breach that is not cured within a specific timeframe or in the event of liquidation, bankruptcy or insolvency of the other party.

Ralinepag

Ralinepag is a next-generation, oral, selective, and potent prostacyclin receptor agonist being developed for treatment of PAH. We are enrolling two phase 3 studies of ralinepag: (1) *ADVANCE OUTCOMES*, which is an event-driven study of ralinepag in PAH patients with a primary endpoint of time to first clinical worsening event; and (2) *ADVANCE CAPACITY*, studying the effect of ralinepag on exercise capacity in PAH patients with a primary endpoint of change in peak oxygen uptake via cardiopulmonary exercise test. Both of these studies are global, multi-center, placebo-controlled trials of patients on approved oral background PAH therapies.

Aurora-GT

We are conducting a clinical study (called *SAPPHIRE*) 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 nitric oxide synthase, expanded *ex-vivo*, and then delivered back to the same patient. This product is intended to rebuild the blood vessels in the lungs that are compromised by PAH. This study is being conducted in Canada, is intended to be a registration-phase study for Canadian regulatory submission, and is sponsored by Northern Therapeutics, Inc., a Canadian entity in which we have a 49.7 percent voting stake and a 71.8 percent financial stake. We have the exclusive right to pursue this technology in the United States and will evaluate seeking FDA approval of Aurora-GT if *SAPPHIRE* is successful.

Organ Manufacturing

Each year, end-stage organ failure kills millions of people. A significant number of these patients could have benefited from an organ transplant. Unfortunately, the number of usable, donated organs available for transplantation has not grown significantly over the past half century while the need has soared. Our long-term goals are aimed at addressing this shortage. With advances in technology, we believe that creating an unlimited supply of tolerable manufactured organs is now principally an engineering challenge, and we are dedicated to finding engineering solutions. We are engaged in research and development of a variety of technologies designed to increase the supply of transplantable organs and tissues and to improve outcomes for transplant recipients through regenerative medicine, 3-D organ bioprinting, xenotransplantation, and *ex-vivo* lung perfusion.

In 2019, we entered into a collaboration agreement with the University of Alabama at Birmingham (**UAB**) to develop a pilot-scale, designated pathogen-free facility to house genetically modified pigs, with a goal of commencing human clinical trials of xenotransplanted kidneys we call UKidneys™ from pigs to humans in the near term. In August 2020, UAB began to conduct operations at the facility with the first introduction of genetically-modified pigs, and in March 2021, the facility received its recertification of compliance from the American Association for Accreditation of Laboratory Animal Care. In 2019, we also entered into and amended agreements with NYU Langone Health (**NYU**) and University of Maryland Baltimore, respectively, to conduct preclinical testing of our porcine xenografts, which have been generating data regarding our UKidneys, UThymoKidneys™, and UHearts™.

While we continue to develop and commercialize therapies for rare and life-threatening conditions, we view organ manufacturing as a complementary solution for a broad array of diseases, many of which (such as PAH) have proven incurable to date through more traditional pharmaceutical and biologic therapies. For this reason, in 2015 we created a wholly-owned PBC called Lung Biotechnology PBC, chartered with the express purpose of *"address[ing] the acute national shortage of transplantable lungs and other organs with a variety of technologies that either delay the need for such organs or expand the supply.*" It is also why we included the development of "*technologies that expand the availability of transplantable organs*" as part of our express public benefit purpose when we converted United Therapeutics to a PBC in 2021.

Recently, we announced several key achievements in our organ manufacturing program:

- **First Successful Xenotransplantation of a Porcine Heart:** In January 2022, University of Maryland School of Medicine surgeons successfully transplanted an experimental, genetically-modified UHeart into a living human under an expanded access authorization by the FDA.
- **Successful UKidney Tests in Preclinical Human Models:** In September 2021, collaborators at NYU and UAB tested UThymoKidneys and UKidneys from our genetically modified pigs in brain-dead organ donors, providing preclinical evidence that genetically modified pig organs could transcend the most proximate immunological barriers to xenotransplantation. Results of the UAB experiment were published in the *American Journal of Transplantation* in January 2022.
- ***Ex-Vivo* Lung Perfusion:** In January 2022, we announced that more than 200 patients had received lung transplants following use of our centralized *ex-vivo* lung perfusion service. *Ex-vivo* lung perfusion technology increases the number of transplantable lungs by giving surgeons the ability to assess the function of marginal lungs to determine if the lungs are suitable for transplantation. This allows for the use of lungs that would have otherwise not been transplanted.
- **Drone Delivery of Organs:** In October 2021, we successfully completed the first-ever delivery of a lung for transplant at Toronto General Hospital, demonstrating the feasibility of our goal of delivering our manufactured organs with zero carbon footprint aircraft.

Discontinued Programs

- ***Trevyent*.** In August 2018, we acquired SteadyMed Ltd. (**SteadyMed**), which was developing Trevyent, a drug-device combination product for delivery of subcutaneous treprostinil. Following our acquisition of SteadyMed, we submitted an NDA for Trevyent to the FDA in June 2019. In April 2020, the FDA issued us a CRL declining to approve the NDA. Following the CRL, additional comments provided by the FDA indicated that we would need to both redesign the product to improve pump accuracy in certain respects and conduct a clinical study of the redesigned product. These additional steps would have caused considerable additional delay, and additional development efforts may not ultimately have been successful in addressing the FDA's comments. We decided that continued development of Trevyent was no longer commercially reasonable in light of this additional FDA feedback, and discontinued our efforts to develop the product for the U.S. market.

- ***Implantable System for Remodulin*.** On June 22, 2021, we and Medtronic, Inc. (**Medtronic**) agreed to discontinue further efforts to develop and commercialize the Implantable System for Remodulin (**ISR**). As background, we had been collaborating with Medtronic since 2009 to develop the ISR to deliver Remodulin for patients with PAH via an implantable system developed by Medtronic. On February 25, 2019, we entered into a Commercialization Agreement with Medtronic governing the parties' collaboration to commercialize the ISR in the United States (the **Commercialization Agreement**). Despite FDA approval of Medtronic's premarket approval application (**PMA**) for the ISR in December 2017, commercial launch of the product required Medtronic, as the applicant, to satisfy certain conditions to its PMA approval. Based on the evolution of treatment options and paradigms in PAH over the past few years, and the anticipated efforts required to satisfy the FDA's conditions of approval, we and Medtronic decided to discontinue further efforts to develop and commercialize the ISR. We are working with Medtronic on a mutually-agreed approach to wind-down the development program, and to support patients already enrolled in clinical studies of the ISR, at our sole expense. Effective June 22, 2021, the parties mutually agreed to terminate the Commercialization Agreement.
- ***OreniPro*.** In February 2022, we discontinued the development of the oral prodrug version of Orenitram we called OreniPro, as a result of recent pharmacokinetic analyses suggesting that OreniPro's dosing schedule would be similar to that of Orenitram.

Sales and Marketing

Our marketing strategy for our commercial PAH and PH-ILD products is to use our sales and marketing teams to reach out to the prescriber community to: (1) increase PAH and PH-ILD awareness; (2) increase understanding of the progressive nature of PAH and the importance of early treatment; and (3) increase awareness of our commercial products and how they fit into the various stages of disease progression and treatment.

Distribution of Commercial Products

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

We distribute Tyvaso, Remodulin, the Remunity Pump, and Orenitram throughout the United States through two contracted specialty pharmaceutical distributors: Accredo Health Group, Inc. and its affiliates (**Accredo**) and Caremark, L.L.C. (**CVS Specialty**). Assuming FDA approval, we plan to distribute Tyvaso DPI through these same distributors. 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 CVS Specialty 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 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 CVS Specialty assist us with the administration of these programs.

We distribute Unituxin throughout the United States through an exclusive distribution agreement with ASD Specialty Healthcare, Inc. (**ASD**), an affiliate of AmerisourceBergen Corporation. 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 typically in the single-digit percentages per year.

United States Distribution of Adcirca

Under our manufacturing and supply agreement with Lilly, Lilly manufactures and distributes Adcirca on our behalf through its wholesaler network 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. Upon shipment, 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 the December 31, 2023 expiration or earlier termination of our license agreement for Adcirca. 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. 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 Tyvaso, Remodulin, Orenitram, and Unituxin

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, the Middle East, Asia, and South and Central America. Our primary distributor outside the United States is Grupo Ferrer Internacional, S.A. (**Ferrer**), which holds Remodulin marketing authorization rights in many of these territories. We sell Tyvaso commercially to distributors that have exclusive distribution rights in Israel and Argentina. We also distribute Remodulin and Unituxin in Canada through a specialty pharmaceutical wholesaler. In some of the markets where we are not licensed to market Remodulin, such as Turkey, Taiwan, and the United Kingdom, Remodulin is available, but not marketed, 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. Similar named-patient programs are also available for Tyvaso in certain countries. In November 2020, we entered into an exclusive agreement with Ferrer to distribute Orenitram throughout the territories where it also has distribution rights for Remodulin. Ferrer plans to submit a Marketing Authorization Application for Orenitram to the European Medicines Agency (**EMA**) in 2022. In December 2021, we entered into an exclusive agreement with Ferrer to distribute Tyvaso throughout the territories where it also has distribution rights for Remodulin. Ferrer plans to seek marketing authorization approval for Tyvaso to treat PH-ILD in Europe and several other territories. We distribute Unituxin in Japan through a third-party distributor that obtained Japanese marketing authorization during the second quarter of 2021.

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 (**IPR**), 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.

Tyvaso, Remodulin, and Orenitram Proprietary Rights

We have a number of issued patents and pending patent applications covering our treprostinil-based products, Tyvaso, Remodulin, and Orenitram. We have been granted two patents related to manufacturing treprostinil that expire in 2028 and are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the **Orange Book** (see *Orange Book* below), for Tyvaso, Remodulin, and Orenitram. Both of these patents are subject to the IPR proceedings discussed below under *Generic Competition and Challenges to our Intellectual Property Rights*.

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

- *Tyvaso.* We have been granted two patents directed to a method of treating pulmonary hypertension and a kit for treating pulmonary hypertension. These two patents expire in 2028 and are listed in the Orange Book. Counterparts to these two patents are issued in several other countries. We have also been granted two patents on methods of treating pulmonary hypertension by administering treprostinil by inhalation, which expire in 2024. These two patents are also listed in the Orange Book.
- *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. We have been granted two patents covering a treprostinil formulation with a citrate buffer, which expire in 2024. We have been granted another patent covering a method of treating pulmonary hypertension by administering treprostinil at a certain rate intravenously, which expires in 2024. All seven of these patents are listed in the Orange Book.

- *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 related to Tyvaso, Remodulin, 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 nine unexpired Orange Book-listed patents with expiration dates ranging from 2024 to 2029. Tyvaso currently has six unexpired Orange Book-listed patents expiring in 2028. Orenitram currently has twelve unexpired Orange Book listed patents with expiration dates ranging from 2024 to 2031. Additional patent applications are pending, and if granted, may be eligible for listing in the Orange Book.

Regulatory Exclusivity

- *Tyvaso.* In 2010, the FDA granted orphan drug designation for Tyvaso, which resulted in an orphan exclusivity period that expired in July 2016. In March 2021, the FDA granted Tyvaso three-year clinical trial exclusivity for PH-ILD as a result of the *INCREASE* study and the expansion of the Tyvaso label to include a PH-ILD indication. This exclusivity period will extend through March 2024, and will also cover Tyvaso DPI if it is approved for PH-ILD. In 2004, the European Commission designated Tyvaso an orphan medicinal product for 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. In December 2020, the FDA granted orphan designation for treprostinil for treatment of IPF. Thus, if our *TETON* studies are successful and the FDA approves our supplemental NDA to update the Tyvaso labeling to include an IPF indication, the FDA should grant seven-year orphan drug exclusivity for the new indication.
- *Remodulin.* Regulatory exclusivity for Remodulin in the United States and Europe has expired.
- *Orenitram.* In November 2019, following approval of our supplemental NDA to reflect the *FREEDOM-EV* results in the Orenitram label, the FDA granted orphan exclusivity for the new indication that Orenitram delays disease progression in PAH patients. This exclusivity expires in October 2026.

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. The term of this royalty expires during the second quarter of 2026.

Generic Competition and Challenges to our Intellectual Property Rights

Remodulin – Generic Competition

We settled litigation with Sandoz, Inc. (**Sandoz**) related to its ANDA seeking FDA approval to market a generic version of Remodulin and in March 2019, Sandoz announced the availability of its generic product in the United States. We have also entered into similar settlement agreements with other generic companies, some of which have also launched sales of generic versions of Remodulin. Through December 31, 2021, we have seen minimal erosion of Remodulin sales as a result of generic treprostinil competition in the United States. We are currently engaged in litigation with Sandoz and its marketing partner, RareGen, a subsidiary of Liquidia Corporation (**Liquidia**), related to the infusion devices used to deliver Remodulin subcutaneously. We understand that generic treprostinil was initially launched by Sandoz/RareGen for use only by intravenous administration. In May 2021, Liquidia announced that Sandoz's generic treprostinil has been made available for subcutaneous use, following FDA clearance of a cartridge that can deliver the product via the Smiths Medical MS-3 pump. See Note 14—*Litigation,* to our consolidated financial statements included in this Report.

Regulatory authorities in various European countries began approving generic versions of Remodulin in 2018, followed by pricing approvals and launches in most of these countries in 2019 and 2020. As a result, our international Remodulin revenues have come under pressure due to increased competition and a reduction in our contractual transfer price for Remodulin sold by certain international distributors for sales in countries in which the pricing of Remodulin is impacted by the generic competition.

Tyvaso and Orenitram – Potential Future Generic Competition

We also settled litigation with Watson and Actavis related to their ANDAs seeking FDA approval to market generic versions of Tyvaso and Orenitram, respectively, before the expiration of certain of our U.S. patents. Under the settlement agreements, Watson and Actavis can market their generic versions of Tyvaso and Orenitram in the United States beginning in January 2026

and June 2027, respectively, although they may be permitted to enter the market earlier under certain circumstances. Competition from these generic companies could reduce our net product sales and profits. We recently filed a patent infringement action against ANI based on its ANDA seeking FDA approval to market a generic version of Orenitram. The litigation is in its very early stages, with trial set for May 2023. If ANI is successful in the pending litigation, it could accelerate the launch of generic competition for Orenitram, which could reduce our net product sales and profits. See Note 14—*Litigation,* to our consolidated financial statements included in this Report.

Liquidia – Yutrepia

We are engaged in patent litigation with Liquidia concerning three patents related to Tyvaso. The litigation is proceeding in parallel in two fora: (1) federal district court; and (2) the Patent Trial and Appeal Board (**PTAB**) of the U.S. Patent and Trademark Office.

As background, in January 2020 Liquidia submitted its initial NDA to the FDA for approval of Yutrepia™ (formerly known as LIQ861), a dry powder formulation of treprostinil for inhalation. The Yutrepia NDA was submitted under the 505(b)(2) regulatory pathway with Tyvaso as the reference listed drug, and received tentative approval from the FDA in November 2021. If and when Liquidia launches Yutrepia, it would compete directly with Tyvaso, Tyvaso DPI (if approved), and our other treprostinil-based products.

Following the initial submission of the Yutrepia NDA, we filed a lawsuit in federal district court against Liquidia for infringement of three of our patents. As a result, the FDA is automatically precluded from granting final approval of Liquidia's NDA for up to 30 months (a period that expires in October 2022) or until final judgment is issued in the district court litigation, whichever occurs first. Liquidia contends that each asserted claim of these three patents is invalid and/or not infringed by Yutrepia. Trial is scheduled for March 2022.

Separately, Liquidia has been attempting to invalidate these patents by filing petitions for IPR with the PTAB. Challengers in IPR proceedings have a lower burden of proof (preponderance of the evidence) relative to district court litigation (clear and convincing evidence) to successfully challenge the validity of patent claims. The PTAB refused to institute one of the IPRs, and the other two are proceeding on separate timelines:

- *U.S. Patent No. 9,593,066*: In October 2020, the PTAB declined to institute IPR proceedings relating to this patent because Liquidia failed to establish a reasonable likelihood of prevailing on any claim of this patent.
- *U.S. Patent No. 9,604,901*: In October 2021, the PTAB issued a final written decision on Liquidia's IPR relating to this patent. The PTAB upheld the patentability of two of the claims of this patent, one of which was being asserted against Liquidia in the district court litigation, and found that seven other claims of this patent were unpatentable. All claims of this patent remain valid until any IPR appeals are exhausted. In December 2021, we filed a stipulation in the district court litigation that the '901 patent is not infringed by Liquidia based on the court's claim construction ruling. That stipulation is subject to our right to appeal the court's claim construction at the appropriate time.
- *U.S. Patent No. 10,716,793*: In August 2021, the PTAB instituted IPR proceedings related to this patent. The PTAB has until August 2022 to issue a final written decision regarding this IPR.

In order to prevail in our district court litigation against Liquidia, we need a judgment that at least one of the claims of at least one of these patents is not invalid and is infringed by Yutrepia. We must prove infringement by a preponderance of the evidence, and in order for Liquidia to prevail on its invalidity defense, it must prove invalidity by clear and convincing evidence. For further details, please see Note 14—*Litigation*, to our consolidated financial statements.

Adcirca – Generic Competition

A U.S. patent for Adcirca for treatment of pulmonary hypertension expired in November 2017, and FDA-conferred regulatory exclusivity expired in May 2018, leading to the launch of a generic version of Adcirca by Mylan N.V. in August 2018, and by additional companies in February 2019. Generic competition for Adcirca has had a material adverse impact on Adcirca net product sales.

General

We intend to vigorously enforce our intellectual property rights related to our products. However, we cannot assure you 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 our products. If any ANDA filer or filer of a 505(b)(2) NDA for a branded treprostinil product were to receive approval to sell its treprostinil product and/or prevail in any patent litigation, our affected product(s) would become subject to increased competition. Patent expiration, patent litigation, and competition from generic or other branded treprostinil manufacturers could have a significant, adverse impact on our treprostinil-based product revenues — including the anticipated revenues from new products such as Tyvaso DPI — our profits, and our stock price. These potential effects are 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 *Part I*, *Item 1A—Risk Factors* included in this Report.

Adcirca License Agreement

In 2008, Lilly granted us an exclusive license to develop, market, promote, and commercialize Adcirca for treatment of pulmonary hypertension in the United States. We agreed to pay Lilly royalties based on our net product sales of Adcirca. Lilly retained the exclusive rights to develop, manufacture, and commercialize pharmaceutical products containing tadalafil, the active pharmaceutical ingredient in Adcirca, for treatment of pulmonary hypertension outside of the United States and for 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. In May 2017, we amended our Adcirca license agreement with Lilly in order to clarify and extend the term of the agreement and to amend the economic terms of the agreement following a patent expiry in November 2017. As a result, we are required to make milestone payments to Lilly equal to $325,000 for each $1.0 million in net product sales, plus a royalty equal to ten percent of our net product sales. In June 2020, we amended our Adcirca license agreement to extend its term through December 31, 2023. Previously, the agreement was scheduled to expire at the end of 2020. Following expiration, we will remain obligated to refund the purchase price of any Adcirca that we previously sold to distributors that expires unsold. For additional discussion, refer to our *Adcirca* product description contained in *Part I, Item 1—Business Overview—Products to Treat Pulmonary Arterial Hypertension.*

We also agreed to purchase Adcirca at a fixed manufacturing cost. The agreement provides a mechanism, generally related to the increase in the national cost of pharmaceutical manufacturing, pursuant to which Lilly may raise the manufacturing cost of Adcirca.

Unituxin Proprietary Rights and Regulatory Exclusivity

We have orphan drug exclusivity in the United States for Unituxin, expiring March 2022, which precludes the FDA from approving any application to market the same drug for the same indication, except in limited circumstances. In addition, approval of our BLA conferred a 12-year data exclusivity period through March 2027, during which the FDA may not approve a biosimilar for Unituxin. Under a non-exclusive license agreement with The Scripps Research Institute, we pay a royalty of one percent of Unituxin net sales. We have no patents covering Unituxin.

DEKA Agreements

In December 2014, we entered into an exclusive agreement with DEKA to develop a pre-filled, semi-disposable system for subcutaneous delivery of Remodulin, which we refer to as the Remunity Pump. Our agreement with DEKA expires on the last to occur of 25 years from the first product launch under the agreement, or upon the expiration of the last valid claim of a patent licensed from DEKA under the agreement that covers the Remunity Pump. Under the terms of the agreement, we funded the development costs related to the Remunity Pump, and will continue to fund further development costs associated with new versions of the pump. We will pay product fees and a single-digit royalty to DEKA based on commercial sales of the Remunity Pump and the Remodulin drug product sold for use with the system. Either party may terminate the agreement immediately upon a material breach by the other party that is uncured following the relevant cure period, or in the event of the other party's bankruptcy or insolvency. In November 2019, we entered into a supply agreement with an affiliate of DEKA to manufacture and supply the Remunity Pump. Under this supply agreement, we are responsible for all costs associated with manufacturing the Remunity Pump. The Remunity Pump is covered by issued patents and pending patent applications both in the U.S. and other countries. The expiration dates of currently issued U.S. patents range from 2027 through 2033.

Tyvaso DPI and the MannKind Agreement

In September 2018, we entered into a worldwide, exclusive license and collaboration agreement with MannKind for the development and commercialization of Tyvaso DPI for treatment of PAH. The agreement became effective on October 15, 2018.

Under our agreement with MannKind, we are responsible for global development, regulatory, and commercial activities related to Tyvaso DPI, and we share manufacturing responsibilities with MannKind. Under the terms of the agreement, we paid MannKind $45.0 million following the effectiveness of the agreement in October 2018, and we paid $25.0 million in each of 2019 and 2020 following the achievement of specific development targets. MannKind is also entitled to receive low double-digit royalties on our net sales of the product. In addition, we have the option, in our sole discretion, to expand the license to include other active ingredients for treatment of pulmonary hypertension. We will pay MannKind up to $40.0 million in additional option exercise and development milestone payments for each product (if any) added to the license pursuant to this option, as well as a low double-digit royalty on our net sales of any such product.

Under our license agreement with MannKind, we have an exclusive license to a variety of granted and pending patents and patent applications related to treprostinil inhalation powder and the Dreamboat device, including multiple patent families covering the U.S. and other major market countries. These patents cover drug formulation, devices and device components, and manufacturing processes and intermediates. Expiration dates for issued patents range from the mid-2020s to the mid-2030s. Additional patents subject to pending patent applications, if issued, would have expiration dates in the late 2030s. We believe that certain of the issued and pending patents (if issued) we license from MannKind would be eligible for listing in the Orange Book for Tyvaso DPI.

Ralinepag and the Arena Agreement

On November 15, 2018, we entered into an exclusive license agreement with Arena Pharmaceuticals, Inc. (**Arena**) related to ralinepag. On January 24, 2019, in connection with the closing of the transactions contemplated by the license agreement: (1) Arena granted to us perpetual, irrevocable, and exclusive rights throughout the universe to develop, manufacture, and commercialize ralinepag; (2) Arena transferred to us certain other assets related to ralinepag, including, among others, related domain names and trademarks, permits, certain contracts, inventory, regulatory documentation, Investigational New Drug (**IND**) Application No. 109021 (related to ralinepag), and non-clinical, preclinical, and clinical trial data; (3) we assumed certain limited liabilities from Arena, including, among others, all obligations arising after the closing under the assumed contracts and the IND described above; and (4) we paid Arena $800.0 million, which we expensed as acquired in-process research and development and included within research and development expenses in our consolidated statements of operations for the year ended December 31, 2019. We will also pay Arena: (1) a one-time payment of $250.0 million for the first, if any, marketing approval we receive in the United States for an inhaled version of ralinepag to treat PAH; (2) a one-time payment of $150.0 million for the first, if any, marketing approval we receive in any of Japan, France, Italy, the United Kingdom, Spain, or Germany for an oral version of ralinepag to treat any indication; and (3) low double-digit, tiered royalties on net sales of any pharmaceutical product containing ralinepag as an active ingredient, subject to certain adjustments for third-party license payments. Under our license agreement with Arena, we have an exclusive license to a variety of granted and pending patents and applications related to ralinepag covering drug formulation, manufacturing and dosage, among others. Many of these patents and patent applications would be eligible for listing in the Orange Book. Based on potential patent term extensions and additional patent filings, we believe that U.S. patent protection for ralinepag will likely last through at least the mid-2030s.

Other

We are party to various other license agreements related to therapies and technologies under development. These license agreements require us to make payments based on a percentage of sales if we are successful in commercially developing these therapies, and may require other payments upon the achievement of certain milestones.

Manufacturing and Supply

We manufacture our primary supply of Tyvaso, Remodulin, Orenitram, and Unituxin at our own facilities. In particular, we synthesize treprostinil, the active ingredient in Tyvaso and Remodulin, and treprostinil diolamine, the active ingredient in Orenitram, at our facility in Silver Spring, Maryland. We produce dinutuximab, the active ingredient in Unituxin, at our Silver Spring facility. We manufacture Tyvaso, Remodulin, and Unituxin drug product at our Silver Spring facility. We manufacture Orenitram drug product and we package, warehouse, and distribute Tyvaso, Remodulin, Orenitram, and Unituxin at our facility in Research Triangle Park, North Carolina.

We maintain, at a minimum, a two-year inventory of Tyvaso, Remodulin, and Orenitram based on expected demand, and we contract with third-party contract manufacturers to supplement our capacity for some products, in order to mitigate the risk that we might not be able to manufacture internally sufficient quantities to meet patient demand. For example, Baxter Pharmaceutical Solutions, LLC is approved by the FDA, the EMA, and various other international regulatory agencies to manufacture Remodulin for us. We rely on Woodstock Sterile Solutions to serve as an additional manufacturer of Tyvaso, and we rely entirely on Minnetronix Inc. to manufacture the nebulizer used in our Tyvaso Inhalation System. We have no plans to develop a redundant manufacturing source for dinutuximab, the active ingredient in Unituxin, or for finished Unituxin or Orenitram drug product.

DEKA and its affiliates are currently entirely responsible for manufacturing the Remunity Pump. MannKind is the sole manufacturer of Tyvaso DPI. We currently rely on third-party contract manufacturers to produce ralinepag.

Although we believe that additional third parties could provide similar products, services, and materials, there are few companies that could replace our existing third-party manufacturers and suppliers. A change in supplier or manufacturer could cause a delay in the manufacturing, distribution and research efforts associated with our respective products or result in increased costs. See also *Item 1A—Risk Factors* included in this Report.

Competition

Many drug companies engage in research, development, and commercialization of products to treat cardiopulmonary diseases and cancer. For treatment of PAH, we compete with many approved products in the United States and the rest of the world, including the following:

- *Generic treprostinil and generic tadalafil*. These products have been available in the United States since 2019 and 2018, respectively, as discussed above under *Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity–Generic Competition.*

- *Flolan, Veletri, and generic epoprostenol.* Flolan (epoprostenol) is a prostacyclin that is delivered by intravenous infusion. GlaxoSmithKline (**Glaxo**) began marketing Flolan in the United States in 1996. In 2008, the FDA approved generic epoprostenol for treatment of PAH. In 2010, Actelion Limited (**Actelion**) (which was acquired by Johnson & Johnson in 2017) commenced sales of Veletri, which is another version of intravenous epoprostenol.
- *Tracleer® and generic bosentan*. Tracleer (bosentan), an oral ETRA therapy for treatment of PAH, was approved in 2001 in the United States and in 2002 in Europe. Tracleer is marketed worldwide by Actelion. Generic bosentan became available in the United States in 2019 and is also available in other countries.
- *Ventavis and Ilomedin®*. Approved in 2004 in the United States and in 2003 in Europe, Ventavis (iloprost) is an inhaled prostacyclin analogue. Ventavis is currently marketed by Actelion in the United States and by Bayer Schering Pharma AG (**Bayer**) in Europe. Iloprost is also marketed by Bayer in certain countries outside the United States in an intravenous form known as Ilomedin.
- *Revatio® and generic sildenafil citrate.* Approved in 2005 in the United States, Revatio (sildenafil citrate) is an oral PDE-5 inhibitor therapy manufactured by Pfizer Inc. Revatio contains sildenafil citrate, the same active ingredient as Viagra®. In 2012, several companies began marketing generic formulations of sildenafil citrate.
- *Letairis® and generic ambrisentan.* Approved in 2007 in the United States, Letairis (ambrisentan) is an oral ETRA therapy marketed by Gilead Sciences, Inc. (**Gilead**) for treatment of PAH. In 2008, Glaxo received marketing authorization from the EMA for Letairis in Europe, where it is known as Volibris®. In 2015, Gilead announced the positive results of the *AMBITION* study of ambrisentan and tadalafil as an up-front combination therapy for PAH, which we believe has driven increased use of ambrisentan and tadalafil. Generic ambrisentan became available in the United States in 2019.
- *Opsumit®.* Approved in 2013 in both the United States and in the EU, Opsumit (macitentan) is an oral ETRA therapy marketed by Actelion for treatment of PAH.
- *Adempas®.* Approved in 2013 in the United States and 2014 in the EU, Adempas (riociguat) is an sGC stimulator, which targets a similar vasodilatory pathway as PDE-5 inhibitors and is approved for chronic thromboembolic pulmonary hypertension and PAH. Adempas is an oral therapy marketed by Bayer.
- *Uptravi®.* Approved in the United States in December 2015 and by the EMA in May 2016, Uptravi (selexipag) is an oral IP prostacyclin receptor agonist marketed by Actelion. Actelion also has applications pending in various other jurisdictions. Uptravi is also marketed in Japan by Nippon Shinyaku Co., Ltd.

There are also a variety of investigational PAH therapies in the later stages of development, including the following:

- *Yutrepia,* a dry powder formulation of treprostinil designed for deep-lung delivery using a disposable inhaler being developed by Liquidia. In November 2021, Liquidia announced the FDA granted tentative approval for its NDA for Yutrepia to treat PAH, with final approval pending resolution of the regulatory stay triggered by the litigation described above under *Patent and Other Property Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights.* In late 2020, Liquidia completed a business combination with RareGen, LLC, which markets a generic version of Remodulin. Liquidia has indicated that it plans to seek approval to expand Yutrepia's label to include PH-ILD, following expiration of Tyvaso's regulatory exclusivity in that indication in March 2024.
- *Sotatercept*, an injected TGF-beta modulator being developed by Acceleron Pharma, Inc. (**Acceleron**), which was acquired by Merck & Co., Inc. in November 2021. Acceleron announced the successful completion of a phase 2 study in PAH patients in January 2020. A phase 3, registration trial called *STELLAR* was initiated in December 2020, and three additional phase 3 studies have begun. Acceleron has indicated it may also study sotatercept in PH-ILD.
- *Imatinib*, a drug currently used to treat cancer under the trade name Gleevec®, is being developed for treatment of PAH by three companies. Tenax Therapeutics, Inc. announced plans to initiate a phase 3 study of an oral formulation during 2022. Aerovate Therapeutics, Inc. announced it initiated a phase 2/3 clinical study of an inhaled formulation of imatinib. Aerami Therapeutics Holdings, Inc. is conducting a phase 1 trial of an inhaled formulation of imatinib, and has announced plans to initiate a phase 2/3 trial in early 2022.
- *TPIP (NS1009),* a treprostinil palmitil inhalation (dry powder nanoparticle formulation of a treprostinil prodrug) being developed by Insmed Incorporated (**Insmed**) for PAH. TPIP is currently undergoing phase 2 studies in PAH patients, and Insmed has announced plans to commence studies in PH-ILD and IPF patients.
- *L606*, an inhaled, liposomal form of treprostinil being developed by Pharmosa Biopharm Inc. (**Pharmosa**) for PAH, which completed a phase 1 study in healthy volunteers. Pharmosa initiated a phase 3 study in August 2021.
- *Pemziviptadil (PB1046)*, a subcutaneously-injected, sustained release analogue of the native human vasoactive intestinal peptide, which is being developed by PhaseBio Pharmaceuticals, Inc. (**PhaseBio**). In December 2021, PhaseBio announced discontinuation of its phase 2 study in PAH patients due to the impact of the COVID-19 pandemic on manufacturing, associated drug supply, and the rate of enrollment in the study.
- *Rodatristat ethyl (RVT-1201)*, a tryptophan hydroxylase inhibitor being developed by Altavant Sciences, Inc. (**Altavant**), a wholly-owned subsidiary of Sumitovant Biopharma Ltd., to treat PAH. Altavant is conducting a phase 2 clinical study in PAH patients, and is conducting phase 1 studies for IPF.
- *Seralutinib (GB002)*, an inhaled PDGF receptor kinase inhibitor being developed by Gossamer Bio, Inc. to treat PAH. Two phase 2 clinical studies are ongoing.

- *TIVUS*™, an ultrasound catheter system being developed by SoniVie for treatment of denervation associated with PAH, has undergone phase 1 trials in PAH patients. A pivotal trial is ongoing.
- *MK-5475*, an inhaled once-daily sGC stimulant being developed by Merck Sharpe & Dohme Corp. for PAH (phase 2/3) and PH-COPD (phase 1).
- *Zamicastat (BIA 5-1058)*, an oral potent and selective dopamine beta hydroxylase inhibitor being developed by Bial Portela C.S.A., for PAH. A Phase 2 study was completed in October 2021.

Oral non-prostacyclin therapies (such as PDE-5 inhibitors and ETRAs) are commonly prescribed as first-line treatments for the least severely ill PAH patients (functional class II patients). As patients progress in their disease severity (functional classes III and IV), more advanced approved therapies, such as inhaled prostacyclin analogues (such as Tyvaso) or infused prostacyclin analogues (such as Remodulin) are then commonly added. Orenitram was the first approved oral prostacyclin-class therapy for PAH in the United States, and offers a more convenient alternative therapy to Remodulin and Tyvaso. The use of available oral therapies could delay many patients' need for inhaled or infused prostacyclin therapy. As a result, the availability of oral therapies affects demand for our inhaled and infused products.

Orenitram faces direct competition from Uptravi, which is indicated to delay disease progression and reduce the risk of hospitalization for PAH. Orenitram's initial indication was limited to the improvement of exercise capacity, which may have led physicians to prescribe Uptravi instead of Orenitram. As noted above, however, Uptravi is an oral IP prostacyclin receptor agonist. While prostacyclin analogues such as Orenitram broadly mimic the effect of prostacyclin, IP prostacyclin receptor agonists bind selectively to the IP receptor, one of several prostacyclin receptors. In addition, Orenitram's label allows physicians flexibility to titrate each patient's dosing up to a level according to tolerability, without any stated maximum. By contrast, Uptravi's label limits uptitration to a specific maximum dose. Given the progressive nature of PAH, we believe that many patients will initiate Orenitram or another one of our treprostinil-based therapies after their disease progresses on Uptravi. In August 2018, we announced the results of our *FREEDOM-EV* clinical study, which demonstrated that Orenitram delays time to clinical worsening, demonstrated improvement across key clinical measures, and, at study closure, indicated a positive impact on survival rates. In October 2019, the FDA approved a supplement to our Orenitram NDA expanding the Orenitram label to indicate that it also delays disease progression, in addition to improving exercise capacity. We believe that these clinical results and updated labeling have resulted in increased use of Orenitram.

We have faced generic competition for Adcirca since the launch of generic tadalafil in the United States in August 2018, which has significantly reduced our Adcirca revenues. We have also faced generic competition for Remodulin in the United States and certain European countries since 2019. Finally, we have entered into settlement agreements with Actavis and Watson, permitting them to launch generic versions of Orenitram and Tyvaso in June 2027 and January 2026, respectively, or earlier under certain circumstances. For details regarding these and other potential generic competitors, see the section above entitled *Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights*.

Tyvaso, Tyvaso DPI (if approved), and our other treprostinil-based products may face competition from Liquidia if it obtains final approval of Yutrepia, a dry powder inhaled version of treprostinil.

Aside from Tyvaso, there are no approved therapies to treat PH-ILD. No therapy is approved to treat PH-COPD. We plan to pursue a PH-COPD indication for Tyvaso and Tyvaso DPI (if approved), assuming our *PERFECT* study is successful. As noted above, several PAH drug candidates may also be developed for PH-ILD or PH-COPD (*e.g.,* Yutrepia, sotatercept, MK-5476, and TPIP). Other companies are now developing, or may in the future develop, therapies to treat WHO Group 3 pulmonary hypertension, including INOpulse®, an inhaled nitric oxide delivery system being developed by Bellerophon Therapeutics, Inc. for fibrotic interstitial lung disease (**fILD**) patients at risk of pulmonary hypertension, as well as pulmonary hypertension associated with other indications such as COPD and sarcoidosis. A phase 3 study in fILD is ongoing.

In addition, the use of antifibrotic therapies to treat underlying lung disease (such as the IPF therapies discussed below) could delay the onset of WHO Group 3 pulmonary hypertension.

Following the results of the *INCREASE* study, we expanded our investigational efforts with inhaled treprostinil to examine its use to treat the lung diseases underlying PH-ILD, including our *TETON* studies of Tyvaso in IPF patients. If the *TETON* program is successful, we anticipate seeking an IPF indication for Tyvaso and Tyvaso DPI (if approved). There are currently two therapies that are approved to treat IPF: Ofev® (nintedanib), which is marketed by Boehringer Ingelheim International GmbH, and Esbriet® (pirfenidone), which is marketed by F. Hoffman-La Roche Ltd. (**Roche**). However, clinical studies have indicated that these therapies only slow lung function decline in IPF patients, resulting in a significant unmet need for therapies that halt or reverse lung function decline in IPF. There are a number of potentially competing therapies in advanced clinical development for IPF. These therapies include, but are not limited to, Galapagos NV's GLPG4716 (phase 1), FibroGen, Inc.'s pamrevlumab (phase 3), F. Hoffmann-La Roche AG's rhPTX-2; formerly PRM-151 (recombinant human pentraxin-2) (phase 3), Galecto, Inc.'s GB0139 (phase 2), Sanofi S.A.'s belumosudil (KD025) (phase 2), MediciNova, Inc.'s tipelukast (MN-001) (phase 2), Nitto Denko Corporation's ND-L02-s0201 (phase 2), Bristol Myers Squibb Company's Orencia® (abatacept) (phase 2) and BMS-986278 (phase 2), Celgene Corporation's CC-90001 (phase 2), and Horizon Therapeutics plc's HZN-825 (phase 2).

Unituxin may face competition from Qarziba® (dinutuximab beta), an antibody product developed by Apeiron Biologics AG that is approved in Europe to treat high-risk neuroblastoma, but is not approved in the United States. In October 2016, EUSA Pharma (UK) Ltd. announced it had acquired global commercialization rights to Qarziba. In addition, Y-mAbs Therapeutics, Inc. (**Y-mAbs**), is developing several GD-2 targeting drug candidates, and in November 2020 obtained FDA approval for Danyelza® (naxitamab-

gqgk) to treat pediatric and adult patients with relapsed and refractory (second line) high-risk neuroblastoma in bone or bone marrow. Y-mAbs is also conducting studies of naxitamab for frontline high-risk neuroblastoma.

We compete with the developers, manufacturers, and distributors of all of the products noted above for customers, funding, access to licenses, personnel, third-party collaborators, product development, and commercialization. Many of these companies have substantially greater financial, marketing, sales, distribution and technical resources, and more experience in research and development, product development, manufacturing and marketing, clinical trials, and regulatory matters, than we have.

Governmental Regulation

Pharmaceutical Product Approval Process

The research, development, testing, manufacture, promotion, marketing, distribution, sampling, storage, approval, labeling, record keeping, post-approval monitoring and reporting, and import and export of pharmaceutical products are extensively regulated by governmental agencies in the United States and in other countries. In the United States, failure to comply with requirements under the Federal Food, Drug, and Cosmetic Act (**FDC Act**), the Public Health Service Act (**PHSA**), and other federal statutes and regulations, may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending NDAs or BLAs, warning letters, product recalls, product seizures, total or partial suspension of manufacturing or distribution, injunctions, fines, civil penalties, and criminal prosecution.

Satisfaction of FDA pre-market approval requirements is extremely costly and typically takes many years. The actual cost and time required may vary substantially based upon the type, complexity, and novelty of the product or disease. Drugs are subject to rigorous regulation by the FDA in the United States, the EMA in the EU, and similar regulatory authorities in other countries. The steps ordinarily required before a new drug may be marketed in the United States, which are similar to steps required in most other countries, include: (1) preclinical testing; (2) submission to the FDA of an IND; (3) clinical studies, including well-controlled clinical trials, in healthy volunteers and patients to establish safety, efficacy, and dose-response characteristics for each drug indication; (4) submission of an NDA to the FDA; and (5) FDA review and approval of the NDA.

Preclinical Testing

Preclinical tests include laboratory evaluation of product chemistry and formulation, as well as animal studies to explore toxicity and for proof-of-concept. The conduct of the preclinical tests must comply with federal regulations and requirements including good laboratory practices.

Submission of IND

The results of preclinical testing are submitted to the FDA as part of an IND, along with other information including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Absent FDA objection within 30 days after submission of an IND, the IND becomes effective and the clinical trial proposed in the IND may begin.

Clinical Studies

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (1) in compliance with federal regulations; (2) in compliance with good clinical practices (**GCP**), an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; and (3) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be approved by an institutional review board (**IRB**). An IRB may also require the clinical trial at a site to be halted temporarily or permanently for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials in support of an NDA typically are conducted in sequential phases, but the phases may overlap.

- *Phase 1* involves the initial introduction of the drug into healthy human subjects or patients to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness.
- *Phase 2* usually involves studies in a limited patient population to assess the efficacy of the drug in specific, targeted indications, explore tolerance and optimal dosage, and identify possible adverse effects and safety risks.
- *Phase 3* trials, also called pivotal studies, major studies or advanced clinical trials, demonstrate clinical efficacy and safety in a larger number of patients, typically at geographically diverse clinical study sites, and permit the FDA to evaluate the overall benefit-risk relationship of the drug and provide adequate information for drug labeling.

- *Phase 4* studies are often conducted following marketing approval, in order to meet regulatory requirements or to provide additional data related to drug use.

FDA Approval Process

After successful completion of the required clinical testing, an NDA is typically submitted to the FDA in the United States, and a marketing authorization application is typically submitted to the EMA in the EU. FDA approval of the NDA is required before the product may be marketed in the United States. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data related to the product's pharmacology, chemistry, manufacture, and controls.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing. If the FDA determines that the application is not sufficiently complete to permit substantive review, it may request additional information and decline to accept the application for filing until the information is provided. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Most applications for non-priority drugs are reviewed within ten to twelve months. Special pathways, including "accelerated approval," "fast track" status, "breakthrough therapy" status, and "priority review" status are granted for certain drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. These special pathways can significantly reduce the time it takes for the FDA to review an NDA, but do not guarantee that a product will receive FDA approval. In May 2018, the Right to Try Act established a new regulatory pathway to increase access to unapproved, investigational treatments for patients diagnosed with life-threatening diseases or conditions who have exhausted approved treatment options and who are unable to participate in a clinical trial.

The FDA may refer applications for novel pharmaceutical products or pharmaceutical products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. During the review process, the FDA also reviews the drug's product labeling to ensure that appropriate information is communicated to health care professionals and consumers. In addition, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and the facility or the facilities at which the drug is manufactured to ensure they are in compliance with the FDA's current Good Manufacturing Practices (**cGMP**).

After the FDA evaluates the NDA and the manufacturing facilities, the FDA may issue either an approval letter or a complete response letter, which generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those conditions have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even after a resubmission, the FDA may decide that the application does not satisfy the regulatory criteria for approval.

Post-Approval Regulatory Requirements

Once an NDA is approved, the product is subject to continuing regulation. For instance, pharmaceutical products may be marketed only for their approved indications and in accordance with the provisions of their approved labeling. The FDA closely regulates the post-approval marketing, labeling, and advertising of prescription drugs, including direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the Internet.

Adverse event reporting and submission of periodic reports continue to be required following FDA approval of an NDA. In addition, as a condition of NDA approval, the FDA may require post-marketing testing, including phase 4 clinical studies, and/or a risk evaluation and mitigation strategy (**REMS**) to help ensure that the benefits of the drug outweigh the potential risks. A REMS can include medication guides, communication plans for healthcare professionals, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. Additionally, quality control as well as drug manufacture, packaging, and labeling procedures must continue to conform to cGMP requirements. Manufacturing facilities are subject to continual review and periodic inspections by the FDA and certain state agencies.

Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards or if previously unrecognized problems are subsequently discovered. Discovery of previously unknown problems with a product, including adverse events or problems with manufacturing processes of unanticipated severity or frequency, or failure to comply with regulatory requirements, may also result in (1) revisions to the approved labeling; (2) imposition of post-market studies or clinical trials to assess new safety risks; or (3) imposition of distribution or other restrictions under a REMS program. Other potential consequences include: (1) restrictions on the marketing or manufacturing of the product; (2) fines, warning letters, or holds on post-approval clinical trials; (3) refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals; (4) product seizure or detention, or refusal to permit the import or export of products; or (5) injunctions or the imposition of civil or criminal penalties.

Approval of Changes to an Approved Product

Certain changes to the conditions established in an approved application, including changes in indications, labeling, equipment, or manufacturing processes or facilities, require submission and FDA approval of an NDA or NDA supplement before the change

can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing supplements as it does in reviewing NDAs.

Orphan Drugs

Under the Orphan Drug Act, an applicant can request the FDA to designate a product as an “orphan drug” in the United States if the drug is intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States, or for which there is no reasonable expectation that U.S. sales will be sufficient to recoup the development and production costs. Orphan drug designation must be requested before submitting an NDA or BLA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA or BLA applicant to receive orphan drug designation and FDA approval for a particular active ingredient to treat a particular disease via a particular delivery method is entitled to a seven-year exclusive marketing period in the United States. During the seven-year period, the FDA may not approve any other application to market the same drug for the same disease, except in limited circumstances such as a showing of clinical superiority to the product with orphan drug exclusivity, meaning that it has greater effectiveness or safety, or provides a major contribution to patient care (such as a change in delivery system). Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. The 21st Century Cures Act (**Cures Act**), which became law in December 2016, expanded the types of studies that qualify for orphan drug grants. Orphan drug designation also may qualify an applicant for federal tax credits related to research and development costs.

Patent Term and Regulatory Exclusivity

In 1984, the Hatch-Waxman Act created a faster approval process for generic drugs, called the ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strength(s), route of administration, and dosage form as an approved drug and has been shown through bioequivalence testing to be therapeutically equivalent to the approved drug, which is known as the reference listed drug (**RLD**). ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as “generic equivalents” to the approved drug, and can often be substituted by pharmacists under prescriptions written for the original approved drug. In 2018, the FDA advanced policies aimed at promoting drug competition and patient access to generic drugs, such as issuing guidance about making complex generic drugs and the circumstances in which approval of a generic product application may be delayed.

NDA applicants are required to identify each patent with claims that cover the drug (drug substance or drug product) or FDA-approved method of using the drug. Upon product approval, these patents are listed in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. The Orange Book Transparency Act of 2020, enacted in January 2021, amends the statutory provisions regarding the types of patents and exclusivity-related information listed in the Orange Book. The impact of these changes is not yet known. Every ANDA applicant must make one of several certifications to the FDA with regard to each Orange Book listed patent for the RLD. A Paragraph III certification states that the ANDA applicant seeks approval after the patent expires. A Paragraph IV certification asserts that the patent does not block approval of the ANDA, either because the patent is invalid or unenforceable or because the patent, even if valid, is not infringed by the new product. If the applicant does not challenge the listed patents, the ANDA will not be approved until all the listed patents claiming the referenced product have expired. Alternatively, for a method of use patent covering an approved indication, an ANDA applicant may submit a statement to the FDA that the company is not seeking approval for the covered indication. As a practical matter, this is available only if the RLD is approved for multiple indications, at least one of which is not patent protected.

If the ANDA applicant has submitted a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

The Hatch-Waxman Act also provides that patent terms may be extended to compensate for some of the patent life that is lost during the FDA regulatory review period for a product. This extension period is generally one-half of the time between the effective date of an IND and the submission date of an NDA, plus all of the time between the submission date of an NDA and its approval, subject to a maximum extension of five years, and the limitation that the patent term cannot be extended more than 14 years after approval. Generally, patent term extension is available if the product represents the first permitted commercial marketing of a drug containing the active ingredient. Similar patent term extensions are available under European laws.

An ANDA also will not be approved until any non-patent exclusivity, such as exclusivity for obtaining approval of an NDA for a new chemical entity, has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active ingredient, during which ANDAs for generic versions of those drugs cannot be submitted unless the submission contains a Paragraph IV certification, in which case the submission may be made four years following the original product approval. Following approval of an application to market a drug that contains previously approved active ingredients in a new dosage form, route of administration or combination, or for a new condition of use that was required to be supported by new

clinical trials conducted by or for the sponsor, the FDC Act provides three years of exclusivity during which the FDA cannot grant effective approval of an ANDA for such new condition of use, dosage form, or strength that meets certain statutory requirements.

Section 505(b)(2) New Drug Applications

Most drug products (other than biological products) obtain FDA marketing approval pursuant to an NDA submitted under Section 505(b)(1) of the FDC Act, or an ANDA. A third alternative is a special type of NDA submitted under Section 505(b)(2) of the FDC Act, commonly referred to as a Section 505(b)(2) NDA, which enables the applicant to rely, in part, on the FDA's finding of safety and efficacy data for an existing product, or published literature, in support of its application.

Section 505(b)(2) NDAs may provide an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) permits the filing of an NDA in which the applicant relies, at least in part, on information from studies made to show whether a drug is safe or effective that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. A Section 505(b)(2) applicant may eliminate the need to conduct certain preclinical or clinical studies, if it can establish that reliance on studies conducted for a previously-approved product is scientifically appropriate. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication for which the Section 505(b)(2) NDA applicant has submitted data.

To the extent that the Section 505(b)(2) applicant relies on prior FDA findings of safety and efficacy, the applicant is required to certify to the FDA concerning any patents listed for the previously approved product in the Orange Book to the same extent that an ANDA applicant would. Thus, approval of a Section 505(b)(2) NDA can be delayed until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new active ingredient, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Marketing Pharmaceutical Products Outside the United States

Outside of the United States, our ability to market our products is also contingent upon receiving marketing authorizations from regulatory authorities. The foreign regulatory approval process may include some or all of the risks associated with the FDA review and approval process set forth above, and the requirements governing the conduct of clinical trials and marketing authorization vary widely from country to country.

Biologics

Biological products used for the prevention, treatment, or cure of a disease, or condition, of a human being are subject to regulation under the FDC Act and the PHSA. Biological products are approved for marketing via a BLA that follows an application process and carries approval requirements that are very similar to those for NDAs. To help reduce the increased risk of the introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there is a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction, or spread, of communicable diseases in the United States.

After a BLA is approved, the product may also be subject to official lot release, meaning the manufacturer must submit samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. As with drugs, after approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

The Biologics Price Competition and Innovation Act of 2009, or BPCI Act, created an abbreviated approval pathway for biological products shown to be "biosimilar" to an FDA-licensed reference biological product to minimize duplicative testing. Biosimilarity requires the absence of clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, which, absent a waiver, must be shown through analytical studies, animal studies, and at least one clinical study. Intricacies associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation that are still being addressed by the FDA. In July 2018, the FDA announced an action plan to encourage the development and efficient review of biosimilars, including the establishment of a new office within the agency that will focus on therapeutic biologics and biosimilars. On December 20, 2020, Congress amended the Public Health Services Act as part of the COVID-19 relief bill to further simplify the biosimilar review process by making it optional to show that conditions of use proposed in labelling have been previously approved for the reference product, which used to be a requirement of the application. In September 2021, the FDA issued two guidance documents intended to inform prospective applicants and facilitate the development of proposed biosimilars and

interchangeable biosimilars, as well as to describe the FDA's interpretation of certain statutory requirements added by the BPCIA.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is approved as a biosimilar and also meets additional standards for interchangeability with the reference product, has exclusivity against other biologics submitted under the abbreviated approval pathway for a set period. Effective March 2020, certain products that were approved as drugs under the FDC Act, such as insulin and human growth hormone, are now deemed to be biologics under the PHSA, which means they may face competition through the biosimilars pathway and they may not be eligible for the twelve-year period of exclusivity granted to new BLAs. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Cell-Based and Tissue-Based Products

Manufacturers of cell- and tissue-based products must comply with the FDA's current good tissue practices (**cGTP**), which are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of such products. The primary intent of the cGTP requirements is to ensure that cell- and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission, and spread of communicable diseases. Cell and tissue-based products may also be subject to the same approval standards, including demonstration of safety and efficacy, as other biologic and drug products, if they meet certain criteria such as if the cells or tissues are more than minimally manipulated or if they are intended for a non-homologous use (a use different from the cell's origin).

The Cures Act established a new FDA Office of Tissues and Advanced Therapies and Regenerative Advanced Therapy (**RAT**) designation, which makes a product eligible for FDA priority review and accelerated approval. Therapies that are eligible for RAT designation include cell therapies, therapeutic tissue engineering products, human cell and tissue products, or any combination product using these therapies, with certain exceptions. For RAT designation, the product also must be intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and the preliminary clinical evidence must indicate that the product has the potential to address unmet medical needs for the disease or condition.

Regulation of Medical Devices

We currently do not hold any stand-alone medical device authorizations, but we do hold FDA authorization for the Tyvaso Inhalation System as part of the drug-device combination NDA for Tyvaso. In addition, our business partners have the medical device clearances required to deliver our drugs, including, for example, the Remunity Pump. Medical devices may also be subject to FDA approval and extensive regulation under the FDC Act. Medical devices are classified into one of three classes: Class I, Class II, or Class III. A higher class indicates a greater degree of risk associated with the device and a greater amount of control needed to ensure safety and effectiveness.

All devices, unless exempt by FDA regulation, must adhere to a set of general controls, including compliance with the applicable portions of the FDA's Quality System Regulation (**QSR**), which sets forth good manufacturing practice requirements; facility registration and product listing; reporting of adverse medical events; truthful and non-misleading labeling; and promotion of the device consistent with its cleared or approved intended uses. Class II and III devices are subject to additional special controls and may require FDA clearance of a premarket notification (**510(k)**) or approval of a PMA application.

Most Class I devices are exempt from FDA premarket review or approval. Class II devices, with some exceptions, must be "cleared" by the FDA through the 510(k) process, which requires a company to show that the device is "substantially equivalent" to certain "predicate" devices already on the market. To be substantially equivalent, the proposed device must have the same intended use as the predicate device, and either have the same technological characteristics as the predicate device or have different technological characteristics and not raise different questions of safety or effectiveness than the predicate device. Once a 510(k) is cleared, any change that could significantly affect the safety or effectiveness of the device requires the submission and clearance of a new 510(k) before the change can be implemented. In November 2018, the FDA announced plans to significantly revise the 510(k) program to encourage reliance on modern predicates (e.g., predicates that are less than 10 years old). In January 2019, the FDA also finalized guidance on the alternative 510(k) pathway for well-known device types, the "Safety and Performance Based Pathway," which relies on modern performance-based criteria and current technological principles to demonstrate substantial equivalence.

Devices deemed by the FDA to pose the greatest risks, such as life-sustaining, life-supporting, or some implantable devices, or devices that have a new intended use, or use advanced technology that is not substantially equivalent to that of a legally-marketed device, are placed in Class III, requiring approval of a PMA application. A PMA generally requires data from clinical trials that establish the safety and effectiveness of the device. Once approved, certain changes, such as changes to manufacturing facilities, methods, or quality control procedures, or changes in the design specifications, which affect the safety or effectiveness of the device, require the submission of a PMA Supplement. Some "pre-amendment" devices (devices that were legally marketed prior to May 28, 1976) are unclassified, but are subject to FDA's premarket notification and clearance process in order to be commercially distributed. A 510(k) application also sometimes requires clinical data.

The FDA also allows the submission of a direct *de novo* petition. This procedure allows a manufacturer whose novel device is automatically classified into Class III to request down-classification of its medical device into Class I or Class II on the basis that the device presents low or moderate risk, rather than requiring the submission and approval of a PMA. Prior to the enactment of the Food and Drug Administration Safety and Innovation Act of 2012 (**FDASIA**), a medical device could only be eligible for *de novo* classification if the manufacturer first submitted a 510(k) premarket notification and received a determination from the FDA that the device was not substantially equivalent. FDASIA streamlined the *de novo* classification pathway by permitting manufacturers to request *de novo* classification directly without first submitting a 510(k) premarket notification to the FDA and receiving a not substantially equivalent determination.

The 510(k), de-novo or PMA processes can be expensive, lengthy, and unpredictable. The FDA's 510(k) clearance process usually takes from three to 12 months, but can last longer. The process of obtaining a PMA approval is much more costly and uncertain than the 510(k) clearance process and generally takes from one to three years, or even longer, from the time the application is filed with the FDA. In addition, a PMA approval generally requires the performance of one or more clinical trials. Despite the time, effort, and cost invested by a sponsor, a device may not be approved or cleared by the FDA. The Cures Act requires the FDA to establish a program that would expedite access to devices that provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions, for which no approved or cleared treatment exists or which offer significant advantages over existing approved or cleared alternatives. In December 2018, the FDA published final guidance on this "breakthrough" devices pathway which allows for sponsors to interact directly with the FDA during the development process and to receive prioritized review of their submission. In January 2021, the FDA released final guidance on the Safer Technologies Program (**STeP**), to encourage the innovation and market entry of device technologies that are safer than current alternatives but that do not otherwise satisfy the breakthrough device criteria, including device technologies to treat non-life-threatening or reasonably reversible conditions. STeP is modeled after the breakthrough device program and is intended to provide similar benefits, including increased communication with the FDA and prioritized review.

Clinical trials for medical devices are subject to similar requirements as clinical trials with respect to drugs or biologics. Clinical trials involving significant risk devices (e.g., devices that present a potential for serious risk to the health, safety, or welfare of human subjects) are required to obtain both FDA approval of an investigational device exemption (**IDE**) application and IRB approval before study initiation. Clinical trials involving non-significant risk devices are not required to submit an IDE for FDA approval but must obtain IRB approval before study initiation. During a study, the sponsor is required to comply with the applicable FDA requirements, including, for example, trial monitoring, selecting clinical investigators and providing them with the investigational plan, ensuring IRB review, adverse event reporting, record keeping requirements, and prohibitions on the promotion of investigational devices or on making safety or effectiveness claims about them. The clinical investigators in the clinical study are also subject to FDA regulations and must obtain patient informed consent, rigorously follow the investigational plan and study protocol, control the disposition of the investigational device, and comply with all reporting and recordkeeping requirements. Additionally, after a trial begins, the sponsor, the FDA, or the IRB could suspend or terminate a clinical trial at any time for various reasons, including a belief that the risks to study subjects outweigh the anticipated benefits.

After a device is cleared or approved for marketing, numerous and pervasive regulatory requirements continue to apply. These include:

- establishment registration and device listing with the FDA;
- QSR requirements, which require manufacturers, including third-party manufacturers, to follow stringent design, testing, control, documentation, and other quality assurance procedures during all aspects of the design and manufacturing process;
- labeling regulations and FDA prohibitions against the promotion of investigational products, or the promotion of ''off-label'' uses of cleared or approved products;
- requirements related to promotional activities;
- clearance or approval of product modifications to 510(k)-cleared devices that could significantly affect safety or effectiveness or that could constitute a major change in intended use of one of our cleared devices, or approval of certain modifications to PMA-approved devices;
- medical device reporting regulations, which require that a manufacturer report to the FDA if a device it markets may have caused or contributed to a death or serious injury, or has malfunctioned and the device or a similar device that it markets would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur;
- correction, removal, and recall reporting regulations, which require that manufacturers report to the FDA field corrections and product recalls or removals if undertaken to reduce a risk to health posed by the device or to remedy a violation of the FDCA that may present a risk to health;
- the FDA's recall authority, whereby the agency can order device manufacturers to recall from the market a product that is in violation of governing laws and regulations; and
- post-market surveillance activities and regulations, which apply when deemed by the FDA to be necessary to protect the public health or to provide additional safety and effectiveness data for the device.

The FDA has broad regulatory and enforcement powers with respect to medical devices, similar to those for drugs and biologics. The regulations are complex and have tended to become more stringent over time. Regulatory changes could result in additional restrictions or requirements. The FDA enforces these regulatory requirements through, among other means, periodic

unannounced inspections. Any failure to comply with applicable regulatory requirements could result in enforcement action by the FDA, which may include any of the following sanctions:

- adverse publicity, warning letters, untitled letters, it has come to our attention letters, fines, injunctions, consent decrees, and civil penalties;
- repair, replacement, refunds, recall, or seizure of products;
- operating restrictions, partial suspension, or total shutdown of production;
- denial of requests for regulatory clearance or PMA approval of new products or services, new intended uses, or modifications to existing products or services;
- withdrawal of regulatory clearance or PMA approvals that have already been granted; or
- criminal prosecution.

States also impose regulatory requirements on medical device manufacturers and distributors. The FDA also administers certain controls over the import and export of medical devices to and from the United States. Additionally, each foreign country subjects medical devices to its own regulatory requirements. States also impose regulatory requirements on medical device manufacturers and distributors. Failure to comply with the applicable federal or state requirements could result in, among other things: (1) fines, injunctions, and civil penalties; (2) recall or seizure of products; (3) operating restrictions, partial suspension, or total shutdown of manufacturing; (4) refusing requests for approval of new products; (5) withdrawing approvals already granted; and (6) criminal prosecution.

The FDA also administers certain controls over the import and export of medical devices to and from the United States. Additionally, each foreign country subjects medical devices to its own regulatory requirements. In the EU, there is no authorization process for medical devices. Medical devices are CE marked and placed on the market in the EU at the discretion and on the liability of their manufacturer following a conformity assessment process that may include the participation of a notified body.

Combination Products

A combination product is a product composed of a combination of two or more FDA-regulated product components or products, e.g., drug-device or device-biologic. A combination product can take a variety of forms, such as a single entity made by physically or chemically combining components, or a single unit made of separately packaged products. Each combination product is assigned a lead FDA Center, which has jurisdiction for the premarket review and regulation, based on which constituent part of the combination product provides the primary mode of action, i.e., the mode of action expected to make the greatest contribution to the overall intended therapeutic effect of the product. If the classification as a combination product or the lead Center assignment is unclear or in dispute, a sponsor may request a meeting, submit a Request for Designation (**RFD**), and the FDA will issue a designation letter within 60 calendar days of the filing of the RFD. Depending on the type of combination product, the FDA may require a single application for approval, clearance, or licensure of the combination product, or separate applications for the constituent parts. During the review of marketing applications, the lead Center may consult or collaborate with other FDA Centers. In 2017, the FDA released final documents addressing the application of cGMP requirements and classification issues related to combination products.

The Cures Act sets forth a number of provisions pertaining to combination products, such as procedures for negotiating disagreements between sponsors and the FDA and requirements intended to streamline FDA premarket reviews of combination products that contain an already-approved component. For drug-device combination products, comprised of an FDA-approved drug and device primary mode of action, the Cures Act applies Hatch Waxman requirements to the premarket review process such that a patent dispute regarding the listed drug may result in the delay of the 510(k) clearance or PMA approval of the combination product. Furthermore, the Cures Act applies exclusivity provisions (e.g., new chemical entity and orphan drug exclusivities) to the device clearance and approval process for combination products with a device primary mode of action.

Government Reimbursement of Pharmaceutical Products

In the United States, many independent third-party health plans, and government health care programs, such as Medicaid and Medicare, pay for patient use of our commercial products. A material portion of our product sales are reimbursed under these government programs. The availability of adequate government reimbursement for our products is subject to regulatory changes and controls affecting these programs.

Medicaid is a joint federal and state program that is administered by the states for low-income and disabled beneficiaries. We participate in the Medicaid Drug Rebate program, pursuant to which, as a condition of having federal funds made available for our drugs under Medicaid and Medicare Part B, we are required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are reimbursed by Medicaid. Medicaid rebates are based on pricing data we report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services (**CMS**), the federal agency that administers the Medicaid and Medicare programs. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all applicable sales and associated rebates, discounts, and other price concessions. If we become

aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for up to three years after those data originally were due.

On December 31, 2020, CMS issued a final regulation that modified prior Medicaid Drug Rebate program regulations to permit reporting multiple best price figures with regard to value-based purchasing arrangements (beginning in 2022); provide definitions for “line extension,” “new formulation,” and related terms, with the practical effect of expanding the scope of drugs considered to be line extensions that are subject to an alternative rebate formula (beginning in 2022); and revise best price and average manufacturer price exclusions of manufacturer-sponsored patient benefit programs, specifically regarding applicability of such exclusions in the context of pharmacy benefit manager “accumulator” programs (beginning in 2023).

Medicare is a federal program that is administered by the federal government that provides covered health care benefits to individuals age 65 or over and to certain disabled and chronically ill persons. We are required to provide average sales price (**ASP**) information for certain of our products to CMS on a quarterly basis. The ASP we report must be calculated based on a statutorily-defined formula as well as regulations and interpretations of the statute by CMS. The ASP information is used by CMS to compute Medicare reimbursement rates for our drugs that are covered by Medicare Part B.

Unituxin is administered entirely as an in-patient therapy and would typically be reimbursed under Medicare Part A, which covers inpatient hospital benefits. However, because Unituxin is indicated for the treatment of a pediatric cancer, Medicare is unlikely to cover treatment, but Medicaid programs may cover pediatric patients requiring care.

Remodulin and Tyvaso are reimbursable under Medicare Part B, which covers physician services and outpatient care. The Medicare Part B contractors who administer the program cover Remodulin and Tyvaso under local coverage determinations and provide reimbursement according to statutory guidelines.

We pay rebates to sponsors that reimburse Medicare Part D products (Adcirca and Orenitram) as part of the Medicare Part D program, a voluntary outpatient prescription drug benefit to Medicare beneficiaries. We anticipate that Tyvaso DPI will also be reimbursed under Medicare Part D, if it is approved by the FDA.

State Medicaid programs also reimburse the cost of our commercial products at rates established by statutory guidelines. As noted above, when Remodulin, Tyvaso, Adcirca, Orenitram, and Unituxin are reimbursed by state Medicaid programs, we must pay rebates on our products to those state Medicaid programs. We anticipate that the same will be true for Tyvaso DPI, if it is approved by the FDA. Federal law requires that any company that participates in the Medicaid Drug Rebate program also participate in the Public Health Service’s 340B drug pricing program, in order for federal funds to be available for the manufacturer’s drugs under Medicaid and Medicare Part B. The 340B program, which is administered by the Health Resources and Services Administration (**HRSA**), requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B “ceiling price” for the manufacturer’s covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate program, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement.

A regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities became effective on January 1, 2019. Implementation of this regulation could affect our obligations and potential liability under the 340B program in ways we cannot anticipate. We also are required to report our 340B ceiling prices to HRSA on a quarterly basis, which HRSA then publishes to 340B covered entities. Moreover, HRSA established an administrative dispute resolution (**ADR**) process under a final regulation effective January 13, 2021, for claims by covered entities that a manufacturer engaged in overcharging, and by manufacturers that a 340B covered entity violated the prohibitions against diversion or duplicate discounts. Such claims are to be resolved through an ADR panel of government officials rendering a decision that could be appealed only in federal court. An ADR proceeding could potentially subject us to discovery by covered entities and other onerous procedural requirements and could result in additional liability. Further, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities, expand manufacturer ceiling price obligations to so-called “contract pharmacies,” or require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting. Any additional future changes to the definition of average manufacturer price and the Medicaid rebate amount could affect our 340B ceiling price calculations and negatively impact our results of operations.

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, we also participate in the U.S. Department of Veterans Affairs (**VA**) Federal Supply Schedule (**FSS**) pricing program. Under this program, we are obligated to make our products available for procurement under an FSS contract under which we must comply with standard government terms and conditions and charge a price to certain federal agencies that is no higher than the statutory Federal Ceiling Price (**FCP**). The FCP is based on the non-federal average manufacturer price (**Non-FAMP**), which we calculate and report to the VA on a quarterly and annual basis. We also participate in the Tricare Retail Pharmacy program, under which we pay quarterly rebates on utilization of innovator products that are dispensed through the Tricare Retail Pharmacy network to Tricare beneficiaries. The rebates are calculated as the difference between the annual Non-FAMP and FCP. Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies, and the courts, which can change and evolve over time.

In addition, in the U.S., drug pricing by pharmaceutical companies is currently, and is expected to continue to be, under close scrutiny, including with respect to companies that have increased the price of products after acquiring those products from other companies. There are numerous ongoing efforts at the federal and state level seeking to indirectly or directly regulate drug prices to reduce overall healthcare costs using tools such as price ceilings, value-based pricing, and increased transparency and disclosure obligations. Several states have passed or are considering legislation that requires or purports to require companies to report pricing information, including proprietary pricing information. For example, in 2017, California adopted a prescription drug price transparency state bill requiring advance notice of and an explanation for price increases of certain drugs that exceed a specified threshold. Similar bills have been introduced previously at the federal level and also enacted in other states, and additional legislation could be introduced in the future.

Anti-Kickback, False Claims Laws, and The Prescription Drug Marketing Act

The federal Anti-Kickback Statute (**AKS**) prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of, or referring an individual for the furnishing of, any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. This statute has been interpreted broadly to apply to arrangements between pharmaceutical manufacturers and prescribers, purchasers, formulary managers, and others. The term “remuneration” has been broadly interpreted to apply to anything of value including, for example, gifts, cash payments, donations, waivers of payment, ownership interests, and providing any item, service, or compensation for something other than fair market value. Liability under the AKS may be established without proving actual knowledge of the statute or specific intent to violate it. Although there are a number of statutory exceptions and regulatory safe harbors to the AKS protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals as consultants, advisors, and speakers, may be subject to scrutiny if they do not fit squarely within an exception or safe harbor. Moreover, there are no safe harbors for many common practices, such as educational and research grants, charitable donations, product support, and patient assistance programs. The regulatory safe harbors also are subject to regulatory revision and interpretation by a number of government agencies.

For example, in November 2020, the U.S. Department of Health and Human Services finalized a previously abandoned proposal to amend the discount safe harbor regulation of the AKS in a purported effort to create incentives to manufacturers to lower their list prices, and to lower federal program beneficiary out-of-pocket costs. The rule revises the AKS discount safe harbor to exclude manufacturer rebates to Medicare Part D plans, either directly or through pharmacy benefit managers (**PBMs**), creates a new safe harbor for point-of-sale price reductions that are set in advance and are available to the beneficiary at the point-of-sale, and creates a new safe harbor for service fees paid by manufacturers to PBMs for services rendered to the manufacturer. In response to a legal challenge brought by a trade association representing PBMs, the Biden Administration has agreed to delay the effective date of the rule by one year to January 1, 2023. It is too early to know whether the Biden Administration will further delay, rewrite, or allow the rule to go into effect, and if so, what the effect of the rule will be on negotiations of coverage for our products under Medicare Part D plans, or whether the rule will affect our coverage arrangements with commercial insurers. It is also unclear whether the rule will have the intended effect of reducing net prices and beneficiary out-of-pocket costs without also increasing Medicare Part D premiums, which may impact the willingness of Part D plans to cover our products and the price concessions or other terms the plans or their PBMs may seek from us. Violations of the AKS are punishable by imprisonment, criminal fines, damages, civil monetary penalties, exclusion from participation in federal healthcare programs, and liability under the federal civil False Claims Act (**FCA**).

The FCA prohibits any person from, among other things, presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or making, or causing to be made, a false statement material to a false or fraudulent claim. Actions under the FCA may be brought by the Attorney General or as a *qui tam* action by a private individual in the name of the government. Such private individuals may share in amounts paid by the defendant to the government in recovery or settlement. Many pharmaceutical and other healthcare companies have been prosecuted under the FCA for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates; for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product; for violating the AKS; for materially deviating from statutorily required manufacturing standards; and on the basis of allegations related to certain marketing practices, including off-label promotion. FCA liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement, as well as exclusion from participation in federal healthcare programs.

Many states also have statutes or regulations similar to the AKS and the FCA, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs; file periodic reports with the state, including reports on gifts and payments to individual health care providers; make periodic public disclosures on sales, marketing, pricing, clinical trials, and other activities; and/or register their sales representatives. Some states prohibit certain sales and marketing practices, including the provision of gifts, meals, or other items to health care providers, and still others prohibit offering co-pay support to patients for certain prescription drugs.

The federal Physician Payments Sunshine Act, implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children’s Health

Insurance Program (with certain exceptions) to report annually to CMS information related to payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives.

We are also subject to numerous other anti-bribery and anti-fraud laws, including the U.S. Foreign Corrupt Practices Act, the UK Bribery Act, and the federal Civil Monetary Penalties Law.

As part of the sales and marketing process, pharmaceutical companies frequently provide samples of approved drugs to physicians. The Prescription Drug Marketing Act (**PDMA**) imposes requirements and limitations upon the distribution of drugs and drug samples, and prohibits states from licensing distributors of prescription drugs unless the state licensing program meets certain federal guidelines that include minimum standards for storage and handling, as well as record keeping requirements for information regarding sample requests and distribution. The PDMA sets forth civil and criminal penalties for violations. In addition, PDMA requires manufacturers and distributors to submit similar drug sample information to the FDA.

Sanctions under these federal and state laws may include treble damages, civil penalties, exclusion of a manufacturer's products from reimbursement under government programs, criminal fines, and imprisonment.

Outside the U.S., interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct, and physicians' codes of professional conduct. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order, or use of medicinal products, which is prohibited in the EU, is governed by the national anti-bribery laws of the EU member states. Violation of these laws could result in substantial fines and imprisonment. Certain EU member states, or industry codes of conduct, require that payments made to physicians be publicly disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, his/her competent professional organization, and/or the competent authorities of the individual EU member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

The Patient Protection and Affordable Care Act of 2010 (**PPACA**)

The PPACA expanded healthcare coverage within the United States. The PPACA substantially changed the way healthcare is financed by both governmental and commercial payers, and significantly impacted the U.S. pharmaceutical industry. Among other things, the PPACA subjects biologics to potential competition by lower-cost biosimilars; establishes a different methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program, or MDRP, are calculated for covered outpatient drugs that are inhaled, infused, instilled, implanted, or injected; increases the minimum Medicaid rebates owed by manufacturers under the MDRP and extends the rebate program to individuals enrolled in Medicaid managed care organizations; establishes annual fees and taxes on manufacturers of certain branded prescription drugs; creates a Medicare Part D coverage gap discount program in which, as a condition of coverage of its products under Medicare Part D, manufacturers must agree to offer point-of-sale discounts off of negotiated prices for applicable brand drugs to eligible beneficiaries during their coverage gap period; and expands the Public Health Service Act's 340B drug pricing program, including by creating new penalties for non-compliance.

The PPACA and certain of its provisions have been subject to judicial challenges as well as efforts to repeal or replace them or to alter their interpretation or implementation. For example, the Tax Cuts and Jobs Act, enacted in December 2017, eliminated the tax-based payment required of individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code of 1986, commonly referred to as the "individual mandate," effective January 1, 2019. On December 14, 2018, a United States District Court judge in Texas ruled that the Affordable Care Act is unconstitutional in its entirety because of Congress's repeal of the individual mandate. On December 18, 2019, the United States Court of Appeals for the Fifth Circuit (**Fifth Circuit**) affirmed the portion of the district court's ruling declaring the individual mandate unconstitutional and remanded for the district court to conduct analysis in the first instance on which provisions of the statute are severable from it and thus remain intact. The Supreme Court was asked to hear the case before it was remanded to the district court. The Supreme Court heard the case, and overturned the Fifth Court's affirmation on the basis that the plaintiffs lacked standing to challenge the law and did not address its constitutionality. The Supreme Court's decision left open the opportunity for additional challenges to the ACA.

The Bipartisan Budget Act of 2018, among other things, amended the Medicare Act (as amended by the PPACA) to increase the point-of-sale discounts that manufacturers must agree to offer under the Medicare Part D coverage discount program from 50 percent to 70 percent off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs being covered under Medicare Part D. Section 4408 of the CARES Act temporarily suspended Medicare sequestration during the period of May 1, 2020 through December 31, 2020, while extending the Medicare sequestration sunset date through 2030. There may be additional legislative changes, regulatory changes, and judicial challenges related to the PPACA. It is unclear how the PPACA and its implementation, as well as any efforts to repeal, replace or otherwise modify, or invalidate, the PPACA, or portions thereof, will affect our business.

21st Century Cures Act

The Cures Act, which was signed into law on December 13, 2016, contains a wide range of provisions designed to promote clinical research and streamline and expedite the FDA review and approval process. For example, the law clarifies the FDA's authority regarding drugs that target rare diseases, and broadens the type of data and information that may be used to support a drug or biologic application for a genetically targeted drug or variant protein targeted drug. The law requires the FDA to facilitate development programs for, and provides expedited review of, regenerative advanced therapies. The law further requires the FDA to establish a program to evaluate the use of real-world evidence, i.e., evidence from sources other than randomized clinical trials, to support the approval of certain drug and biological product applications and to satisfy post-approval requirements; in 2018, the FDA published a framework for evaluating real-world evidence. In 2019, the FDA announced numerous initiatives and guidance documents intended to improve and streamline the drug approval process. The effects of these initiatives, which are still being implemented and announced, are not yet known. Other key provisions related to orphan drugs, combination products, and medical devices, are discussed separately above.

State Pharmaceutical and Medical Device Marketing Laws

If not preempted by the PPACA, several jurisdictions require pharmaceutical companies to report expenses related to the marketing and promotion of pharmaceutical products and to report gifts and payments to healthcare practitioners in those jurisdictions, or to obtain licenses for sales representatives and require them to satisfy educational and other requirements. Some of these jurisdictions also prohibit various marketing related activities. Still other states require the disclosure of information related to drug pricing and clinical studies and their outcomes. In addition, certain states require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws face civil penalties or other civil enforcement action.

Privacy Laws

We must comply with numerous federal, state, and non-U.S. laws that govern the privacy and security of health and other personal information. In the U.S., numerous federal and state laws and regulations govern the collection, use, disclosure, and protection of health related and other personal information. Many of these laws differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Compliance with these laws is difficult, constantly evolving, and time consuming. Federal regulators, state attorneys general, and plaintiffs' attorneys, including class action attorneys, have been and will likely continue to be active in this space.

The Health Insurance Portability and Accountability Act of 1996 (**HIPAA**) imposes privacy, security, and breach reporting obligations, including mandatory contractual terms, with respect to safeguarding the privacy and security of individually-identifiable health information upon covered entities subject to the rule. Although we are not directly subject to HIPAA—other than with respect to providing certain employee benefits—we could be subject to criminal penalties if we knowingly obtain, use, or disclose individually-identifiable health information maintained by a HIPAA covered entity in a manner that is not authorized or permitted by HIPAA. We also may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA.

In addition, we are required to comply with the California Consumer Privacy Act (**CCPA**). The CCPA became effective on January 1, 2020 and establishes certain requirements for data use and sharing transparency, and provides California residents certain rights concerning the use, disclosure, and retention of their personal data. The CCPA and its implementing regulations have already been amended multiple times since their enactment. Similarly, there are a number of legislative proposals in the United States, at both the federal and state level, that could impose new obligations or limitations in areas affecting our business. These laws and regulations are evolving and subject to interpretation, and may impose limitations on our activities or otherwise adversely affect our business. The obligations to comply with the CCPA and evolving legislation require us, among other things, to update our notices and develop new processes internally and with our partners. We may be subject to fines, penalties, or private actions in the event of non-compliance with these laws.

Outside the U.S., the legislative and regulatory landscape for privacy and data security continues to evolve. There has been increased attention to privacy and data security issues that could potentially affect our business, including the EU General Data Protection Regulation (**GDPR**), which became effective on May 25, 2018 and imposes potential penalties up to the greater of €20 million or four percent of annual global revenue for failure to comply with its requirements. In addition, the CCPA and laws and regulations enacted in the United States, Europe, Asia, and Latin America, increase potential enforcement and litigation activity.

In the event we enroll subjects in our ongoing or future clinical trials in the EU, we may be subject to additional privacy restrictions, including restrictions relating to the collection, use, storage, transfer, and other processing of personal data, including personal health data, regarding individuals in the European Economic Area (**EEA**) as governed by the GDPR. The GDPR imposes several requirements on companies that process personal data, strict rules on the transfer of personal data out of the EEA, including to the U.S., and fines and penalties for failure to comply with the requirements of the GDPR and the related

national data protection laws of the EU member states. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. The obligations under the GDPR may be onerous and adversely affect our business, financial condition, results of operations, and prospects. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any European activities. Further, the United Kingdom's exiting of the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated.

Because of the remote work policies we implemented due to the COVID-19 pandemic, information that is normally protected, including company confidential information, may be less secure. Cybersecurity and data security threats continue to evolve and raise the risk of an incident that could affect our operations or compromise our business information or sensitive personal information, including health data.

We may also need to collect more extensive health-related information from our employees to manage our workforce. If we or our third-party partners fail to comply or are alleged to have failed to comply with applicable data protection and privacy laws and regulations, and related employment rules, or if we were to experience a data breach involving personal information, we could be subject to government enforcement actions or private lawsuits.

In addition, our business could be adversely impacted if our ability to transfer personal data outside of the EEA or Switzerland is restricted, which could adversely impact our operating results.

Other Laws and Regulations

Numerous other statutory and regulatory regimes affect our business and operations. For example, our research and development efforts may be subject to laws, regulations, and recommendations related to safe working conditions, laboratory practices, use of animals in research and development activities, and the purchase, storage, movement, import, export, and use and disposal of hazardous or potentially hazardous substances. Antitrust and competition laws may restrict our ability to enter into certain agreements involving exclusive license rights. Future legislation and administrative action will continue to affect our business, the extent and degree of which we cannot accurately predict.

Environmental Matters

We are subject to a number of laws and regulations that require compliance with federal, state, and local regulations for the protection of the environment. We believe that our operations comply in all material respects with such applicable laws and regulations. Our compliance with these requirements did not change during the past year, and is not expected to have a material effect upon our capital expenditures, cash flows, earnings, or competitive position.

Human Capital

We are united by our commitment to developing innovative therapies for unmet needs and our dedication to be responsible citizens that have a positive impact on patients, the environment, and society. Our employees, whom we call "**Unitherians**," are mission critical to these commitments because they share the same passion and dedication to meeting our purpose. As of December 31, 2021, we had approximately 965 employees working across our 11 facilities worldwide.

Our people mission focuses on five key commitments, providing Unitherians with:

- Challenging, innovative work
- Opportunities for career advancement
- Autonomy to do their best work
- Inspiring work environment allowing for work/life integration
- Competitive pay and benefits

In 2021, we achieved $1.75 million in revenue per employee, which ranks near the top of our industry peer group. We feel strongly that such industry-leading productivity cannot be maintained without a core focus on our family of Unitherians, and a dedication to ensuring they are healthy and engaged. The Compensation Committee of our Board of Directors (**Board**) oversees our human capital management priorities.

The "Unitherian" Culture. We are intentional in our effort to maintain our entrepreneurial culture. We believe this instills a greater sense of ownership, meaning, and commitment in Unitherians, motivating them to work as hard as possible to achieve our ambitious goals. Moreover, we are confident that our culture provides us with a competitive advantage by enabling us to attract the best talent to drive innovation and excellence in pursuit of our key strategic objectives.

PBC Conversion. In 2021, we converted United Therapeutics into a public benefit corporation, becoming the only company in our industry to do so. As a public benefit corporation, our Board is now obligated to balance the interests of its patient-focused public benefit purpose, the financial interests of shareholders, and the interest of other stakeholders who are materially impacted by our conduct, such as Unitherians. We believe that this conversion has helped further underscore our commitment to Unitherians, and well as our mission-driven public benefit purpose of creating a brighter future for patients.

Recruitment, Retention, and Talent Development. We strive to hire exceptionally smart people who are passionately committed to our goals and who will thrive in our unique culture. We provide Unitherians with a variety of personal and professional development opportunities for them to grow and thrive. We believe that our recruitment and talent development efforts are key factors in our low turnover compared to our industry peer group, which historically has trended well below the industry average. In 2021, we continued that trend with our voluntary turnover at 7.2 percent, well below industry average of 13.6 percent (based on June 1, 2020 through June 1, 2021 data from Aon/Radford's *Turnover Study for the Life Sciences and Medical Devices Sector*, published December 2021).

Diversity and Inclusion. We are proud of our diverse workforce, and we firmly believe that being a great place to work means being diverse and inclusive. Women represent 50 percent of all Unitherians and 36 percent of our workforce identify as members of a racial or ethnic minority. We foster diversity and inclusion in many different ways, including support of Unitherian resource groups and through our Inclusion Advisory Group that provides ongoing input to our DEI Executive Council on diversity, equity, and inclusion strategies and initiatives. In 2021, 100% of Unitherians participated in training, facilitated discussions, and other activities as part of our multi-year, company-wide training initiative to promote and enrich awareness of important diversity, equity, and inclusion topics.

Employee Communication and Engagement. We encourage Unitherians to speak up, and we take action when they identify a concern. We also take steps to promote proactive communication by our management team, including Unitherian recognition, personal updates from leadership, and cross-functional engagement. Our Unitherian engagement initiatives include town hall meetings to connect Unitherians with company management, patient-focused sessions to connect Unitherians to the patient experience, and using Workplace by Facebook to create an Unitherian-only social environment to connect Unitherians across functions. We also regularly conduct broad surveys to solicit the views of Unitherians. Our efforts are borne out in the results of recent Unitherian engagement surveys, which showed that approximately 93 percent of respondents "have a high degree of trust and are likely to be retained."

A Holistic Approach to Total Rewards and Employee Wellness. We require an exceptionally talented workforce. Because Unitherians are key to driving our strategic goals, we provide robust people programs that demonstrate the high value we place on the financial, mental, and physical wellness of Unitherians. Our comprehensive total rewards package includes short- and long-term incentive compensation that enables all of our full-time Unitherians to participate in our financial success. For example, all full-time domestic Unitherians are eligible to receive minimum annual compensation of $75,000, including salary and bonus. We also provide meaningful opportunities for Unitherians to share in our success by making every full-time Unitherian a shareholder through our long-term incentive programs. We offer market-leading benefit programs and provide access to a variety of health and wellness facilities and programs, such as on-site childcare centers and state-of-the-art fitness centers, and access to 24/7 Unitherian assistance programs.

Our COVID-19 Response. Our commitment to the wellness of Unitherians, who are working hard to support a continuous supply of medicines to our patients, has been crucial during the COVID-19 pandemic. Throughout the pandemic, we have maintained consistent contact with Unitherians to help keep them safe and feeling connected. Early in the pandemic we moved quickly to pivot all Unitherians who could work remotely into a work-from-home model and focused on providing the safest possible working environment for those Unitherians who were required to work in our facilities. In spring 2021, we communicated to our workforce our plans for a phased return to working in person well in advance to enable Unitherians to plan accordingly, and we continue to provide flexible options for hybrid work arrangements. As part of our continued effort to ensure the health and safety of our Unitherians, we required all Unitherians to be fully vaccinated before returning to in-person work in September 2021. We are also encouraging Unitherians to receive booster shots as they become eligible to do so. We continue to offer paid time off to Unitherians who need to isolate for COVID-related reasons. We remain committed to ensuring the safest possible work environment and acknowledging Unitherians' contributions during this unprecedented time.

Board Oversight. Our Board, through its Compensation Committee, oversees our human capital management strategies, including our focus on diversity, equity, and inclusion; workplace environment and culture; and talent development and retention. These topics are generally reviewed and discussed at meetings of both the Compensation Committee and of the full Board, at least annually.

Corporate Website

Our Internet website address is *http://www.unither.com*. Our filings on Form 10-K, Form 10-Q, Form 3, Form 4, Form 5, Form 8-K, and any and all amendments thereto are available free of charge through this Internet website as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission (**SEC**). They are also available through the SEC at *http://www.sec.gov/edgar/searchedgar/companysearch.html*.

INFORMATION ABOUT OUR EXECUTIVE OFFICERS

The following is a list, as of February 24, 2022, setting forth certain information regarding our executive officers. Each executive officer holds office until the first meeting of the Board of Directors after the annual meeting of shareholders, and until his or her successor is elected and qualified or until his or her earlier resignation or removal. Each executive officer's employment will end pursuant to the terms of his or her employment contract.

Name	Age	Position
Martine Rothblatt, Ph.D., J.D., M.B.A.	67	Chairperson and Chief Executive Officer
Michael Benkowitz	50	President and Chief Operating Officer
James C. Edgemond	54	Chief Financial Officer and Treasurer
Paul A. Mahon, J.D.	58	Executive Vice President, General Counsel, and Corporate Secretary

Martine Rothblatt, Ph.D., J.D., M.B.A., founded United Therapeutics in 1996 and has served as Chairperson and Chief Executive Officer since its inception. Previously, she created the satellite radio company SiriusXM. She is an inventor or co-inventor on nine U.S. patents, with additional patents pending. Her pioneering book, *Your Life or Mine: How Geoethics Can Resolve the Conflict Between Private and Public Interests in Xenotransplantation*, anticipated the need for both global virus bio-surveillance and a greatly expanded supply of transplantable organs.

Michael Benkowitz joined United Therapeutics in 2011 as our Executive Vice President, Organizational Development, and was promoted to President and Chief Operating Officer in 2016. He is responsible for all of our commercial, medical affairs, and corporate compliance activities, most company-wide administrative functions, including human resources and information technology, many of our business development efforts, and several of our key business alliances and partnerships.

James C. Edgemond joined United Therapeutics in January 2013 as Treasurer and Vice President, Strategic Financial Planning. Mr. Edgemond was promoted to Chief Financial Officer and Treasurer in March 2015. Prior to joining United Therapeutics, he was Vice President, Corporate Controller and Treasurer of Clark Construction Group from 2008 through January 2013. He also served in a variety of roles at The Corporate Executive Board Company from 1998 to 2008, serving as Executive Director, Finance from 2005 to 2008. He began his career as a public accountant at KPMG Peat Marwick LLP, from 1990 through 1998, where he served in a variety of roles, including as a Senior Manager prior to his departure.

Paul A. Mahon, J.D., has served as General Counsel and Corporate Secretary of United Therapeutics since its inception in 1996. In 2001, Mr. Mahon joined United Therapeutics full-time as Senior Vice President, General Counsel, and Corporate Secretary. In 2003, Mr. Mahon was promoted to Executive Vice President, General Counsel, and Corporate Secretary. Prior to 2001, he served United Therapeutics, beginning with its formation in 1996, in his capacity as principal and managing partner of a law firm specializing in technology and media law.

Item 1A. Risk Factors

Risks Related to Our Products and Our Operations

We rely heavily on sales of Tyvaso, Remodulin, and Orenitram to generate revenues and support our operations.

Sales of Tyvaso, Remodulin, and Orenitram comprise the vast majority of our revenues. Substantially decreased sales of any of these products could have a material adverse impact on our operations. A wide variety of events, such as withdrawal of regulatory approvals or substantial changes in prescribing practices or dosing patterns, many of which are described in other risk factors below, could cause sales of these products to materially decline, or to grow more slowly than expected. The current and expected availability of generic versions of our products has decreased and may continue to decrease our revenues. The approval of new therapies, such as Yutrepia, may negatively impact sales of our current and potential new products. Sales may decrease if any third party that manufactures, markets, distributes, or sells our commercial products cannot do so satisfactorily, or we cannot manage our internal manufacturing processes. Finally, if we are not able to successfully launch Tyvaso DPI when we anticipate, or at all, for regulatory or other reasons, or demand for Tyvaso DPI following its launch does not meet our expectations, the revenue opportunity for our treprostinil products could be significantly lower than we expect.

If our products fail in clinical trials, we will be unable to sell those products.

To obtain approvals from the FDA and international regulatory agencies to sell new products, or to expand the product labeling for our existing products, we must conduct clinical trials demonstrating that our products are safe and effective. Regulators have substantial discretion over the approval process. Regulators may require us to amend ongoing trials or perform additional trials, which have in the past and could in the future result in significant delays and additional costs and may be unsuccessful. Delays and costs associated with regulatory requirements to change or add trials may cause us to discontinue efforts to develop a product, as they did with Trevyent and the ISR. If our clinical trials are not successful, or we fail to address identified deficiencies adequately, we will not obtain required approvals to market the new product or new indication. We cannot predict with certainty how long it will take, or how much it will cost, to complete necessary clinical trials or obtain regulatory approvals of our current or future products. The time and cost needed to complete clinical trials and obtain regulatory approvals varies by product, indication, and country. In addition, failure to obtain, or delays in obtaining, regulatory approval has in the past and could in the future require us to recognize impairment charges.

Our clinical trials have in the past and may in the future be discontinued, delayed, canceled, or disqualified for various reasons, including: (1) the COVID-19 pandemic, which initially caused us to suspend enrollment of most of our clinical studies, and may do so again; (2) the drug is ineffective, or physicians and/or patients believe that the drug is ineffective, or that other therapies are more effective or convenient; (3) patients do not enroll in or complete clinical trials at the rate we expect; (4) clinical trial sites or third parties do not adhere to trial protocols and required quality controls under good clinical practices (**GCP**) regulations and similar regulations outside the United States; (5) patients experience severe side effects during treatment or die during our trials because of adverse events; and (6) the results of clinical trials conducted in a particular country are not acceptable to regulators in other countries.

We may not compete successfully with established or newly developed drugs or products.

Competition could negatively impact our operating results. We compete with well-established drug companies for market share, as well as, among other things, funding, licenses, expertise, personnel, clinical trial patients and investigators, consultants, and third-party collaborators. Many of these competitors have substantially greater financial, marketing, manufacturing, sales, distribution, and technical resources, and a larger number of approved products, than we do. Many of these competitors also possess greater experience in areas critical to success such as research and development, clinical trials, sales and marketing, and regulatory matters.

Numerous treatments currently compete with our commercial therapies. For example, for treatment of PAH, we compete with over fifteen branded and generic drugs. Sales of a generic version of Adcirca launched in August 2018 have had a material adverse impact on our sales of Adcirca. The availability of generic versions of Remodulin in the United States could materially impact our revenues, and generic competition has materially impacted our Remodulin revenues outside the United States. Our competitors are also developing new products that may compete with ours. For example, Liquidia is developing Yutrepia, which if successful would compete directly with Tyvaso, Tyvaso DPI (if approved), and our other treprostinil-based products.

Patients and doctors may discontinue use of our products if they perceive competing products as safer, more effective, less invasive, more convenient, and/or less expensive than ours. Doctors may reduce the prescribed doses of our products if they prescribe them in combination with competing products. In addition, many competing therapies are less invasive or more convenient than our products, and use of these competing therapies often delays or prevents initiation of our therapies.

The successful commercialization of our products depends on the availability of coverage and adequacy of reimbursement from third-party payers, including governmental authorities and private health insurers. Pharmaceutical pricing and reimbursement pressures may negatively impact our sales.

The commercial success of our products depends, in significant part, on coverage by governmental payers such as Medicare and Medicaid, and private insurance companies. A reduction in the availability or extent of reimbursement from domestic or foreign government health care programs could have a material adverse effect on our business and results of our operations. Government payers and/or third-party payers are increasingly attempting to limit the price of medicinal products and frequently challenge the pricing of new or expensive drugs. In many markets outside the United States, governments control the prices of prescription pharmaceuticals through the implementation of reference pricing, price cuts, rebates, revenue-related taxes, and profit control. Financial pressures may cause United States government payers and/or private health insurers to implement policies that would reduce reimbursement rates for our products, limit future price increases, cap reimbursement rates for pharmaceuticals to rates paid internationally, require the automatic substitution of generic products, demand more rigorous requirements for initial coverage for new products, implement step therapy policies that require patients to try other medicines, including generic products, before using our products, or take other similar steps that could make it more difficult for patients to access our products.

Our prostacyclin analogue products (Tyvaso, Remodulin, and Orenitram) and our oncology product (Unituxin) are expensive therapies. Our specialty pharmacy distributors may not be able to obtain adequate reimbursement for our products from commercial and government payers to motivate them to support our products. Third-party payers may reduce the amount of reimbursement for our products based on changes in pricing of other therapies for the same disease or the development of new payment methodologies to cover and reimburse treatment costs, such as the use of cost-effectiveness research or value-based payment contracts. Third-party payers often encourage the use of less-expensive generic alternative therapies, which has materially impacted our Adcirca revenues and which may materially impact our Remodulin revenues. If commercial and/or government payers do not cover our products or limit payment rates, patients and physicians could choose covered competing products and may have lower out-of-pocket costs.

Our manufacturing strategy exposes us to significant risks.

We must be able to manufacture sufficient quantities of our commercial products to satisfy demand. We manufacture Remodulin, Orenitram, Tyvaso, and Unituxin, including the active ingredient in each of these products, at our own facilities and rely on third parties for additional manufacturing capacity for Remodulin and Tyvaso. We rely on a variety of third-party sole manufacturers for certain elements of our commercial and development-stage products, as detailed under the risk factor below entitled, *We rely in part on third parties to perform activities that are critical to our business.* If any of our internal or third-party manufacturing and supply arrangements are interrupted for compliance issues, issues related to the COVID-19 pandemic, or other reasons, we may not have sufficient inventory to meet future demand. Changes in suppliers and/or service providers could interrupt the manufacturing of our commercial products and impede the progress of our commercial launch plans and clinical trials.

Our internal manufacturing process subjects us to risks as we engage in increasingly complex manufacturing processes. We manufacture our entire supply of Orenitram and Unituxin without an FDA-approved back-up manufacturing site, and do not plan to engage a third party to manufacture these materials. Our long-term organ manufacturing programs will involve exceptionally complicated manufacturing processes, many of which have never been attempted on a clinical or commercial scale. It will take substantial time and resources to develop and implement such manufacturing processes, and we may never be able to do so successfully. Additional risks of our manufacturing strategy include the following:

- We, our third-party manufacturers, and other third parties involved in the manufacturing process, such as third parties that operate testing and storage facilities, are subject to the FDA's current good manufacturing practices regulations, current good tissue practices, and similar international regulatory standards, and other quality standards related to device manufacturing. Our ability to exercise control over regulatory compliance by our third-party manufacturers is limited.
- We may experience difficulty designing and implementing processes and procedures to ensure compliance with applicable regulations as we develop manufacturing operations for new products.
- Natural and man-made disasters (such as fires, contamination, power loss, hurricanes, earthquakes, flooding, terrorist attacks, and acts of war), disease outbreaks, and pandemics such as COVID-19 impacting our internal and third-party manufacturing sites could cause a supply disruption.
- Even if we, our third-party manufacturers, and other third parties involved in the manufacturing process comply with applicable drug and device manufacturing regulations, the sterility and quality of our products could be substandard and such products could not be sold or used or could be subject to recalls.
- The FDA and its international counterparts would require new testing and compliance inspections of new manufacturers of our products, or new manufacturing facilities we operate.
- The FDA and other regulatory agencies may not be able to timely inspect our facilities, or those of our third-party manufacturers, due to COVID-19-related delays or other reasons, which could result in delays in obtaining necessary regulatory approvals for our products.
- We may be unable to contract with needed manufacturers on satisfactory terms or at all.

- The supply of materials and components necessary to manufacture and package our products may become scarce or unavailable, which could delay the manufacturing and subsequent sale of such products. Products manufactured with substituted materials or components must be approved by the FDA and applicable international regulatory agencies before they could be sold.
- Our business partners who manufacture the devices to deliver our products are subject to the FDA's medical device requirements. Any non-compliance, recall, or enforcement action issued against them could adversely impact our sales and operations.
- The infrastructure of our internal manufacturing facilities, along with certain facilities of our third-party manufacturers, is aging. These facilities have highly sophisticated and complex utility systems. If any of these systems requires long-term repair or replacement, the impacted facility may not be able to manufacture product for a substantial period of time.
- We, along with our third-party manufacturers, rely upon local municipalities to supply our facilities with clean water, which is processed into high purity water and used as a key ingredient for three of our commercial drug products. If local municipalities are unable to supply water that meets relevant quality standards, we and our third-party manufacturers may be unable to manufacture product until such a situation is remediated.
- Our supply chain for raw materials and consumables extends worldwide and is complex. Suppliers based in China play a substantial role in our supply chain. Political unrest or trade disputes involving China or other countries in our supply chain could impact our ability and the ability of our third-manufacturers to source raw materials and consumables.

Any of these factors could disrupt sales of our commercial products, delay clinical trials or commercialization of new products, result in product liability claims and product recalls, and entail higher costs. Interruptions in our manufacturing process could be significant given the length of time and complexity involved in obtaining necessary regulatory approvals for alternative arrangements, through either third parties or internal manufacturing processes.

We face risks and uncertainties related to the COVID-19 pandemic, which could significantly disrupt our operations and/or business for an unknown period of time.

Our business, operations, financial results, liquidity, and stock price could be adversely impacted by the effects of the global COVID-19 pandemic. The extent of such impact, including the duration and magnitude of such effects, will depend on numerous evolving factors that we cannot currently accurately predict or assess, including, among others: the duration and scope of the pandemic, including the emergence of new strains, such as the "Delta", "Omicron", and future variants; its impact on global and regional healthcare infrastructure, and the ability of patients to obtain medical care; the negative impact on global and regional economies and economic activity; actions governments, businesses, and individuals take in response to the pandemic; the roll-out and long-term safety and efficacy of vaccines; and how quickly economies and medical systems recover after the pandemic subsides. Our business could be materially adversely affected as a result of the COVID-19 pandemic due to social distancing/self-isolation, the burden the pandemic has placed on healthcare infrastructure, workplace and physician office closures, travel disruptions, quarantines, and other factors, which could cause, among other things:

- ***Interruption of our development pipeline.*** Approvals of new products we are developing, potential label expansions for existing products, and the launch of newly-approved products may be delayed or hindered, which would harm our revenue growth prospects. For example, pandemic-related supply issues delayed our launch of the Remunity Pump. In addition, enrollment in many of our clinical trials was suspended as a result of the onset of the pandemic. Although enrollment in these studies has resumed, we may experience further delays or difficulties, including delays or difficulties with clinical site initiation and recruiting clinical site investigators and clinical site staff. Our clinical trials, including the integrity and completeness of subject data and clinical study endpoints, may also be impacted or delayed by: (1) diversion of healthcare resources away from the conduct of clinical trials due to changes in hospital or research institution policies, governmental regulations, prioritization of hospital and other medical resources toward efforts to cope with the pandemic, or other reasons related to the pandemic; (2) interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by governments, employers, and others, or other interruption of clinical trial participant visits and study procedures; or (3) any supply interruptions of our investigational drug candidates or other study materials due to staffing shortages, production slowdowns, or stoppages and disruptions in distribution systems. In addition, our pipeline may be delayed by interruption or delays in the operations of the FDA or other regulatory authorities, which are extremely busy responding to the COVID-19 pandemic. Any prolongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development and study of our new products and label expansions.
- ***A decrease in revenues from our existing products.*** COVID-19 made it difficult or impossible for many patients to visit their physicians' offices to determine whether our medicines may be appropriate. As a result, in April 2020 we experienced a temporary decline in the number of new patients starting our treprostinil-based medicines. While new patient starts have returned to pre-pandemic levels, a decline could recur as the COVID-19 pandemic continues or if the pandemic causes access to medical care to become further restricted, which could cause a negative impact on our revenues. The potential inability of patients to visit their physicians' offices or receive required diagnostic testing to ensure reimbursement for our therapies or any inability of specialty pharmacy nurses to visit patients as appropriate to provide training and assistance with the use of our therapies, may also cause existing patients to stop using our medicines or prevent new patients from starting to use our medicines. In addition, virtual meetings by our commercial field-based teams with prescribing physicians may not be as effective as in-person meetings, which may negatively impact how often physicians prescribe our medicines. Any disruption of our supply chain caused by COVID-19 could also negatively impact our revenues.

- ***Disruption of our operations.*** COVID-19 could disrupt many aspects of our operations, which could harm our business and prospects. Although we implemented a mandatory vaccine requirement in September 2021 for all staff, subject to certain medical and religious exemptions, we continue to maintain a flexible work-from-home policy for all personnel excluding those necessary to maintain minimum basic operations. Our reliance on personnel working from home may negatively impact productivity, or disrupt, delay, or otherwise adversely impact our business. Working remotely may also increase our cybersecurity risk, create data accessibility concerns, and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with local and federal regulators, manufacturing sites, clinical trial sites, and other third parties. Further, we, and third parties with which we engage to conduct distribution, production, and research and development activities, may experience limitations on the ability to recruit and hire key personnel due to the inability to meet with candidates because of travel restrictions and "shelter-in-place" orders. We and third parties with which we engage also may experience operational challenges caused by sickness of employees or their families, the desire of employees to avoid contact with large groups of people, or employees working from home. Mass vaccine production and distribution efforts (such as Operation Warp Speed), as well as backlogs at major ports of entry, have impacted availability and lead times for certain materials used in the manufacture of our products. If we, or our third-party suppliers and contract manufacturers, are unable to source materials, it may prevent us from manufacturing our products for an indefinite period until such materials become available.

COVID-19, and the volatile regional and global economic conditions stemming from the pandemic, could also precipitate or aggravate the other risk factors discussed in this Report, which could materially adversely affect our business, financial condition, results of operations, liquidity, and stock price. Further, the COVID-19 pandemic, or any future outbreak of disease, may also affect our operating and financial results in a manner that is not presently known to us or that we currently do not consider to present significant risks. The possible extent of the impact of the COVID-19 pandemic is inherently difficult to predict and will ultimately depend on a number of factors outside our control, including the ultimate duration and severity of the pandemic and the resulting economic impact.

We rely in part on third parties to perform activities that are critical to our business.

Third parties assist us in activities critical to our operations, such as: (1) manufacturing our clinical and commercial products; (2) conducting clinical trials, preclinical studies, and other research and development activities; (3) obtaining regulatory approvals; (4) conducting pharmacovigilance-related and product complaint activities, including drug safety, reporting adverse events, and product complaints; (5) obtaining medical device clearances and approvals for the devices used to deliver our drugs; and (6) marketing and distributing our products. Any disruption in the ability of third parties to continue to perform these critical activities, including as a result of the COVID-19 pandemic, could materially adversely impact our business and results of operations. Any change in service providers could interrupt the manufacture and distribution of our products and services, and impede the progress of our clinical trials, commercial launch plans, and related revenues.

We rely on various distributors to market, distribute, and sell Tyvaso, Remodulin, Orenitram, and Unituxin. If they are unsuccessful in, or reduce or discontinue, their sales efforts, our revenues may decline materially. Outside the United States, we rely substantially on our international distributors to obtain and maintain regulatory approvals for our products and to market and sell our products in compliance with applicable laws and regulations. In the United States, we derive all of our treprostinil revenues from sales to two distributors, Accredo and CVS Specialty. If either of these two distributors places significantly larger or smaller orders in a given time period, our revenues can be materially impacted in a way that does not reflect patient demand.

Lilly manufactures and supplies Adcirca for us. We use Lilly's pharmaceutical wholesaler network to distribute Adcirca. If Lilly is unable to manufacture or supply Adcirca or its distribution network is disrupted, it could delay, disrupt, or prevent us from selling Adcirca. We rely entirely on third parties to supply pumps and other supplies necessary to deliver Remodulin. There are a limited number of pumps available in the market, and the discontinuation of any particular pump could have a material, adverse impact on our Remodulin revenues if a viable supply of an alternate pump is not available. We rely entirely on Minnetronix Inc. as the sole manufacturer of the Tyvaso Inhalation System. As Tyvaso is a drug-device combination, we cannot sell Tyvaso without the Tyvaso Inhalation System.

We rely heavily on MannKind and other third parties to manufacture, test, and store Tyvaso DPI, and to meet all FDA requirements related to the manufacture of Tyvaso DPI. This includes maintaining an FDA-compliant facility and addressing any FDA concerns regarding the manufacturing process. If MannKind is unable to manufacture Tyvaso DPI for us for any reason, our commercial sales of Tyvaso DPI (if approved by the FDA) could be materially and adversely impacted.

We rely heavily on DEKA and its affiliates for the development, manufacturing, and regulatory approval of the Remunity Pump for Remodulin. Supply disruptions caused by COVID-19 impacted DEKA's ability to secure certain components and raw materials necessary to manufacture sufficient quantities of Remunity Pumps and accessories, delaying our ability to commence commercial sales. Finally, we also rely on various sole-source suppliers for manufacturing activities related to ralinepag, RemoPro, and other pumps we are developing for Remodulin. For a further discussion of risks created by the use of third-party contract manufacturers, see the risk factor above entitled, *Our manufacturing strategy exposes us to significant risks*.

We rely heavily on third-party contract research organizations, contract laboratories, clinical investigative sites, and other third parties to conduct our clinical trials, preclinical studies and other research and development activities. In addition, the success of certain products we are developing will depend on clinical trials sponsored by third parties. Third-party failure to conduct or assist us in conducting clinical trials in accordance with study protocols, quality controls, GCP, or other applicable requirements

or to submit associated regulatory filings, could limit or prevent our ability to rely on results of those trials in seeking regulatory approvals.

Reports of actual or perceived side effects and adverse events associated with our products could cause our sales to decrease.

Reports of side effects and adverse events associated with our products could affect a physician's decision to prescribe or a patient's willingness to use our products, which may have a significant adverse impact on sales of our products. An example of a known risk associated with the delivery system used for intravenous Remodulin is sepsis, which is a serious and potentially life-threatening infection of the bloodstream caused by a wide variety of bacteria. In addition, Unituxin is associated with severe side effects, and its label contains a boxed warning related to potential infusion reactions and neurotoxicity. We are required to report certain adverse events to the FDA. Development of new products, and new formulations and indications for existing products, could result in new side effects and adverse events which may be serious in nature.

Negative attention from special interest groups may impair our business.

Our early-stage research and development involves animal testing required by regulatory authorities, which we conduct both directly and through contracts with third parties. Our xenotransplantation and regenerative medicine programs rely heavily on the use of animals to manufacture and test our products. Certain special interest groups categorically object to the use of animals for research purposes. Any negative attention, threats or acts of vandalism directed against our animal research activities could impede the operation of our business.

We may not maintain adequate insurance coverage to protect us against significant product liability claims.

The testing, manufacturing, marketing, and sale of drugs and diagnostics involve product liability risks. We may not be able to maintain our current product liability insurance at an acceptable cost, if at all. In addition, our insurance coverage may not be adequate for all potential claims. If losses significantly exceed our liability insurance coverage, we may experience financial hardship or potentially be forced out of business. Clinical testing and eventual marketing and sale of new products, reformulated versions of existing products, or use of existing products in new indications could expose us to new product liability risks that are not covered by our existing policies.

If we fail to attract and retain key management and qualified scientific and technical personnel, we may not be able to achieve our business objectives.

Members of our management team, including our founder, Chairperson and Chief Executive Officer, Dr. Martine Rothblatt, play a critical role in defining our business strategy and maintaining our corporate culture. The loss of the services and leadership of Dr. Rothblatt or any other members of our senior management team could have an adverse effect on our business. We do not maintain key person life insurance on our senior management team members. Failure to identify, hire, and retain suitable successors for members of our senior management team and to transfer knowledge effectively could impede the achievement of our business objectives. Our future success also depends on our ability to attract and retain qualified scientific and technical personnel. Competition for such personnel in our industries is intense. If we fail to attract and retain such Unitherians, we may not be successful in developing and commercializing new therapies for PAH and other diseases.

Risks Related to Legal Compliance

We must comply with extensive laws and regulations in the United States and other countries. Failure to obtain approvals on a timely basis or to comply with these requirements could delay, disrupt, or prevent commercialization of our products.

The products we develop must be approved for marketing and sale by regulatory agencies. Our research and development efforts must comply with extensive regulations, including those promulgated by the FDA and the U.S. Department of Agriculture. The process of obtaining and maintaining regulatory approvals for new drugs is lengthy, expensive, and uncertain. The regulatory approval process is particularly uncertain for our transplantation programs, which include the development of xenotransplantation, regenerative medicine, 3-D organ bioprinting, and cell-based products. Once approved, the manufacture, distribution, advertising, and marketing of our products are subject to extensive regulation, including product labeling, strict pharmacovigilance and adverse event and medical device reporting, complaint processing, storage, distribution, and record-keeping requirements. Our product candidates have in the past and may in the future fail to receive regulatory approval. If granted, product approvals can be conditioned on the completion of post-marketing clinical studies, accompanied by significant restrictions on the use or marketing of a given product and withdrawn for failure to comply with regulatory requirements, such as post-marketing requirements and post-marketing commitments, or upon the occurrence of adverse events subsequent to commercial introduction. Our ability to obtain FDA approval for our products has been, and in the future may be, materially impacted by the outcome and quality of our clinical trials and other data submitted to regulators, as well as the quality of our manufacturing operations and those of our third-party contract manufacturers and contract laboratories. In addition, third parties may submit citizen petitions to the FDA seeking to delay approval of, or impose additional approval conditions for, our products. If successful, citizen petitions can significantly delay, or even prevent, the approval of our products. For example, a third party submitted a citizen petition to the FDA requesting that the FDA refuse to approve Tyvaso DPI, and/or impose additional requirements in order to approve the product. This has prompted the FDA to request additional information concerning Tyvaso DPI, and to delay the anticipated review deadline for the Tyvaso DPI NDA from February 2022 to May 2022.

Regulatory approval for our currently marketed products is limited by the FDA and other regulators to those specific indications and conditions for which clinical safety and efficacy have been demonstrated.

Any regulatory approval of our products is limited to specific diseases and indications for which our products have been deemed safe and effective by the FDA. FDA approval is also required for new formulations and new indications for an approved product. While physicians may prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those approved by regulatory authorities (called "off-label" uses), our ability to promote our products is limited to those indications that are specifically approved by the FDA. Failure to follow FDA rules and guidelines related to promotion and advertising can result in the FDA's refusal to approve a product, suspension or withdrawal of an approved product from the market, product recalls, enforcement action, civil lawsuits, or criminal prosecution.

We must comply with various laws in jurisdictions around the world that restrict certain marketing practices.

Our business activities may be subject to challenge under laws in jurisdictions around the world restricting particular marketing practices, such as:

- Anti-kickback and false claim statutes, the Foreign Corrupt Practices Act, and the United Kingdom Bribery Act. In the United States, the Federal Anti-Kickback Statute prohibits, among other activities, knowingly and willfully offering, paying, soliciting, or receiving remuneration (i.e., anything of value) to induce, or in return for, the purchase, lease, order or arranging the purchase, lease or order of any health care product or service reimbursable under any federally financed healthcare program like Medicare or Medicaid. This statute is interpreted broadly to apply to arrangements between pharmaceutical manufacturers and prescribers, purchasers, specialty pharmacies, formulary managers, patients, and others. Our practices may not always qualify for safe harbor protection under this statute.
- The Federal False Claims Act, which prohibits any person from knowingly presenting or causing to be presented a false or fraudulent claim for payment of government funds, or making or causing a false statement material to a false or fraudulent claim. Pharmaceutical and health care companies have faced liability under this law for causing false claims to be submitted because they marketed a product for unapproved and non-reimbursable uses.
- Analogous state laws and regulations, including anti-kickback and false claims laws, which apply to items and services reimbursed under Medicaid or, in several states, regardless of the payer, including private payers.

Compliance with these and similar laws on a state-by-state basis is difficult, time consuming, and requires substantial resources. Any investigation, inquiry, or other legal proceeding under these laws related to our operations, even if we successfully defend against it, or any penalties imposed upon us for failure to comply, could have a material adverse effect on our business and financial condition or reputation. Sanctions under these federal and state laws may include treble civil monetary penalties, payment of damages, fines, exclusion of our products from reimbursement under federal health care programs, imprisonment, and the curtailment or restructuring of our operations.

Government healthcare reform and other reforms could adversely affect our revenue, costs, and results of operations.

Our industry is highly regulated and changes in law or government health care programs may adversely impact our business, operations, or financial results. We cannot predict how future federal or state legislative or administrative changes related to healthcare reform will affect our business.

Political, economic, and regulatory influences may lead to fundamental changes in the U.S. healthcare industry, particularly given the current atmosphere of mounting criticism of prescription drug costs in the U.S. We expect there will continue to be legislative and regulatory proposals to change the healthcare system in ways that could impact our ability to commercialize and to sell our products profitably. For example, we anticipate that the Biden Administration, U.S. Congress, state legislatures, and regulators may adopt or accelerate adoption of new healthcare policies and reforms intended to curb healthcare costs, such as federal and state controls on government-funded reimbursement for drugs (including in Medicare and Medicaid), new or enhanced requirements to pay prescription drug rebates and penalties to government healthcare programs, and additional pharmaceutical cost transparency measures that aim to require drug companies to justify their prices through required disclosures.

At the federal level, there have been and continue to be a number of healthcare-related legislative and regulatory initiatives and reforms that significantly affect the pharmaceutical industry. For example, PPACA substantially changed the way healthcare is financed by both governmental and commercial payers, and has significantly impacted the U.S. pharmaceutical industry. The PPACA is a broad measure intended to expand healthcare coverage within the United States, primarily through the imposition of health coverage-related mandates on employers and individuals and expansion of the Medicaid program. The PPACA and certain of its provisions have been subject to judicial challenges as well as efforts to repeal or replace them or to alter their interpretation or implementation. It is unclear how the PPACA and its implementation, as well as efforts to repeal, replace, or otherwise modify, or invalidate, the PPACA, or portions thereof, will affect our business.

Additionally, there has been increasing legislative, regulatory, and enforcement interest in the United States regarding drug pricing practices. Among other things, there have been several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things: bring more transparency to drug pricing; reduce the cost of prescription drugs under government payer programs; review the relationship between pricing and manufacturer patient programs; and reform government program reimbursement methodologies for drugs. For example, on November 20, 2020, CMS issued the

Most Favored Nation demonstration project discussed above, and there is also proposed legislation pending that would establish an international reference price-based Medicare Part B drug and biological payment methodology.

Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement limitations, marketing cost disclosure, and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs.

We anticipate that the PPACA and other healthcare reform measures that may be adopted in the future may result in additional downward pressure on coverage and the payment that we receive for any approved product, and adversely impact our business. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payment from commercial payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Further state and federal healthcare reform measures adopted in the future could limit the amounts that state and federal governments will pay for healthcare products and services, which could result in reduced demand for our products or additional pricing pressure. In October 2020, the U.S. Department of Health and Human Services (**HHS**) and the FDA issued a final rule and guidance concerning two new pathways for importing lower-cost drugs into the United States. The final rule allows certain prescription drugs to be imported from Canada, and the guidance describes procedures for drug manufacturers to facilitate the importation of FDA-approved drugs and biologics manufactured abroad and originally intended for sale in a foreign country into the United States. Additionally, in November 2020, the HHS adopted a rule that will eliminate the safe harbor shielding Medicare Part D rebates to pharmacy benefit managers from the Anti-Kickback Statute. In response to a legal challenge brought by a trade association representing PBMs, the Biden Administration agreed to delay the effective date of the rule until January 1, 2023. It is difficult to predict the impact, if any, of any such legislation or executive actions on the use of and reimbursement for our products in the United States, including the potential for the importation of generic versions of our products.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions, and fines, which could adversely impact our business, financial condition, results of operations, and prospects.

We participate in, and have certain price reporting obligations to, the Medicaid Drug Rebate program and other governmental programs that require us to pay rebates or offer discounts on our products. Certain programs, such as the 340B program and the VA FSS pricing program, impose limits on the price we are permitted to charge certain entities for our products or for any future products for which we receive regulatory approval. Statutory and regulatory changes regarding these programs and their requirements could negatively affect the coverage and reimbursement by these programs of our products or any future products for which we receive regulatory approval and could negatively impact our results of operations. Our failure to comply with these price reporting, rebate payment, or pricing requirements could adversely impact our financial results. Applicable laws and regulations, including the PPACA, and regulations promulgated thereunder, could affect our obligations in ways we cannot anticipate.

Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by us, governmental or regulatory agencies, and the courts. If we must restate or recalculate information provided under these programs, our costs of compliance could increase. Additionally, we could be held liable for errors associated with our submission of pricing data, including retroactive rebates and program refunds. We may incur significant civil monetary penalties if we are found to have knowingly submitted false average manufacturer price or best price information to the government, to have made a misrepresentation in our reporting of ASP figures, to have knowingly provided false information in connection with a Non-FAMP filing, or to have charged 340B covered entities more than the statutorily mandated ceiling price. Certain failures to timely submit required data also could result in a civil monetary penalty for each day the information is late. We could also become subject to allegations under the False Claims Act and other laws and regulations. In addition, misreporting and failure to timely report data to CMS also can be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid Drug Rebate program. In the event that CMS terminates our rebate agreement, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs.

CMS, the VA, and the Office of Inspector General of the Department of Health and Human Services (**OIG**) have pursued manufacturers that were alleged to have failed to report data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot guarantee that our submissions will not be found by CMS, the VA, or other governmental agencies to be incomplete or incorrect.

We may be subject to enforcement action or penalties based on our current policy regarding the distribution of 340B program drugs at 340B ceiling prices through third-party pharmacies that contract with covered entities participating in the 340B program, known as “340B contract pharmacies”. Increasing use of 340B contract pharmacies, coupled with a lack of oversight and transparency, has resulted in increased risks of 340B statutory violations related to the diversion of 340B-purchased drugs to individuals who are not patients of the 340B covered entity, and to prohibited “duplicate discounts” when 340B-purchased drugs are also billed to Medicaid. These program integrity risks have been exacerbated by the exponential growth in the use of 340B contract pharmacies over the past decade. We adopted a new 340B contract pharmacy policy to address these risks by limiting shipments to 340B contract pharmacies that meet certain criteria. Our new contract pharmacy policy is intended to

preserve patient access, while addressing compliance and integrity concerns resulting from the proliferation of contract pharmacies — problems that overshadow and threaten to undermine this vital safety net program. Nonetheless, certain 340B covered entities and the HHS, in a non-binding (and now-retracted) Advisory Opinion, stated that, in their view, manufacturers in the 340B program are obligated to sell 340B drugs at the 340B ceiling prices to all contract pharmacies acting as agents of a covered entity.

We and certain other manufacturers initiated litigation challenging the Advisory Opinion and HRSA's position on contract pharmacies generally. HRSA subsequently withdrew the Advisory Opinion, but issued letters to manufacturers, including us, threatening enforcement action if the manufacturers do not abandon their 340B contract pharmacy policies. We filed suit against HHS and HRSA on June 23, 2021 in the U.S. District Court for the District of Columbia. On September 22, 2021, HRSA sent to us, along with the other manufacturers challenging HRSA's 340B interpretation, letters stating that HRSA is referring "this issue to the HHS Office of the Inspector General (**OIG**)" for potential enforcement action. We have not had any communication from OIG regarding our 340B contract pharmacy policy. On November 5, 2021, the court granted our motion for summary judgment, ruling that the letters threatening enforcement action "contain legal reasoning that rests upon an erroneous reading of Section 340B." HRSA filed a notice of appeal on December 28, 2021, and the appeal is pending. If HRSA prevails on appeal or develops a new theory of liability, we may face enforcement action or penalties as well as adverse publicity. We expect the compliance of policies like ours will continue to be litigated.

If we and other manufacturers are unable to curb the proliferation of abuses caused by 340B contract pharmacies, we could see an increased prevalence of sales at reduced 340B ceiling prices, which could have a material adverse impact on our revenues.

Patient assistance programs for pharmaceutical products have come under increasing scrutiny by governments, legislative bodies, and enforcement agencies. These activities may result in actions that effectively reduce prices or demand for our products, harm our business or reputation, or subject us to fines or penalties.

Company-sponsored patient assistance programs, including insurance premium and co-pay assistance programs and manufacturers' donations to third-party charities that provide such assistance, are subject to heightened scrutiny. The Department of Justice (**DOJ**) has taken enforcement action against pharmaceutical companies alleging violations of the Federal False Claims Act and other laws in connection with patient assistance programs. In December 2017, we entered into a civil Settlement Agreement with the U.S. Government to resolve a DOJ investigation of our support of non-profit patient assistance programs and paid $210.0 million, plus interest, to the U.S. Government upon settlement. We also entered into a Corporate Integrity Agreement (the **CIA**) with the OIG, which requires us to maintain our corporate compliance program and to undertake a set of defined corporate integrity obligations for five years.

We may be required to incur significant future costs to comply with the CIA. If we fail to comply with applicable regulatory requirements or the CIA, or if our vendors or donation recipients fail to comply with applicable requirements or guidance, we could be subject to penalties including fines, suspension of regulatory approvals that cause us to suspend production, distribution or marketing activities, product recalls, seizure of our products, criminal prosecution, exclusion from participation in government healthcare programs, including Medicare and Medicaid, and burdensome remediation measures. Any of these penalties could adversely affect our operating results, the value of our company and our reputation. Patients and physicians may avoid using our products even after we have resolved the issues that led to adverse regulatory action.

Members of Congress have called upon the OIG to issue revised guidance about patient assistance programs. Actions taken by the OIG, the DOJ or other agencies as a result of this industry-wide inquiry could reduce demand for our products and/or coverage of our products by federal and state health care. If any or all of these events occur, our business, prospects, and stock price could be materially and adversely affected.

Payers and PBMs have developed mechanisms to limit the benefits of co-pay assistance for commercially insured programs through co-pay accumulator programs. These programs do not allow a patient using co-pay assistance to count the manufacturer's co-payment contribution toward their annual out-of-pocket payment maximum. Therefore, patients using co-pay assistance are penalized financially for using these programs. Some states have passed legislation to limit the use of co-pay accumulator programs, while some other states have indicated that these programs should be allowed to limit cost of care and encourage patients to use lower cost generics. In addition, some states have imposed restrictions on manufacturer co-pay programs when therapeutic equivalents are available. Growing use of such programs, or new laws limiting manufacturer ability to provide co-pay assistance, could affect patient access to our products and limit product utilization, which may, in turn, adversely affect our business, prospects, and stock price.

Improper handling of hazardous materials used in our activities could expose us to significant remediation liabilities.

Our research and development and manufacturing activities involve the controlled use of chemicals and hazardous substances. We are expanding these activities in both scale and location. Patients may dispose of our products using means we do not control. Such activities subject us to numerous federal, state, and local environmental and safety laws and regulations that govern the management, storage, and disposal of hazardous materials. Compliance with current and future environmental laws and regulations can require significant costs. The risk of accidental contamination or injury from these materials cannot be completely eliminated. Once chemical and hazardous materials leave our facilities, we cannot control the manner in which such hazardous waste is disposed of by our contractors. We could be liable for substantial civil damages or costs associated with the cleanup of the release of hazardous materials and such liability could have a material adverse effect on our business.

The increasing use of social media platforms presents new risks and challenges.

Social media is increasingly being used to communicate information about our products and the diseases that our therapies are designed to treat. Social media practices in our industry continue to evolve and regulations related to such use are not always clear. This evolution creates uncertainty and risk of noncompliance. For example, patients and others may use social media channels to comment on the effectiveness of a product or to report an alleged adverse event. When such disclosures occur, we may fail to monitor and comply with applicable adverse event reporting obligations or we may not be able to defend against political and market pressures generated by social media due to restrictions on what we may say about our products. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate comments about us on any social networking website. If any of these events occur or we otherwise fail to comply with applicable regulations, we could incur liability, face overly restrictive regulatory actions, or incur other harm to our business.

Risks Related to Our Intellectual Property and Data Privacy

If any of the agreements under which we license or acquired intellectual property rights are breached or terminated, we could lose our rights to continue to develop, manufacture, and sell the products covered by such agreements.

Our business depends upon our continuing ability to exploit our intellectual property rights acquired from third parties under product license and purchase agreements covering drugs or other products or technology. We may be required to license additional intellectual property owned by third parties to continue to develop and commercialize our products. This dependence on intellectual property developed by others involves the following risks:

- We may be unable to obtain rights to intellectual property that we need for our business at a reasonable cost or at all;
- If any of our product licenses or purchase agreements are terminated, we may lose our rights to develop, make, and sell the products to which such licenses or agreements relate;
- Our rights to develop and market products to which the intellectual property relates are frequently limited to specific territories and fields of use (such as treatment of particular diseases); and
- If a licensor of intellectual property fails to maintain the intellectual property licensed, we may lose any ability to prevent others from developing or marketing similar products covered by such intellectual property. In addition, we may be forced to incur substantial costs to maintain the intellectual property ourselves or take legal action seeking to force the licensor to do so.

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 profits.

The period under which our commercial and developmental therapies are protected by our patent rights is limited. Three of our U.S. patents covering our current methods of synthesizing and producing treprostinil, the active ingredient in Tyvaso, Tyvaso DPI, Remodulin, and Orenitram, expired in October 2017, and three more will expire in 2028. Our patents related to our individual treprostinil-based products expire at various times between 2024 and 2031. We entered into settlement agreements with a number of generic drug companies permitting certain companies to launch generic versions of Remodulin in the United States and other companies to launch generic versions of Orenitram and Tyvaso in the United States. A U.S. patent for Adcirca for treatment of pulmonary hypertension expired in November 2017, and FDA-conferred regulatory exclusivity expired in May 2018, leading to the launch of a generic version of Adcirca in August 2018. We have no issued patents or pending patent applications covering Unituxin. For further details, please see *Part I, Item 1.—Business—Patents and Other Proprietary Rights, Strategic Licenses, and Market Exclusivity—Generic Competition and Challenges to our Intellectual Property Rights.*

We cannot be sure that our existing or any new patents will effectively deter or delay competitors' efforts to bring new products to market, or that additional patent applications will result in new patents. When our patents expire, competitors may develop generic versions of our products and market them at a lower price to compete with our products. Competitors may also seek to design around our patents or exclude patented methods of treatment, such as patent-protected indications, from the label for generic versions of our products in an effort to develop competing products that do not infringe our patents. In addition, patent laws of foreign jurisdictions may not protect our patent rights to the same extent as the patent laws of the United States.

Third parties have challenged, and may in the future challenge, the validity of our patents, through patent litigation and/or initiating proceedings, including re-examinations, IPRs, post-grant reviews, and interference proceedings, before the USPTO or other applicable patent filing office, or other means. In March 2020, Liquidia filed IPR petitions for two of our treprostinil-related patents, and in October 2020 the PTAB instituted IPR proceedings with respect to one of these patents and declined to institute proceedings with respect to the other patent. In April 2020, we received a Paragraph IV notification letter from Liquidia indicating that Liquidia's NDA contains a certification alleging that Yutrepia will not infringe any of the patents currently listed in the Orange Book for Tyvaso because those patents are not valid, not enforceable, and/or will not be infringed by the commercial manufacture, use or sale of Yutrepia. In June 2020, we filed a patent infringement lawsuit against Liquidia related to its NDA for Yutrepia. In January 2021, Liquidia filed an IPR petition for an additional patent that we listed in the Orange Book for Tyvaso and asserted against Liquidia in the pending litigation. We are also engaged in patent litigation with ANI related to its ANDA seeking FDA approval to market a generic version of Orenitram.

Patent litigation can be time consuming, distracting, and costly, and the outcome may be difficult to predict and unfavorable to us. If we are unsuccessful in the defense of our patents, our business could be negatively impacted. Even if our patents are determined to be valid or enforceable, a competitor could circumvent our patents by effectively designing around the claims of our patents. Accordingly, our patents may not provide us with any competitive advantage.

We also rely on trade secrets to protect our proprietary know-how and other technological advances that we do not publicly disclose. Our confidentiality agreements with our Unitherians and others to whom we disclose trade secrets and confidential information may not necessarily prevent our trade secrets from being used or disclosed without our authorization. These agreements may be difficult, time-consuming, and expensive to enforce or may not provide an adequate remedy in the event of unauthorized disclosure. If our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us, and our business and competitive position could be harmed.

Third parties may allege that our products or services infringe their patents and other intellectual property rights, which could result in the payment of royalties that negatively affect our profits, subject us to costly and time-consuming litigation, or cause us to lose the ability to sell the related products.

To the extent third-party patents to which we currently do not hold licenses are necessary for us to manufacture, use, or sell our products, we would need to obtain necessary licenses to prevent infringement. For products or services that utilize intellectual property of strategic collaborators or other suppliers, such suppliers may have an obligation to secure the needed license to these patents at their cost; if not, we would be responsible for the cost of these licenses. Royalty payments and other fees under these licenses would erode our profits from the sale of related products and services. Moreover, we may be unable to obtain these licenses on acceptable terms or at all. If we fail to obtain a required license or are unable to alter the design of the product to avoid infringing a third-party patent, we would be unable to continue to manufacture or sell related products.

If a third party commences legal action against us for infringement, we may incur significant costs to defend the action and our management's attention could be diverted from our day-to-day business operations, whether or not the action has merit. An adverse judgment or settlement resulting from the action could require us to pay substantial amounts in damages for infringement or to obtain a license to continue to use the intellectual property that is the subject of the infringement claim, or could result in injunctive relief limiting our ability to develop, manufacture, or sell our products.

Information technology security breaches and other disruptions could compromise our information and expose us to legal responsibility which would cause our business and reputation to suffer.

We are increasingly dependent on information technology systems and infrastructure, much of which is outsourced to third parties including in “cloud” based platforms. We collect, store, and use sensitive or confidential data, including intellectual property, our proprietary business information and that of our suppliers, customers, and business partners, and personally identifiable information. The secure maintenance of this information is critical to our operations and business strategy. We are subject to laws and regulations in the United States and abroad, such as the Health Insurance Portability and Accountability Act of 1996 and European Union regulations related to data privacy, which require us to protect the privacy and security of certain types of information. Our information technology and infrastructure may be vulnerable to attacks by hackers, breached due to employee error, malfeasance, or other disruptions, or subject to system failures. Because the techniques used to obtain unauthorized access, disable, or degrade service, or sabotage systems change frequently and may be difficult to detect for long periods of time, we may be unable to anticipate these techniques or implement adequate preventive measures. Any breaches or failures could compromise sensitive and confidential information stored on our networks or those of third parties and expose such information to public disclosure, loss, or theft. Any actual or alleged unauthorized access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, disruption of our operations, and damage to our reputation, any of which could adversely affect our business, financial condition, or results of operations. Costs we may incur as a result of any of the foregoing, could adversely affect our business, financial condition, or results of operations. Given the increasing use of conferencing technologies to conduct business virtually in light of the COVID-19 pandemic, these cybersecurity risks are becoming more prevalent.

Risks Related to Our Financing Capacity, Indebtedness, and Investments

If we need additional financing and cannot obtain it, our product development and sales efforts may be limited.

We may be required to seek additional sources of financing to meet unplanned or planned expenditures. Unplanned expenditures could be significant and may result from necessary modifications to product development plans or product offerings in response to difficulties encountered with clinical trials. We may also face unexpected costs in preparing products for commercial sale, or in maintaining sales levels of our currently marketed therapeutic products. Our Credit Agreement contains affirmative and negative covenants that, among other things, limit our ability to incur additional indebtedness. If we are unable to obtain additional funding on commercially reasonable terms or at all, we may be compelled to delay clinical studies, curtail operations, or obtain funds through collaborative arrangements that may require us to relinquish rights to certain products or potential markets.

We may not be able to generate sufficient cash to service or repay our indebtedness, which may have a material adverse effect on our financial position, results of operations, and cash flows.

We may borrow up to $1.5 billion under our Credit Agreement, which matures in December 2025. Currently, our outstanding principal balance is $800.0 million. Our ability to repay or refinance our debt obligations under our Credit Agreement and any future debt that we may incur will depend on our financial condition and operating performance, which are subject to a number of factors beyond our control. We may be unable to maintain a level of cash flows from operating activities sufficient to permit us to pay the principal and interest on our indebtedness. Our inability to generate sufficient cash flows to satisfy our debt obligations would materially and adversely affect our financial position and results of operations. If we cannot repay or refinance our debt as it becomes due, we may be forced to take disadvantageous actions, including reducing or delaying investments and capital expenditures, disposing of material assets or operations, seeking additional debt or equity capital, or restructuring or refinancing our indebtedness. We may not be able to effect any such alternative measures on commercially reasonable terms or at all and, even if successful, such actions may not enable us to meet any such debt service obligations. In addition, our ability to withstand competitive pressures and to react to changes in our industry could be impaired.

We may select interest rates under our Credit Agreement that are calculated using LIBOR. The authority that regulates LIBOR announced that it intends to stop compelling banks to submit rates for the calculation of the LIBOR rate used in the Credit Agreement after June 2023. If the relevant LIBOR rate ceases to exist after June 2023, we and Wells Fargo, as the administrative agent, may amend the Credit Agreement to establish an alternate benchmark reference rate. To the extent our interest rates increase, our interest expense will increase, which could adversely affect our financial condition, operating results and cash flows.

Our portfolio of investments is subject to market, interest, operational, and credit risk that may reduce its value.

We maintain a portfolio of investments that includes: (1) corporate debt securities; (2) strategic investments in publicly-traded equity securities; and (3) strategic debt and equity investments in privately-held companies. These investments are subject to general economic conditions, volatility in the financial marketplace, market- and industry-wide dynamics, changes in interest rates, industry- and company-specific developments impacting the business, prospects, and credit ratings of the issuer of the securities, and other factors, each of which has affected, and may in the future affect, the income that we receive from our investments, the net realizable value of our investments, and our ability to sell them. These factors have caused, and could in the future cause, us to: (a) experience a decline in our investment income; (b) record impairment charges to reduce the carrying value of our investment portfolio; or (c) sell investments for less than our acquisition cost; each of which in turn could negatively impact our liquidity and our earnings. Our efforts to mitigate these risks through diversification of our investments and monitoring of our portfolio's overall risk profile may not be successful and the value of our investments may decline. The privately-held companies we have invested in may be particularly susceptible to the factors described above as these companies are typically in the early stages of developing technologies or products that may never materialize, which could result in a loss of all or a substantial part of our investment in these companies.

Risks Related to Our Common Stock

The price of our common stock can be highly volatile and may decline.

The price of common stock can be highly volatile within the pharmaceutical and biotechnology sector. Consequently, significant price and volume fluctuations in the market may not relate to operating performance. The price of our common stock could decline sharply due to general market conditions as well as the following factors, among others:

- Developments related to the COVID-19 pandemic and the associated economic impact, and their effects on our business, financial condition, or results of operations;
- Quarterly and annual financial results and any failure to meet our expectations or those of securities analysts;
- Timing of enrollment and results of our clinical trials;
- Announcements regarding generic or other challenges to the intellectual property related to our products, the launch of generic versions of our products or other competitive products, and the impact of competition from generic and other products on our revenues;
- Announcements regarding litigation matters, including the lawsuit filed against us by Sandoz and RareGen and our ongoing patent litigation with Liquidia related to its NDA for Yutrepia, among others;
- Announcements regarding our efforts to obtain FDA approval of, and to launch, new products, such as Tyvaso DPI;
- Physician, patient, investor, or public concerns regarding the efficacy and/or safety of products marketed or being developed by us or by others;
- Changes in, or new laws and regulations affecting reimbursement of, our therapeutic products by government payers, changes in reimbursement policies of private insurance companies, and negative publicity surrounding the cost of high-priced therapies;
- Announcements of technological innovations or new products or announcements regarding our existing products, including in particular the development of new, competing PAH therapies;

- Substantial sales of our common stock by us or our existing shareholders, or concerns that such sales may occur;
- Future issuances of common stock by us or other activity which could be viewed as being dilutive to our shareholders;
- Rumors or incorrect statements by investors and/or analysts concerning our company, our products, or our operations;
- Failures or delays in our efforts to obtain or maintain domestic or international regulatory approvals;
- Discovery of previously unknown problems with our marketed products, or problems with our manufacturing, regulatory, compliance, promotional, marketing or sales activities that result in regulatory penalties or restrictions on our products, up to the withdrawal of our products from the market; and
- Accumulation of significant short positions in our common stock by hedge funds or other investors or the significant accumulation of our common stock by hedge funds or other institutional investors with investment strategies that may lead to short-term holdings.

Provisions of Delaware law, our charter, bylaws and employment and license agreements, among other things, could prevent or delay a change of control or change in management that may be beneficial to our public shareholders.

Certain provisions of Delaware law, our restated certificate of incorporation, and our ninth amended and restated bylaws may prevent, delay, or discourage a merger, tender offer, or proxy contest; the assumption of control by a holder of a large block of our securities; and/or the replacement or removal of current management by our shareholders. For example, our restated certificate of incorporation previously divided our Board of Directors into three classes. The recent declassification of our Board will be phased in and all directors will not be elected annually until our 2023 annual meeting of shareholders. This provision may make it more difficult for shareholders to replace the majority of directors until such time. It may also deter the accumulation of large blocks of our common stock by limiting the voting power of such blocks. In addition, as a result of our recent conversion to a PBC, our Board is required to consider and balance the financial interests of shareholders, the interests of stakeholders materially affected by our conduct, and the pursuit of our specific public benefit purpose when evaluating takeover offers. This requirement of Delaware PBC law may make our company a less attractive takeover target than a traditional for-profit corporation.

Non-competition and all other restrictive covenants in most of our employment agreements will terminate upon a change of control that is not approved by our Board. Similarly, a change of control, under certain circumstances, could accelerate the vesting of outstanding stock options, and restricted stock units. Any increase in our stock price resulting from the announcement of a change of control, and our broad-based change of control severance program, under which Unitherians may be entitled to severance benefits if they are terminated without cause (or they terminate their employment for good reason) following a change of control, could make an acquisition of our company significantly more expensive to the purchaser.

We enter into certain license agreements that generally prohibit our counterparties or their affiliates from taking necessary steps to acquire or merge with us, directly or indirectly throughout the term of the agreements, plus a specified period thereafter. We are also party to certain license agreements that restrict our ability to assign or transfer the rights licensed to us to third parties, including parties with whom we wish to merge, or those attempting to acquire us. These agreements often require that we obtain prior consent of the counterparties if we contemplate a change of control. If these counterparties withhold consent, related agreements could be terminated and we would lose related license rights. For example, Lilly and MannKind have the right to terminate our license agreements related to Adcirca and Tyvaso DPI, respectively, in the event of certain change of control transactions. These restrictive change of control provisions could impede or prevent mergers or other transactions that could benefit our shareholders.

Our shareholders must rely on stock appreciation for any return on their investment in us.

We have never paid, and do not intend to pay, cash dividends. Our Credit Agreement may restrict us from doing so. As a result, the return on an investment in our common stock depends entirely upon the future appreciation, if any, in the price of our common stock.

Our exclusive forum bylaw may limit our shareholders' ability to bring a claim in a forum that they find favorable for disputes with us or our directors, officers, or other Unitherians.

Our bylaws provide that, to the fullest extent permitted by law, unless we agree in writing to an alternative forum, (a) the Delaware Court of Chancery (or, if such court does not have, or declines to accept, jurisdiction, another state court or a federal court located in Delaware) will be the exclusive forum for any complaint asserting any internal corporate claims, including claims in the right of the corporation based upon a violation of a duty by a current or former director, officer, Unitherian, or stockholder in such capacity, or as to which the Delaware General Corporation Law confers jurisdiction upon the Court of Chancery, and (b) the federal district courts will be the exclusive forum for any complaint asserting a cause of action arising under the Securities Act of 1933, as amended. The choice of forum provision may limit our shareholders' ability to bring a claim in a forum that they find favorable for disputes with us or our directors, officers, or other Unitherians, and may discourage such lawsuits. There is uncertainty as to whether a court would enforce this provision. If a court ruled the choice of forum provision was inapplicable or unenforceable in an action, we may incur additional costs to resolve such action in other jurisdictions. Our choice of forum provision is intended to apply to the fullest extent permitted by law to the above-specified types of actions and proceedings, including any derivative actions asserting claims under state law or the federal securities laws. Our shareholders will not be

deemed, by operation of the choice of forum provision, to have waived our obligation to comply with all applicable federal securities laws and the rules and regulations thereunder.

In September 2021, we converted to a Delaware PBC. Conversion may not result in the benefits that we anticipate, requires our directors to balance the interest of shareholders with other interests, and may subject us to additional litigation and other risks.

On September 30, 2021, our shareholders approved an amendment to our restated certificate of incorporation to become a PBC, and we completed the conversion to a PBC that same day. While our Board believes that our conversion to a PBC is in the best interest of shareholders, our status as a PBC may not result in the benefits that we anticipate. For example, we may not be able to achieve our public benefit purpose or realize the expected positive impact from being a PBC.

One of the primary distinctions between a PBC and a traditional Delaware for-profit corporation is that, in making decisions, the directors of a PBC have an obligation to balance the financial interests of shareholders, the interests of stakeholders materially affected by the PBC's conduct, and the pursuit of the corporation's specific public benefit purpose. The application of this balancing obligation may allow our directors to make decisions that they could not have made pursuant to the fiduciary duties applicable prior to PBC conversion. There is no guarantee that our Board will resolve conflicts among the financial interests of our shareholders, our specific public benefit purpose, or stakeholders materially affected by our conduct, in favor of our shareholders' financial interests. For instance, in a sale of control transaction, our Board would be required to consider and balance the factors listed above and might choose to accept an offer that does not maximize short-term shareholder value due to its consideration of other factors. This requirement of Delaware PBC law may make our company a less attractive takeover target than a traditional for-profit corporation.

A Delaware PBC must also provide its shareholders with a statement, at least every other year, as to the PBC's assessment of the success of its efforts to promote its public benefit purpose and the best interests of those materially affected by the PBC's conduct. If the public perceives that we are not successful in promoting our public benefit purpose, or that our pursuit of our public benefit purpose is having a negative effect on the financial interests of our shareholders, that perception could negatively affect our reputation, which could adversely affect our business, results of operations and stock price. In addition, Delaware's PBC statute may be amended to require more explicit or burdensome reporting requirements that could increase the time and expense required to comply.

As a Delaware PBC, we may be subject to increased litigation risk.

Shareholders of a Delaware PBC (if they, individually or collectively, own the lesser of (1) two percent of the PBC's outstanding shares; or (2) shares with a market value of $2 million or more on the date the lawsuit is instituted) can file a derivative lawsuit claiming the directors failed to balance shareholder and public benefit interests. Traditional Delaware for-profit corporations are not subject to this potential liability. As a PBC, we may be subject to increased derivative litigation, which may be costly and require management's attention, which may adversely affect our financial condition and results of operations. In addition, there is currently limited case law involving PBCs (including case law interpreting and applying the balancing obligation of PBC directors), which may expose us to additional litigation risk generally until additional case law develops or additional legislative action is taken.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Maryland—We own a 415,000 square foot combination laboratory and office building complex in Silver Spring, Maryland that serves as our co-headquarters and is used to manufacture our products. These manufacturing activities include the synthesis of treprostinil, the active ingredient in Tyvaso, Tyvaso DPI, and Remodulin, and treprostinil diolamine, the active ingredient in Orenitram, as well as dinutuximab, the active ingredient in Unituxin. We also manufacture Tyvaso, Remodulin, and Unituxin drug product in our Silver Spring complex. In 2019, we completed construction of a new cell culture and purification facility. In early 2021, we decided to repurpose this facility to produce autologous cells that will be used to cellularize lung scaffolds for clinical studies.

North Carolina—We own a 380,000 square foot combination manufacturing facility and office building in Research Triangle Park, North Carolina (**RTP facility**), which serves as our co-headquarters and is occupied by our clinical research and development, commercialization, and our logistics and manufacturing personnel. We manufacture Orenitram drug product and we package, warehouse, and distribute Tyvaso, Remodulin, Orenitram, and Unituxin at this location. We also own a 132-acre site containing approximately 160,000 square feet of building space adjacent to our RTP facility, which we use for our research, development, and manufacturing facilities related to our lung regeneration program, office space, and for future expansion.

We believe that these facilities, along with various other owned and leased facilities, are adequate for our current operations and that additional land and facilities for future expansion are reasonably available.

Item 3. Legal Proceedings

Currently, and from time to time, we are subject to claims in legal proceedings arising in the normal course of business. While we presently believe that the ultimate outcome of these proceedings, individually and in the aggregate, will not materially harm our financial position, cash flows or results of operations, legal proceedings are inherently uncertain, and unfavorable rulings could, individually or in aggregate, have a material adverse effect on our business, financial condition, or operating results. Please refer to Note 14—*Litigation*, to our consolidated financial statements, which is incorporated herein by reference.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock trades on the Nasdaq Global Select Market under the symbol "UTHR".

Number of Holders

As of February 17, 2022, there were 34 holders of record of our common stock.

Dividend Policy

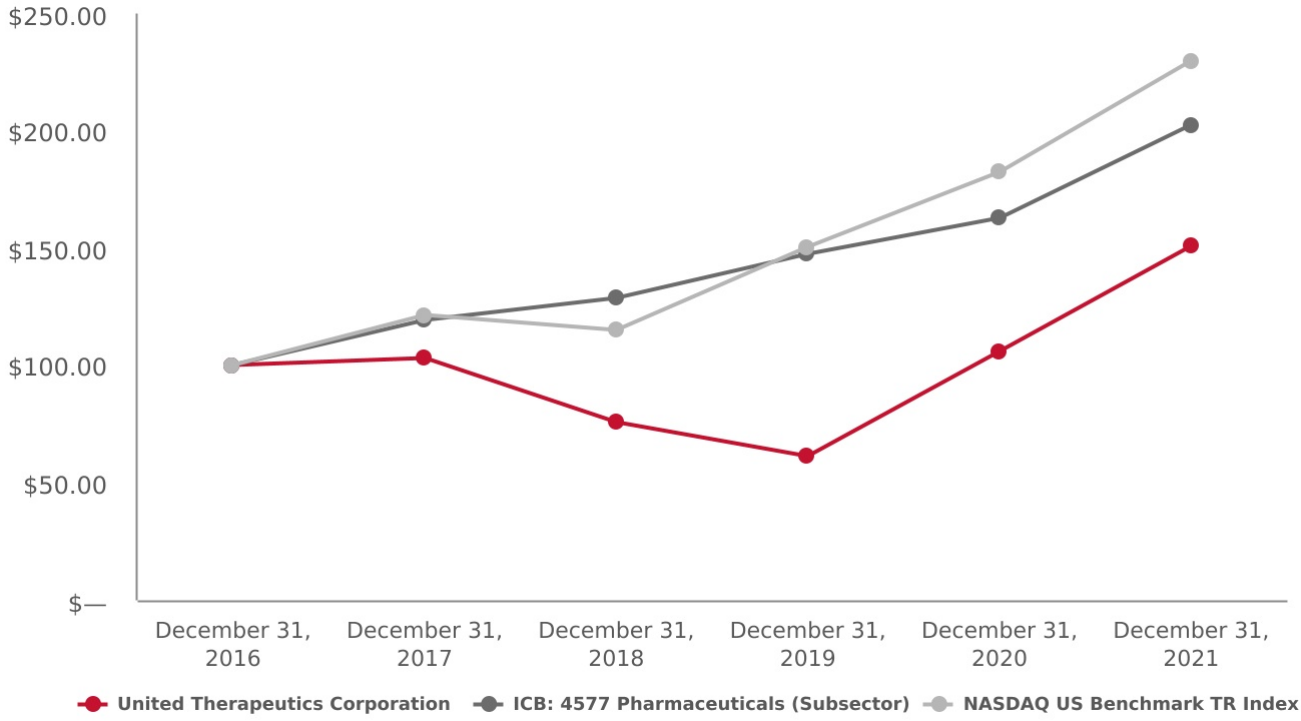
We have never paid and have no present intention to pay cash dividends on our common stock in the foreseeable future, and our Credit Agreement contains covenants that may restrict us from doing so. We intend to retain any earnings for use in our business operations.

Issuer Purchases of Equity Securities

We did not repurchase any of our outstanding equity securities during the year ended December 31, 2021.

Comparison of Five-Year Total Cumulative Shareholder Return

The following chart shows the performance from December 31, 2016 through December 31, 2021 of our common stock, compared with an investment in the stocks represented in each of the Nasdaq U.S. Benchmark TR Index and the Nasdaq ICB: 4577 Pharmaceutical Stock Index, assuming the investment of $100 at the beginning of the period and the reinvestment of dividends, if any.



Item 6. [Reserved]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion should be read in conjunction with our consolidated financial statements and related notes to our consolidated financial statements. All statements in this filing are made as of the date this Report is filed with the U.S. Securities and Exchange Commission (**SEC**). We undertake no obligation to publicly update or revise these statements, whether as a result of new information, future events, or otherwise.

The following Management's Discussion and Analysis of Financial Condition and Results of Operations and other sections of this Report contain forward-looking statements made pursuant to the safe harbor provisions of Section 21E of the Securities Exchange Act of 1934 (the **Exchange Act**) and the Private Securities Litigation Reform Act of 1995. These statements, which are based on our beliefs and expectations about future outcomes and on information available to us through the date this Report on Form 10-K is filed with the SEC, include, among others, statements related to the following:

- The potential impact of the COVID-19 pandemic on our business, results of operations, liquidity, and operations, and our ability to mitigate this potential impact;
- Expectations of revenues, expenses, profitability, and cash flows, including anticipated growth in Tyvaso revenues as a result of the expansion of its label to include pulmonary hypertension associated with interstitial lung disease (**PH-ILD**);
- The sufficiency of our cash on hand to support operations;
- Our ability to obtain financing on terms favorable to us or at all;
- Our ability to obtain and maintain domestic and international regulatory approvals;
- Our ability to maintain attractive pricing for our products, in light of increasing competition, including from generic products, and pressure from government and other payers to decrease the costs associated with healthcare;
- The expected volume and timing of sales of our commercial products, as well as potential future commercial products, including the anticipated effect of various research and development efforts on sales of these products;
- The timing and outcome of clinical studies, other research and development efforts, and related regulatory filings and approvals, including our pending new drug application (**NDA**) for Tyvaso DPI;
- The outcome of pending and potential future legal and regulatory actions by the FDA and other regulatory and government enforcement agencies, and the anticipated duration of regulatory exclusivity for our products;
- The timing and outcome of ongoing litigation, including the lawsuit filed against us by Sandoz, Inc. (**Sandoz**) and Liquidia PAH, LLC (formerly known as RareGen, LLC) (**RareGen**); the lawsuit filed against us by MSP Recovery; our patent litigation with Liquidia Technologies, Inc. (**Liquidia**) related to its NDA for Yutrepia, and with ANI Pharmaceuticals, Inc. (**ANI**) related to its abbreviated new drug application (**ANDA**) seeking FDA approval to market a generic version of Orenitram; and our litigation with the U.S. Department of Health and Human Services (**HHS**) and the U.S. Health Resource Services Administration (**HRSA**) related to the Public Health Service's 340B drug pricing program (the **340B program**);
- The impact of competing therapies on sales of our commercial products and the amount of inventory of our products that will expire unsold, including the impact of generic versions of Adcirca and Remodulin; established therapies such as Uptravi; and newly-developed therapies such as Yutrepia;
- The expectation that we will be able to manufacture sufficient quantities and maintain adequate inventories of our commercial products, through both our in-house manufacturing capabilities and third-party manufacturing sites, and our ability to obtain and maintain related approvals by the FDA and other regulatory agencies;
- The adequacy of our intellectual property protection and the validity and expiration dates of the patents we own or license, as well as the regulatory exclusivity periods for our products;
- The effect of our recent conversion to a Delaware public benefit corporation (**PBC**);
- Any statements that include the words "believe," "seek," "expect," "anticipate," "forecast," "project," "intend," "estimate," "should," "could," "may," "will," "plan," or similar expressions; and
- Other statements contained or incorporated by reference in this Report that are not historical facts.

We caution you that these statements are not guarantees of future performance and are subject to numerous evolving risks and uncertainties that we may not be able to accurately predict or assess, and that may cause our actual results to differ materially from anticipated results, including the risks and uncertainties we describe in *Part I, Item 1A—Risk Factors* of this Report and factors described in other cautionary statements, cautionary language, and risk factors set forth in our other filings with the SEC.

Impact of COVID-19 on our Business

As the COVID-19 pandemic enters its third year, we remain focused on the health and well-being of our patients and our employees, whom we refer to as **Unitherians**, while maintaining business continuity. It remains difficult to predict what impact this pandemic, and the associated economic impacts, will ultimately have on our business, particularly as new variants, such as Delta and Omicron, continue to emerge.

Our financial position is strong. We continue to believe our healthy balance sheet makes us well-positioned to endure the impact of this pandemic. With enough cash, cash equivalents, and marketable securities on hand to fund our operations as we conduct them today for at least two years regardless of our future revenues, we are able to retain and hire new Unitherians, continue our research and development and commercial activities, subject to the limitations described below, and make new strategic investments.

We have an ample supply of our products. The COVID-19 pandemic has placed significant strains on the supply chain for pharmaceutical and medical device manufacturers. However, so far we have managed to avoid any material supply disruption as a result of our long-standing inventory policies and supply redundancies.

In the case of our treprostinil-based products, and in accordance with our long-standing inventory policy, we have sufficient inventory of finished treprostinil-based drug products (Tyvaso, Remodulin, and Orenitram) to supply the market for at least two years at current levels of demand. In addition, we manufacture our own treprostinil active pharmaceutical ingredient (**API**) at our Silver Spring, Maryland facility and have three years' worth of treprostinil API on hand at any given time, as well as a substantial inventory of the key raw material necessary to manufacture it. These products and API supplies are all stored at our own warehouses in the United States. Manufacturing of our treprostinil-based products, both internally and at our contract manufacturers, continues mostly as usual, and we do not currently anticipate any supply shortages of our treprostinil-based products.

We also maintain a significant amount of inventory of Unituxin drug supply and raw materials for additional production, and intend to continue manufacturing Unituxin in quantities sufficient to meet current patient demand. Unlike our treprostinil-based products, Unituxin is a biologic with a shorter shelf life, so our ability to maintain longer-term inventories is limited. Therefore, supply-chain disruptions are more likely to cause a disruption of Unituxin availability than our treprostinil-based products. In addition, COVID-19 vaccine production has had a greater adverse impact on the availability of supplies used in Unituxin manufacturing, as compared to our treprostinil-based products.

We have redundant qualified manufacturing sites for our two current best-selling products: Tyvaso and Remodulin. Should either site be impacted by an outbreak, production activities could be diverted to the other qualified site, each of which is capable of supplying the worldwide market. Our internal manufacturing and packaging operations are independently staffed and physically segregated by technical capability (e.g., oral solid dose, aseptic vial filling, etc.). If any internal operation is impacted by an outbreak, we believe that area and staff could shut down and isolate, respectively, without affecting the other manufacturing areas.

To date, we have not experienced any interruption of our supply of drug products and devices needed to support our ongoing clinical trials.

Distribution of drug product to patients continues without interruption. Specialty pharmacy distributors, which we require to maintain at least 30 days' worth of inventory on hand at any given time, continue to ship our products to patients and hospitals. Specialty pharmacies have assured us that they have exercised their business continuity plans to avoid supply disruptions. They have also assured us that their nursing support services, which are required for therapy initiation and over the course of treatment to train patients to safely administer their medicine, continue through a combination of in-person and virtual visits. Similarly, we are not aware of any disruption to the distribution of Unituxin treatment for patients with neuroblastoma. We have a contingency plan in place to secure alternative product transportation capability to deliver our products to distributors in the event traditional freight operations are disrupted.

Our commercialization efforts remain flexible. At the start of the pandemic, our field-based commercial teams were only able to meet with physicians virtually. In addition, it became more difficult for patients to begin our therapies due to the inability of patients to visit their physician's office to determine whether our medicines may be appropriate, and physician concerns about initiating new pulmonary arterial hypertension (**PAH**) therapies via telemedicine. This had a negative impact on our revenues during the second quarter of 2020, and we believe muted the potential growth of Orenitram sales following the successful *FREEDOM-EV* study and improved FDA-labeling for Orenitram. Since then, our field-based teams have been increasingly able to resume in-person visits with physicians, although virtual visits remain common depending on the impact of the pandemic, including variants, on any particular region or hospital.

Our clinical studies have been impacted. Most of our ongoing clinical studies initially paused enrollment during the first quarter of 2020 due to the pandemic, but patients already enrolled in studies continued to receive the study drug and complete necessary clinical evaluations as appropriate. This enrollment pause was lifted for all of our studies, but initially we were only able to re-open enrollment at a limited number of clinical trial sites. We continue to experience COVID-19 related delays in enrollment but are increasingly resuming more typical, pre-pandemic enrollment rates.

For additional discussion of the risks to our business associated with COVID-19, please see the risk factor above entitled, *We face risks and uncertainties related to the COVID-19 pandemic, which could significantly disrupt our operations and/or business for an unknown period of time*.

Overview of Marketed Products

We market and sell the following commercial products:

- *Tyvaso*, an inhaled formulation of the prostacyclin analogue treprostinil, approved by the FDA and regulatory authorities in Argentina and Israel to improve exercise ability in PAH patients. Tyvaso was also approved by the FDA in March 2021 to improve exercise ability in patients with PH-ILD.
- *Remodulin*, a continuously-infused formulation of treprostinil, approved by the FDA for subcutaneous and intravenous administration to diminish symptoms associated with exercise in patients with PAH. Remodulin has also been approved in various countries outside of the United States. In February 2021, we launched U.S. sales of the Remunity Pump, a new subcutaneous delivery system for Remodulin.
- *Orenitram*, a tablet dosage form of treprostinil, approved by the FDA to delay disease progression and improve exercise capacity in PAH patients.
- *Unituxin*, a monoclonal antibody approved in the United States, Canada, and Japan for treatment of high-risk neuroblastoma.
- *Adcirca*, an oral PDE-5 inhibitor approved by the FDA to improve exercise ability in PAH patients.

For additional detail regarding our commercial products, see *Part I, Item 1—Business—Our Commercial Products.*

Research and Development

We are engaged in research and development of new indications and delivery devices for our existing products. This includes Tyvaso DPI, a dry powder inhalation form of Tyvaso. We also recently developed a new pump for Remodulin, called the Remunity Pump, and are currently developing a new version of the Remunity Pump. We are also working with two medical device manufacturers to develop new delivery systems for Remodulin. We are studying Tyvaso in patients with PH-COPD (the *PERFECT* study) and idiopathic pulmonary fibrosis (the *TETON* studies).

In addition, we are developing new products to treat PAH (RemoPro, ralinepag, and Aurora-GT). We are also heavily engaged in early-stage research and development of a number of organ transplantation-related technologies including regenerative medicine, 3-D organ bioprinting, xenotransplantation, and *ex-vivo* lung perfusion. For additional detail regarding our research and development programs, see *Part I, Item 1—Business—Research and Development.*

Revenues

Our net product sales consist of sales of the five commercial products noted above. We have entered into separate, non-exclusive distribution agreements with Accredo Health Group, Inc. and its affiliates (**Accredo**) and Caremark, L.L.C. (**CVS Specialty**) to distribute Tyvaso, Remodulin, the Remunity Pump, and Orenitram in the United States, and we have entered into an exclusive distribution agreement with ASD Specialty Healthcare, Inc., an affiliate of AmerisourceBergen Corporation, to distribute Unituxin in the United States. We recently amended our agreements with Accredo and CVS Specialty to include the distribution of Tyvaso DPI, if and when it is approved by the FDA. We also sell Tyvaso, Remodulin, and Unituxin to distributors internationally. We sell Adcirca through the pharmaceutical wholesale network of Eli Lilly and Company (**Lilly**). To the extent we have increased the price of any of these products, increases have typically been in the single-digit percentages per year, except for Adcirca, the price of which is set solely by Lilly.

We require our specialty pharmaceutical distributors to maintain reasonable levels of inventory reserves for our treprostinil-based therapies because the interruption of these therapies can be life threatening. Our specialty pharmaceutical distributors typically place monthly orders based on current utilization trends and contractual minimum and maximum inventory requirements. As a result, sales of our treprostinil-based therapies can vary depending on the timing and magnitude of these orders and do not precisely reflect changes in patient demand.

Operating Expenses

We devote substantial resources to our various clinical trials and other research and development efforts, which are conducted both internally and through third parties. From time to time, we also license or acquire additional technologies and compounds to be incorporated into our development pipeline. Our operating expenses include the costs described below.

Cost of Product Sales

Our cost of product sales primarily includes costs to manufacture our products, royalty and milestone payments under license agreements granting us rights to sell related products, direct and indirect distribution costs incurred in the sale of our products, and the costs of inventory reserves for current and projected obsolescence. These costs also include share-based compensation and salary-related expenses for direct manufacturing and indirect support personnel, quality review and release for commercial distribution, direct materials and supplies, depreciation, facilities-related expenses, and other overhead costs.

Research and Development

Our research and development expenses primarily include costs associated with the research and development of products and post-marketing research commitments. These costs also include share-based compensation and salary-related expenses for research and development functions, professional fees for preclinical and clinical studies, costs associated with clinical manufacturing, facilities-related expenses, regulatory costs, and costs associated with payments to third-party contract manufacturers before FDA approval of the relevant product. Expenses also include costs for third-party arrangements, including upfront fees and milestone payments required under license arrangements for therapies under development. We have incurred, and expect to continue to incur, significant clinical trial-related expenses, driven by the expansion of our pipeline programs.

Selling, General, and Administrative

Our selling, general, and administrative expenses primarily include costs associated with the commercialization of approved products and general and administrative costs to support our operations. Selling expenses also include share-based compensation, salary-related expenses, product marketing and sales operations costs, and other costs incurred to support our sales efforts. General and administrative expenses also include our core corporate support functions such as human resources, finance, and legal, external costs to support our core business such as insurance premiums, legal fees, and other professional service fees.

Share-Based Compensation

Historically, we granted stock options under our Amended and Restated Equity Incentive Plan and awards under our Share Tracking Awards Plans (**STAP**). Issuance of awards under these plans was discontinued in 2015. Currently, we grant stock options and restricted stock units under the United Therapeutics Corporation Amended and Restated 2015 Stock Incentive Plan (as amended to date, the **2015 Plan**), which provides for the issuance of up to 11,000,000 shares of our common stock, including the 1,000,000 shares added pursuant to an amendment and restatement of the 2015 Plan approved by our shareholders in June 2021. In February 2019, our Board of Directors approved the 2019 Inducement Stock Incentive Plan (the **2019 Inducement Plan**), which provides for the issuance of up to 99,000 shares of our common stock pursuant to awards granted to newly-hired Unitherians. Currently, we grant equity-based awards to Unitherians and members of our Board of Directors in the form of stock options and restricted stock units under the 2015 Plan, and we grant restricted stock units to newly-hired Unitherians under the 2019 Inducement Plan. The grant date fair values of stock options and restricted stock units are recognized as share-based compensation expense ratably over their vesting periods.

The fair value of STAP awards and stock options is measured using inputs and assumptions under the Black-Scholes-Merton model. The fair value of restricted stock units is measured using our stock price on the date of grant. Although we no longer grant STAP awards, we still had approximately 1.1 million STAP awards outstanding as of December 31, 2021. We account for STAP awards as liabilities because they are settled in cash. As such, we must re-measure the fair value of STAP awards at the end of each financial reporting period until the awards are no longer outstanding. Changes in our STAP liability resulting from such re-measurements are recorded as adjustments to share-based compensation expense (benefit) and can create substantial volatility within our operating expenses from period to period. The following factors, among others, have a significant impact on the amount of share-based compensation expense (benefit) recognized in connection with STAP awards from period to period: (1) volatility in the price of our common stock (specifically, increases in the price of our common stock will generally result in an increase in our STAP liability and related compensation expense, while decreases in our stock price will generally result in a reduction in our STAP liability and related compensation expense); and (2) changes in the number of outstanding awards.

Future Prospects

We anticipate that overall revenue growth over the near-term will be driven primarily by: (1) growth in sales of Tyvaso as a result of the expansion of its label to include PH-ILD; (2) continued growth in the number of patients prescribed with Orenitram following our expansion of the Orenitram label to reflect the results of the *FREEDOM-EV* study; (3) the launch of sales of Tyvaso DPI if and when it is approved; (4) the potential approval of Tyvaso to treat PH-ILD in Europe and other new markets; and (5) modest price increases for some of our products; partially offset by further generic erosion for Adcirca. We believe that additional revenue growth in the medium- and longer-term will be driven by commercializing four key therapeutic platforms in our pipeline, which are comprised of the enabling technologies described below:

Platform	Enabling Technologies
Tyvaso (inhaled treprostinil)	Tyvaso DPI, *PERFECT* study, *TETON* studies
Remodulin (parenteral treprostinil)	RemoPro, Remunity (machine-filled), additional next-generation pump systems
New Chemical Entities and New Biologics	Ralinepag, *SAPPHIRE* study
Organ Manufacturing and Transplantation	Xenotransplantation, three-dimensional organ bioprinting, regenerative medicine, *ex-vivo* lung perfusion

We believe that this diverse portfolio of four therapeutic platforms will lead to significant revenue growth over the medium- and longer-term. For further details regarding our research and development initiatives, please see *Part I, Item 1—Business—Research and Development.*

Our ability to achieve our objectives, grow our business, and maintain profitability will depend on many factors, including among others: (1) the timing and outcome of preclinical research, clinical trials, and regulatory approval applications for products we develop; (2) the timing and degree of our success in commercially launching new products; (3) the demand for our products; (4) the price of our products and the reimbursement of our products by public and private health insurance organizations; (5) the competition we face within our industry, including competition from generic companies and new PAH therapies; (6) our ability to effectively manage our business in an increasingly complex legal and regulatory environment; (7) our ability to defend against challenges to our patents; (8) the duration and severity of the COVID-19 pandemic; and (9) the risks identified in *Part I, Item 1A—Risk Factors*, included in this Report.

We operate in a highly competitive market in which a small number of large pharmaceutical companies control a majority of available PAH therapies. These pharmaceutical companies are well established in the market and possess greater financial, technical, and marketing resources than we do. In addition, there are a number of investigational products in late-stage development that, if approved, may erode the market share of our existing commercial therapies and make market acceptance more difficult to achieve for any therapies we attempt to market in the future.

Results of Operations

This section of this Report generally discusses 2021, 2020, and 2019 items and year-to-year comparisons between 2021 and 2020. Discussions of year-to-year comparisons between 2020 and 2019 that are not included in this Report can be found in *Part II, Item 7—Management's Discussion and Analysis of Financial Condition and Results of Operations—Results of Operations* of our Form 10-K filed on February 24, 2021 (our **2020 Annual Report**).

Revenues

The table below presents the components of total revenues (dollars in millions):

	Year Ended December 31,			Dollar Change		Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019	2021 v. 2020	2020 v. 2019
Net product sales:							
Tyvaso	$ 607.5	$ 483.3	$ 415.6	$ 124.2	$ 67.7	26 %	16 %
Remodulin	513.7	516.7	587.0	(3.0)	(70.3)	(1)%	(12)%
Orenitram	306.1	293.1	225.3	13.0	67.8	4 %	30 %
Unituxin	202.3	122.9	113.7	79.4	9.2	65 %	8 %
Adcirca	55.9	67.3	107.2	(11.4)	(39.9)	(17)%	(37)%
Total revenues	$ 1,685.5	$ 1,483.3	$ 1,448.8	$ 202.2	$ 34.5	14 %	2 %

Net product sales from our treprostinil-based products (Tyvaso, Remodulin, and Orenitram) grew by $134.2 million in 2021, as compared to 2020.

Tyvaso net product sales increased in 2021, as compared to 2020, primarily due to an increase in quantities sold, reflecting an increased number of patients following the PH-ILD label expansion and, to a lesser extent, price increases.

Remodulin net product sales decreased in 2021, as compared to 2020, driven by a $28.9 million decrease in U.S. Remodulin net product sales, partially offset by a $25.9 million increase in international Remodulin net product sales. The decrease in U.S. Remodulin net product sales was primarily due to a decrease in quantities sold and, to a lesser extent, higher gross-to-net deductions. The increase in international Remodulin net product sales was primarily due to reduced orders by an international distributor in 2020 in order to reduce its inventory as a result of the anticipated impact of generic competition.

Unituxin net product sales increased in 2021, as compared to 2020, due to an increase in quantities sold and, to a lesser extent, price increases. The increase in quantities sold in 2021 included $18.4 million related to the launch of Unituxin in Japan.

Gross-to-Net Deductions

We recognize revenues net of: (1) rebates and chargebacks; (2) prompt pay discounts; (3) allowance for sales returns; and (4) distributor fees. These are referred to as gross-to-net deductions and are primarily based on estimates reflecting historical experiences as well as contractual and statutory requirements. We currently estimate our allowance for sales returns using reports from our distributors and available industry data, including our estimate of inventory remaining in the distribution channel. The tables below include a reconciliation of the liability accounts associated with these deductions (in millions):

	Year Ended December 31, 2021				
	Rebates & Chargebacks	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2021	$ 65.3	$ 3.0	$ 12.5	$ 3.7	$ 84.5
Provisions attributed to sales in:					
Current period	217.0	38.5	—	31.3	286.8
Prior periods	1.6	—	(3.9)	0.2	(2.1)
Payments or credits attributed to sales in:					
Current period	(151.8)	(34.7)	—	(22.4)	(208.9)
Prior periods	(64.3)	(3.0)	(2.3)	(4.9)	(74.5)
Balance, December 31, 2021	$ 67.8	$ 3.8	$ 6.3	$ 7.9	$ 85.8

	Year Ended December 31, 2020				
	Rebates & Chargebacks	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2020	$ 51.7	$ 2.6	$ 14.2	$ 4.1	$ 72.6
Provisions attributed to sales in:					
Current period	196.1	32.5	—	20.6	249.2
Prior periods	(0.2)	—	—	(0.3)	(0.5)
Payments or credits attributed to sales in:					
Current period	(139.7)	(29.6)	—	(16.9)	(186.2)
Prior periods	(42.6)	(2.5)	(1.7)	(3.8)	(50.6)
Balance, December 31, 2020	$ 65.3	$ 3.0	$ 12.5	$ 3.7	$ 84.5

	Year Ended December 31, 2019				
	Rebates & Chargebacks	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2019	$ 54.7	$ 3.2	$ 22.4	$ 4.8	$ 85.1
Provisions attributed to sales in:					
Current period	172.8	31.3	(2.6)	19.0	220.5
Prior periods	5.9	—	(3.6)	—	2.3
Payments or credits attributed to sales in:					
Current period	(126.1)	(28.9)	—	(15.0)	(170.0)
Prior periods	(55.6)	(3.0)	(2.0)	(4.7)	(65.3)
Balance, December 31, 2019	$ 51.7	$ 2.6	$ 14.2	$ 4.1	$ 72.6

Cost of Product Sales

The table below summarizes cost of product sales by major category (dollars in millions):

	Year Ended December 31,			Dollar Change		Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019	2021 v. 2020	2020 v. 2019
Category:							
Cost of product sales	$ 116.7	$ 101.0	$ 117.4	$ 15.7	$ (16.4)	16 %	(14)%
Share-based compensation expense[1]	5.8	7.1	0.2	(1.3)	6.9	(18)%	NM[2]
Total cost of product sales	$ 122.5	$ 108.1	$ 117.6	$ 14.4	$ (9.5)	13 %	(8)%

(1) Refer to *Share-Based Compensation* section below for discussion.

(2) Calculation is not meaningful.

Cost of product sales, excluding share-based compensation. The increase in cost of product sales for the year ended December 31, 2021, as compared to the same period in 2020, was primarily attributable to shipments of the Remunity Pump following launch in February 2021.

Research and Development

The table below summarizes research and development expense by major category (dollars in millions):

	Year Ended December 31,			Dollar Change		Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019	2021 v. 2020	2020 v. 2019
Category:							
Research and development projects	$ 515.7	$ 328.2	$ 1,182.2	$ 187.5	$ (854.0)	57 %	(72)%
Share-based compensation expense[1]	24.4	29.5	0.4	(5.1)	29.1	(17)%	NM[2]
Total research and development expense	$ 540.1	$ 357.7	$ 1,182.6	$ 182.4	$ (824.9)	51 %	(70)%

(1) Refer to *Share-Based Compensation* section below for discussion.

(2) Calculation is not meaningful.

Research and development, excluding share-based compensation. The increase in research and development expense for the year ended December 31, 2021, as compared to the same period in 2020, was due to: (1) a $107.3 million in-process research and development impairment charge related to our March 2021 decision to discontinue the U.S. development of Trevyent; (2) a $105.0 million purchase of a pediatric disease priority review voucher, which we redeemed upon submission of the Tyvaso DPI NDA; and (3) an $11.6 million impairment charge related to repurposing one of our facilities. These increases were partially offset by a decrease in milestone payments under our license and collaboration agreement with MannKind and reduced costs following the completion of the phase 3 *DISTINCT* study of Unituxin in 2020.

Selling, General, and Administrative

The table below summarizes selling, general, and administrative expense by major category (dollars in millions):

	Year Ended December 31,			Dollar Change		Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019	2021 v. 2020	2020 v. 2019
Category:							
General and administrative	$ 294.3	$ 241.8	$ 230.7	$ 52.5	$ 11.1	22 %	5 %
Sales and marketing	64.4	54.9	60.7	9.5	(5.8)	17 %	(10)%
Share-based compensation expense[1]	108.3	127.2	44.8	(18.9)	82.4	(15)%	184 %
Total selling, general, and administrative expense	$ 467.0	$ 423.9	$ 336.2	$ 43.1	$ 87.7	10 %	26 %

(1) Refer to *Share-Based Compensation* section below for discussion.

General and administrative, excluding share-based compensation. The increase in general and administrative expense for the year ended December 31, 2021, as compared to the same period in 2020, was primarily due to: (1) an increase in litigation expenses; and (2) an increase in consulting expenses.

Share-Based Compensation

The table below summarizes share-based compensation expense (benefit) by major category (dollars in millions):

	Year Ended December 31,			Dollar Change		Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019	2021 v. 2020	2020 v. 2019
Category:							
Stock options	$ 25.4	$ 44.0	$ 70.5	$ (18.6)	$ (26.5)	(42)%	(38)%
Restricted stock units	24.7	20.5	13.3	4.2	7.2	20 %	54 %
STAP awards	86.6	97.8	(39.7)	(11.2)	137.5	(11)%	346 %
Employee stock purchase plan	1.8	1.5	1.3	0.3	0.2	20 %	15 %
Total share-based compensation expense	$ 138.5	$ 163.8	$ 45.4	$ (25.3)	$ 118.4	(15)%	261 %

The table below summarizes share-based compensation expense by line item in our consolidated statements of operations (dollars in millions):

	Year Ended December 31,			Dollar Change		Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019	2021 v. 2020	2020 v. 2019
Cost of product sales	$ 5.8	$ 7.1	$ 0.2	$ (1.3)	$ 6.9	(18)%	NM(1)
Research and development	24.4	29.5	0.4	(5.1)	29.1	(17)%	NM(1)
Selling, general, and administrative	108.3	127.2	44.8	(18.9)	82.4	(15)%	184 %
Total share-based compensation expense	$ 138.5	$ 163.8	$ 45.4	$ (25.3)	$ 118.4	(15)%	261 %

(1) Calculation is not meaningful.

The decrease in share-based compensation expense for the year ended December 31, 2021, as compared to the same period in 2020, was primarily due to: (1) a decrease in stock option expense due to fewer awards granted and outstanding in 2021; and (2) a decrease in STAP expense driven by a 42 percent increase in our stock price during 2021, as compared to a 72 percent increase in our stock price during 2020, partially offset by an increase in restricted stock unit expense. Refer to Note 8—*Share-Based Compensation*, to our consolidated financial statements for more information.

Other Income, Net

The change in other income, net for the year ended December 31, 2021, as compared to the same period in 2020, was primarily due to the recognition of net unrealized and realized gains on our investments in equity securities and net unrealized gains and losses on our contingent consideration assets. Refer to Note 4—*Investments* and Note 5—*Fair Value Measurements,* to our consolidated financial statements for more information.

Impairments of Investments in Privately-Held Companies

During the years ended December 31, 2021 and 2020, we recorded $2.3 million and $9.1 million, respectively, of impairment charges related to our investments in privately-held companies.

Income Tax Expense (Benefit)

Income tax expense was $118.1 million for the year ended December 31, 2021, as compared to $124.1 million for the same period in 2020. For the years ended December 31, 2021 and 2020, our effective income tax rates (**ETR**) were approximately 20 percent and 19 percent, respectively. Our ETR for the year ended December 31, 2021 increased, as compared to our ETR for the year ended December 31, 2020, primarily due to increases in blended state income tax rates and decreases in tax credits, partially offset by a decrease in the valuation allowance on deferred taxes. For additional details, refer to Note 10—*Income Taxes* to our consolidated financial statements.

Financial Condition, Liquidity, and Capital Resources

We have funded our operations principally through sales of our commercial products and, from time-to-time, third-party financing arrangements. We believe that our current liquidity is sufficient to fund ongoing operations and future business plans as we expect aggregate growth in revenues from our commercial products. Furthermore, our customer base remains stable and we believe that it presents minimal credit risk. However, any projections of future cash flows are inherently subject to uncertainty and we may seek other forms of financing. In June 2018, we entered into a credit agreement (the **Credit Agreement**), which provides an unsecured, revolving line of credit of up to $1.5 billion. Our aggregate outstanding balance under the Credit Agreement, which matures in 2025, was $800.0 million and classified as a non-current liability in our consolidated balance sheets as of both December 31, 2021 and 2020.

For information regarding the fluctuation explanations between 2020 and 2019, refer to our 2020 Annual Report.

Cash and Cash Equivalents and Marketable Investments

Cash and cash equivalents and marketable instruments comprise the following (dollars in millions):

	Year Ended December 31,		Percentage Change
	2021	2020	2021 v. 2020
Cash and cash equivalents	$ 894.8	$ 738.7	21 %
Marketable investments—current	1,035.9	1,096.3	(6)%
Marketable investments—non-current	1,649.9	1,149.6	44 %
Total cash and cash equivalents and marketable investments	$ 3,580.6	$ 2,984.6	20 %

Cash Flows

Cash flows comprise the following (dollars in millions):

	Year Ended December 31,			Percentage Change	
	2021	2020	2019	2021 v. 2020	2020 v. 2019
Net cash provided by (used in) operating activities	$ 598.2	$ 755.7	$ (206.6)	(21)%	466 %
Net cash used in investing activities	$ (486.9)	$ (738.5)	$ (335.4)	34 %	(120)%
Net cash provided by (used in) financing activities	$ 44.8	$ (16.9)	$ 611.2	365 %	(103)%

Operating Activities

Our operating assets and liabilities consist primarily of accounts receivable, inventories, accounts payable, accrued expenses, liabilities for our STAP awards, and tax-related payables and receivables.

The decrease of $157.5 million in net cash provided by operating activities for the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily due to: (1) a $105.0 million purchase of a pediatric disease priority review voucher; (2) a $60.5 million increase in cash paid for income taxes; and (3) a $55.0 million increase in cash paid to settle STAP awards, partially offset by a $4.5 million decrease in cash paid for interest and other changes in assets and liabilities.

Investing Activities

The decrease of $251.6 million in net cash used in investing activities for the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily due to a $315.5 million decrease in cash used for total purchases, sales, and maturities of marketable investments, partially offset by a $61.5 million increase in cash paid to purchase property, plant, and equipment.

Financing Activities

The decrease of $61.7 million in net cash used in financing activities for the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily due to: (1) an absence of repayments on our line of credit during the year ended December 31, 2021, as compared to a $50.0 million repayment on our line of credit during year ended December 31, 2020; and (2) a $16.2 million increase in proceeds from the exercise of stock options during the year ended December 31, 2021, as compared to the year ended December 31, 2020.

Unsecured Revolving Credit Facility

In June 2018, we entered into the Credit Agreement, which provides for an unsecured revolving credit facility of up to $1.5 billion. On June 27, 2018, we borrowed $250.0 million under this facility and used the funds to repay outstanding indebtedness under a previous credit facility that was terminated in 2018. In January 2019, we borrowed an additional $800.0 million under this facility and used the funds for an upfront payment related to the global license agreement with Arena. We did not pay down our balance under the Credit Agreement during the year ended December 31, 2021. We paid down $50.0 million and $200.0 million of our balance under the Credit Agreement during the years ended December 31, 2020 and 2019, respectively. The aggregate balance of $800.0 million remained outstanding as of both December 31, 2021 and February 24, 2022. Refer to Note 7—*Debt,* to our consolidated financial statements.

Contractual Obligations

At December 31, 2021, we had the following contractual obligations (in millions):

	Payments Due by Period				
	Total	Less than 1 year	2-3 Years	4-5 Years	More than 5 Years
Operating lease obligations	$ 18.9	$ 3.1	$ 5.1	$ 3.5	$ 7.2
Long-term debt obligations[1]	863.9	16.0	31.9	816.0	—
Obligations under the STAP[2]	99.2	99.2	—	—	—
Obligations under the SERP[3]	86.7	18.2	22.8	6.8	38.9
Purchase obligations[4]	477.1	342.6	100.6	19.3	14.6
Total[5] [6]	$ 1,545.8	$ 479.1	$ 160.4	$ 845.6	$ 60.7

(1) Long-term debt obligations include future principal and interest payments on our LIBOR-based variable rate obligations under the Credit Agreement, assuming contractual maturity of the Credit Agreement. The Credit Agreement will mature in December 2025. As of December 31, 2021, we have classified the entire $800.0 million outstanding balance as a non-current liability, since we have no intention to repay any portion of the outstanding balance during 2022. Refer to Note 7—*Debt* to our consolidated financial statements for further details.

(2) Estimated based on the intrinsic value of exercisable outstanding STAP awards as of December 31, 2021. Refer to Note 8—*Share-Based Compensation* to our consolidated financial statements for further details.

(3) Consists of actuarially derived, undiscounted, estimated future payouts of benefits. Refer to Note 11—*Employee Benefit Plans—Supplemental Executive Retirement Plan* to our consolidated financial statements for further details.

(4) Purchase obligations primarily include: (1) commitments related to research and development (including clinical trials) for new and existing products; (2) open purchase orders for capital expenditures primarily related to our continued investment in construction of additional facilities to support the development and commercialization of our products and technologies; and (3) open purchase orders for the acquisition of goods and services in the ordinary course of business. The timing and amount of our obligations may differ based on certain future events.

(5) In addition to amounts in the table above, we are contractually obligated to make payments upon the achievement of various development, regulatory, and commercial milestones for agreements we have entered into with third parties. These payments are contingent upon the occurrence of various future events, some of which have a high degree of uncertainty of occurring. These contingent payments have not been included in the table above, and, except with respect to the fair value of the contingent consideration obligations, are not recorded in our consolidated balance sheets. Refer to Note 12—*Commitments and Contingencies* to our consolidated financial statements for further details.

(6) As of December 31, 2021, our other non-current liabilities in our consolidated balance sheets includes a liability of $3.9 million for unrecognized tax benefits, including related interest and penalties. Due to the high degree of uncertainty on the timing of future events that could extinguish these unrecognized tax benefits, we are unable to estimate the period of settlement and therefore we have excluded these unrecognized tax benefits from the table above. Refer to Note 10—*Income Taxes* to our consolidated financial statements for further details.

Obligations Under License Agreements

We pay Lilly a royalty equal to ten percent of our net product sales of Adcirca, as well as milestone payments equal to $325,000 for each $1,000,000 in Adcirca net product sales. We pay a single-digit percentage royalty based on net product sales of Orenitram under our license agreement with Supernus. We also pay The Scripps Research Institute a one percent royalty on sales of Unituxin. We have entered into other license agreements under which we are required to make milestone payments upon the achievement of certain developmental and commercialization objectives and royalty payments upon the commercialization of products covered by the license agreements. Refer to Note 12—*Commitments and Contingencies* to our consolidated financial statements for further details.

Off-Balance Sheet Arrangements

We hold an interest in an unconsolidated variable interest entity (**VIE**). We determined that we are not the primary beneficiary of this entity. As a result, we do not consolidate this VIE. Refer to Note 4—*Investments—Variable Interest Entities*. We do not have any other off-balance sheet arrangements within the meaning of Item 303(a)(4) of Regulation S-K.

Summary of Critical Accounting Policies and Estimates

We prepare our consolidated financial statements in conformity with generally accepted accounting principles in the United States (**GAAP**). GAAP requires that we make estimates and assumptions that affect the amounts and timing reported in our consolidated financial statements. As we become aware of updated information or new developments, these estimates and assumptions may change and materially impact reported amounts. We consider the following accounting policies to be critical to our consolidated financial statements because they require the use of our judgment and estimates (including those that are forward-looking) in their application.

Revenue Recognition

We generate revenues from the sale of our five commercial products: Tyvaso, Remodulin, Orenitram, Unituxin, and Adcirca. Revenue is recognized when we transfer control of our products to our distributors, as our contracts have a single performance obligation (delivery of our product). These revenues are subject to various product sales allowances, referred to as gross-to-net deductions, which are deducted from revenues to determine net product sales. For a description of our related accounting policies, refer to Note 2—*Summary of Significant Accounting Policies—Revenue Recognition* to our consolidated financial statements.

The following category of gross-to-net deductions involves the use of significant estimates and judgments and information obtained from external sources.

Rebates and Chargebacks

Our most significant rebates relate to our participation in state Medicaid programs, contractual rebates to certain of our domestic distributors, and contractual rebates offered to managed care organizations covering Medicare Part D and commercial plans. Chargebacks relate to our participation in programs with the U.S. Department of Veterans Affairs and 340B covered entities. Although we accrue for our allowance for rebates and chargebacks in the same period that we recognize revenue, the actual rebate or chargeback on the sale of our product to a distributor is not invoiced to us until a future period, generally within six months from the date of sale. Due to this time lag, we must estimate the amount of rebates and chargebacks to accrue. As of December 31, 2021 and 2020, we had a liability of $67.8 million and $65.3 million, respectively, related to rebates and chargebacks.

Estimates associated with our participation in state Medicaid programs are particularly susceptible to adjustment given the extensive time lag that may occur between our recording of an accrual and its ultimate invoicing by individual state Medicaid programs, which can occur up to several years after the sale of our product. Because of the time lag for Medicaid and other rebates, in any particular quarter, our adjustments may incorporate revisions of accruals for prior quarters. Historically, adjustments to our estimates to reflect actual results or updated expectations have not been material to our overall financial results. Provisions attributed to sales in prior periods have been less than one percent of our net product sales for each of the years ended December 31, 2021, 2020, and 2019.

For a roll-forward of the liability accounts associated with our gross-to-net deductions, see the section above entitled *Results of Operations—Gross-to-Net Deductions*.

Share-Based Compensation

Our share-based awards are classified as either liabilities (STAP awards) or as equity (stock options, restricted stock units, and rights to purchase stock under our employee stock purchase plan). We recognize related share-based compensation expense based on (1) the fair value of outstanding STAP awards on the grant date and at the end of each reporting period; (2) the grant date fair value of stock options and restricted stock units; and (3) the purchase date fair value of stock under our employee stock purchase plan. With the exception of restricted stock units, we estimate the fair value of all share-based awards using the Black-Scholes-Merton valuation model. We measure the fair value of restricted stock units using the stock price on the grant date. Valuation models, like the Black-Scholes-Merton model, require the use of subjective assumptions that could materially impact the estimation of fair value and related compensation expense to be recognized. These assumptions include the expected volatility of our stock price and the expected term of awards. Developing these assumptions requires the use of judgment. For additional information on the assumptions used in the Black-Scholes-Merton valuation model, see Note 8—*Share-Based Compensation,* to our consolidated financial statements.

Recently Issued Accounting Standards

See Note 3—*Recently Issued Accounting Standards*, to our consolidated financial statements for information on our anticipated adoption of recently issued accounting standards.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Investment Risk

As of December 31, 2021, we have invested $2.7 billion in corporate debt securities and U.S. government and agency securities. The market value of these investments varies inversely with changes in prevailing market interest rates. In general, as interest rates increase, the market value of a debt investment would be expected to decrease. Conversely, as interest rates decrease, the market value of a debt investment would be expected to increase. To date, we have not experienced significant volatility in the value of these investments. However, to address market risk, we invest in debt securities with terms no longer than three years and typically hold these investments to maturity so that they can be redeemed at their stated or face value. Many of our investments may be called by their respective issuers prior to maturity. The following table summarizes the expected maturities and weighted average interest rates as of December 31, 2021 (dollars in millions):

	Expected Maturity		
	2022	**2023**	**2024**
Available-for-sale investments	$ 1,004.8	$ 1,153.4	$ 496.5
Weighted average interest rate	1.1 %	0.6 %	0.8 %

During sustained periods of instability and uncertainty in the financial markets, we may be subjected to additional investment-related risks that could materially affect the value and liquidity of our investments. In light of these risks, we actively monitor market conditions and developments specific to the securities and security classes in which we invest. In addition, we believe that we maintain a conservative investment approach in that we invest exclusively in unstructured, highly-rated securities with relatively short maturities that we believe reduce our exposure to undue risks. While we believe that we take prudent measures to mitigate investment related risks, such risks cannot be fully eliminated, as circumstances can occur that are beyond our control.

Interest Rate Risk

As of December 31, 2021 and 2020, we had $800.0 million aggregate principal amounts outstanding under our Credit Agreement, which bears interest at a variable rate. As a result, we are subject to interest rate risk with respect to such floating-rate debt. A 100 basis point increase in the variable interest rate component of our borrowings would increase our annual interest expense by approximately $8.0 million or 43 percent, and $8.0 million or 34 percent, for the years ended December 31, 2021 and 2020, respectively. Refer to Note 7—*Debt,* to our consolidated financial statements.

Stock Price Risk

As of both December 31, 2021 and 2020, we had 1.1 million and 2.1 million awards outstanding under our Share Tracking Awards Plans, respectively. These awards are referred to as **STAP awards**. STAP awards convey the right to receive in cash an amount equal to the appreciation of our common stock, which is measured as the increase in the closing price of our common stock between the dates of grant and exercise. As of December 31, 2021 and 2020, the aggregate STAP awards liability balance was $102.4 million and $96.8 million, respectively. Estimating the fair value of STAP awards requires the use of certain inputs that can materially impact the determination of fair value and the amount of share-based compensation expense (benefit) we recognize. Inputs used in estimating fair value include the price of our common stock, the expected volatility of the price of our common stock, the risk-free interest rate, the expected term of STAP awards, and the expected dividend yield. As of December 31, 2021 and 2020, a one dollar change in our stock price would, holding other factors constant, increase or decrease the fair value of our STAP awards liability by approximately $1.0 million and $1.6 million, respectively.

As of December 31, 2021 and 2020, we held investments in equity securities with readily determinable fair values of $70.4 million and $78.4 million, respectively, which are included in *current marketable investments* in our consolidated balance sheets. Our investments in these publicly-traded equity securities are recorded at fair value and are subject to market price volatility. Changes in the fair value of these investments are recorded in our consolidated statements of operations within *other income, net*. As of December 31, 2021 and 2020, a price change of 10 percent would increase or decrease the fair value of these investments by $7.0 million and $7.8 million, respectively.

Item 8. Financial Statements and Supplementary Data

United Therapeutics Corporation
Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of United Therapeutics Corporation:

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of United Therapeutics Corporation (the **Company**) as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive income, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes and financial statement schedule listed in the Index at Item 15(a)(2) (collectively referred to as the **consolidated financial statements**). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (**PCAOB**), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (**2013 framework**) and our report dated February 24, 2022, expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the Company's Audit Committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing separate opinions on the critical audit matter or on the accounts or disclosures to which it relates.

Revenue Reductions — Accounting for Rebates

Description of the Matter

At December 31, 2021, accrued rebates and chargebacks were $67.8 million, a portion of which related to rebates, and the Company recognized $218.6 million in revenue reductions associated with rebates and chargebacks during the year-ended December 31, 2021. As discussed in Note 2 to the consolidated financial statements, the Company recognizes revenues net of rebates, commonly referred to as “revenue reductions” or “gross-to-net deductions.” Allowances for rebates include mandated discounts due to the Company’s participation in various government health care programs, contractual rebates offered to certain domestic distributors, and contracted discounts with commercial payers. The Company estimates accrued rebates on a product-by-product basis, considering actual revenue, contractual discount rates, expected utilization under each contract, historical payment experience, and changes in product pricing and information regarding changes in program regulations and guidelines. The Company accrues for rebates in the same period the product is sold; however, third-party reporting and payment of the rebate amount occur on a time lag.

Auditing rebates is complex due to the time lag associated with third-party reporting of rebate amounts, calculations of government pricing used to determine the rebate price, and the judgmental nature of the time lag assumptions. The complexities associated with government pricing calculations required the involvement of specialists.

How We Addressed the Matter in Our Audit

We tested controls that address the risks of material misstatement relating to the measurement and valuation of rebates. For example, we tested controls over management’s review of the accrued rebate, including the significant assumptions and data inputs provided by third parties.

To test rebates, our audit procedures included, among others, evaluating the methodologies and assumptions used and the underlying data used by the Company. We evaluated the assumptions used by management against historical trends, evaluated the change in estimated accruals from the prior periods, and assessed the historical accuracy of the Company’s estimates against actual results. We performed substantive analytics disaggregated by product. We utilized government pricing specialists in evaluating the Company’s government pricing methodology and calculations of government prices used to estimate rebates for a sample of the Company’s products.

/s/ Ernst & Young LLP

We have served as the Company’s auditor since 2003.
Tysons, Virginia
February 24, 2022

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of United Therapeutics Corporation:

Opinion on Internal Control Over Financial Reporting

We have audited United Therapeutics Corporation's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the **COSO criteria**). In our opinion, United Therapeutics Corporation (the **Company**) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (**PCAOB**), the consolidated balance sheets of the Company as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive income, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021 and the related notes and financial statement schedule of the Company listed in the Index at Item 15(a)(2) and our report dated February 24, 2022, expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that: (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Tysons, Virginia
February 24, 2022

Consolidated Balance Sheets
(In millions, except share and per share data)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 894.8	$ 738.7
Marketable investments	1,035.9	1,096.3
Accounts receivable, no allowance for 2021 and 2020	198.7	157.4
Inventories, net	93.8	86.5
Other current assets	100.4	88.3
Total current assets	2,323.6	2,167.2
Marketable investments	1,649.9	1,149.6
Goodwill and other intangible assets, net	44.6	158.1
Property, plant, and equipment, net	780.9	731.6
Deferred tax assets, net	261.9	238.6
Other non-current assets	108.2	169.9
Total assets	$ 5,169.1	$ 4,615.0
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 174.6	$ 187.0
Share tracking awards plan	102.4	96.8
Other current liabilities	28.4	39.5
Total current liabilities	305.4	323.3
Line of credit	800.0	800.0
Other non-current liabilities	104.8	96.5
Total liabilities	1,210.2	1,219.8
Commitments and contingencies—Note 12		
Stockholders' equity:		
Preferred stock, par value $.01, 10,000,000 shares authorized, no shares issued	—	—
Common stock, par value $.01, 245,000,000 shares authorized, 71,727,021 and 71,126,314 shares issued, and 45,107,805 and 44,507,098 shares outstanding at December 31, 2021 and 2020, respectively	0.7	0.7
Additional paid-in capital	2,245.4	2,148.7
Accumulated other comprehensive loss	(23.0)	(14.2)
Treasury stock, 26,619,216 shares at December 31, 2021 and 2020	(2,579.2)	(2,579.2)
Retained earnings	4,315.0	3,839.2
Total stockholders' equity	3,958.9	3,395.2
Total liabilities and stockholders' equity	$ 5,169.1	$ 4,615.0

See accompanying notes to consolidated financial statements.

Consolidated Statements of Operations
(In millions, except per share data)

	Year Ended December 31,		
	2021	2020	2019
Revenues:			
Net product sales	$ 1,685.5	$ 1,483.3	$ 1,448.8
Total revenues	1,685.5	1,483.3	1,448.8
Operating expenses:			
Cost of product sales	122.5	108.1	117.6
Research and development	540.1	357.7	1,182.6
Selling, general, and administrative	467.0	423.9	336.2
Total operating expenses	1,129.6	889.7	1,636.4
Operating income (loss)	555.9	593.6	(187.6)
Interest income	16.7	28.6	44.2
Interest expense	(18.6)	(23.5)	(44.2)
Other income, net	42.2	49.3	22.6
Impairments of investments in privately-held companies	(2.3)	(9.1)	—
Total other income, net	38.0	45.3	22.6
Income (loss) before income taxes	593.9	638.9	(165.0)
Income tax (expense) benefit	(118.1)	(124.1)	60.5
Net income (loss)	$ 475.8	$ 514.8	$ (104.5)
Net income (loss) per common share:			
Basic	$ 10.60	$ 11.65	$ (2.39)
Diluted	$ 10.06	$ 11.54	$ (2.39)
Weighted average number of common shares outstanding:			
Basic	44.9	44.2	43.8
Diluted	47.3	44.6	43.8

See accompanying notes to consolidated financial statements.

Consolidated Statements of Comprehensive Income
(In millions)

	Year Ended December 31,		
	2021	2020	2019
Net income (loss)	$ 475.8	$ 514.8	$ (104.5)
Other comprehensive (loss) income:			
Defined benefit pension plan:			
Actuarial gain (loss) arising during period, net of tax	5.6	(8.0)	(10.6)
Amortization of actuarial gain and prior service cost included in net periodic pension cost and settlement, net of tax	0.6	1.3	(1.7)
Total defined benefit pension plan, net of tax	6.2	(6.7)	(12.3)
Unrealized (loss) gain on available-for-sale securities, net of tax	(15.0)	6.7	6.0
Other comprehensive (loss) income, net of tax	(8.8)	—	(6.3)
Comprehensive income (loss)	$ 467.0	$ 514.8	$ (110.8)

See accompanying notes to consolidated financial statements.

Consolidated Statements of Stockholders' Equity (In millions)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Treasury Stock	Retained Earnings	Stockholders' Equity
	Shares	Amount					
Balance, December 31, 2018	70.2	$ 0.7	$ 1,940.2	$ (7.9)	$ (2,579.2)	$ 3,434.8	$ 2,788.6
Net loss	—	—	—	—	—	(104.5)	(104.5)
Unrealized gains on available-for-sale securities	—	—	—	6.0	—	—	6.0
Defined benefit pension plan	—	—	—	(12.3)	—	—	(12.3)
Shares issued under employee stock purchase plan	—	—	4.1	—	—	—	4.1
Common stock issued for restricted stock units (**RSUs**) vested	0.1	—	—	—	—	—	—
RSUs withheld for taxes	—	—	(2.1)	—	—	—	(2.1)
Exercise of stock options	0.2	—	9.9	—	—	—	9.9
Share-based compensation	—	—	85.1	—	—	—	85.1
Cumulative effect of accounting change	—	—	—	—	—	(5.1)	(5.1)
Reclassification from temporary equity to permanent equity[(1)]	—	—	10.8	—	—	—	10.8
Deconsolidation of variable interest entity	—	—	(0.1)	—	—	—	(0.1)
Balance, December 31, 2019	70.5	$ 0.7	$ 2,047.9	$ (14.2)	$ (2,579.2)	$ 3,325.2	$ 2,780.4
Net income	—	—	—	—	—	514.8	514.8
Unrealized gains on available-for-sale securities	—	—	—	6.7	—	—	6.7
Defined benefit pension plan	—	—	—	(6.7)	—	—	(6.7)
Shares issued under employee stock purchase plan	0.1	—	4.7	—	—	—	4.7
Common stock issued for RSUs vested	0.1	—	—	—	—	—	—
RSUs withheld for taxes	—	—	(3.7)	—	—	—	(3.7)
Exercise of stock options	0.4	—	33.8	—	—	—	33.8
Share-based compensation	—	—	66.0	—	—	—	66.0
Cumulative effect of accounting change	—	—	—	—	—	(0.8)	(0.8)
Balance, December 31, 2020	71.1	$ 0.7	$ 2,148.7	$ (14.2)	$ (2,579.2)	$ 3,839.2	$ 3,395.2
Net income	—	—	—	—	—	475.8	475.8
Unrealized losses on available-for-sale securities	—	—	—	(15.0)	—	—	(15.0)
Defined benefit pension plan	—	—	—	6.2	—	—	6.2
Shares issued under employee stock purchase plan	0.1	—	5.6	—	—	—	5.6
Common stock issued for RSUs vested	0.1	—	—	—	—	—	—
RSUs withheld for taxes	—	—	(10.8)	—	—	—	(10.8)
Exercise of stock options	0.4	—	50.0	—	—	—	50.0
Share-based compensation	—	—	51.9	—	—	—	51.9
Balance, December 31, 2021	71.7	$ 0.7	$ 2,245.4	$ (23.0)	$ (2,579.2)	$ 4,315.0	$ 3,958.9

(1) Pursuant to a license agreement with Toray Industries Inc. (**Toray**), we issued 200,000 shares of our common stock (which have since split into 400,000 shares) to Toray in 2007, and provided Toray the right to require us to repurchase the shares at a price of $27.21 per share (the **Put Right**), which resulted in classification of such shares within temporary equity. During 2019, we terminated our license agreement with Toray and the Put Right also terminated. As a result, upon the termination of the license agreement, we reclassified $10.8 million from temporary equity to additional paid-in capital.

See accompanying notes to consolidated financial statements.

Consolidated Statements of Cash Flows
(In millions)

	Year Ended December 31,		
	2021	2020	2019
Cash flows from operating activities:			
Net income (loss)	$ 475.8	$ 514.8	$ (104.5)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Depreciation and amortization	49.9	49.9	45.9
Share-based compensation expense	138.5	163.8	45.4
Impairments of investments in privately-held companies	2.3	9.1	—
Impairments of property, plant, and equipment	19.2	5.4	17.2
Intangible asset impairment charges	113.4	—	—
Realized gain on sale of equity securities	(92.6)	(3.4)	(2.6)
Other	65.9	(47.0)	(29.7)
Changes in operating assets and liabilities:			
Accounts receivable	(41.3)	(6.0)	24.4
Inventories	(7.5)	10.3	12.9
Accounts payable and accrued expenses	(12.5)	38.6	(16.3)
Other assets and liabilities	(112.9)	20.2	(199.3)
Net cash provided by (used in) operating activities	598.2	755.7	(206.6)
Cash flows from investing activities:			
Purchases of property, plant, and equipment	(120.8)	(59.3)	(83.7)
Proceeds from sale of property, plant, and equipment	—	2.4	—
Sales/maturities of held-to-maturity investments	—	—	39.7
Purchases of available-for-sale debt securities	(1,895.3)	(2,308.8)	(1,271.5)
Maturities of available-for-sale debt securities	1,370.1	1,523.4	799.2
Sales of available-for-sale debt securities	47.6	76.5	180.9
Sales of investments in equity securities	111.5	27.3	20.5
Purchases of investments in privately-held companies	—	—	(8.0)
Decrease in cash due to deconsolidation of variable interest entity	—	—	(12.5)
Net cash used in investing activities	(486.9)	(738.5)	(335.4)
Cash flows from financing activities:			
Proceeds from line of credit	—	—	800.0
Repayment of line of credit	—	(50.0)	(200.0)
Payments of debt issuance costs	—	(1.7)	(0.7)
Proceeds from the exercise of stock options	50.0	33.8	9.9
Proceeds from the issuance of stock under employee stock purchase plan	5.6	4.7	4.1
Restricted stock units withheld for taxes	(10.8)	(3.7)	(2.1)
Net cash provided by (used in) financing activities	44.8	(16.9)	611.2
Net increase in cash and cash equivalents	$ 156.1	$ 0.3	$ 69.2
Cash and cash equivalents, beginning of year	738.7	738.4	669.2
Cash and cash equivalents, end of year	$ 894.8	$ 738.7	$ 738.4
Supplemental cash flow information:			
Cash paid for interest	$ 16.2	$ 20.7	$ 41.0
Cash paid for income taxes	$ 153.3	$ 92.8	$ 120.2
Non-cash investing and financing activities:			
Non-cash additions to property, plant, and equipment	$ 3.7	$ 3.5	$ 54.5

See accompanying notes to consolidated financial statements.

Notes to Consolidated Financial Statements

1. Organization and Business Description

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. On September 30, 2021, we converted to a Delaware public benefit corporation, with the express public benefit purpose *to provide a brighter future for patients through (a) the development of novel pharmaceutical therapies; and (b) technologies that expand the availability of transplantable organs*.

We have approval from the U.S. Food and Drug Administration (**FDA**) to market the following therapies: Tyvaso® (treprostinil) Inhalation Solution (**Tyvaso**), Remodulin® (treprostinil) Injection (**Remodulin**), Orenitram® (treprostinil) Extended-Release Tablets (**Orenitram**), Unituxin® (dinutuximab) Injection (**Unituxin**), and Adcirca® (tadalafil) Tablets (**Adcirca**). We also derive revenues outside the United States from sales of Tyvaso, Remodulin, and Unituxin.

As used in these notes to our consolidated financial statements, unless the context otherwise requires, the terms "**we**", "**us**", "**our**", and similar terms refer to United Therapeutics Corporation and its consolidated subsidiaries.

2. Summary of Significant Accounting Policies

Basis of Presentation and Principles of Consolidation

The accompanying consolidated financial statements of United Therapeutics Corporation and its consolidated subsidiaries have been prepared in accordance with accounting principles generally accepted in the United States (**GAAP**). All intercompany balances and transactions have been eliminated in consolidation. Certain prior year amounts have been reclassified to conform to the current year presentation. In the operating activities section of our consolidated statements of cash flows, we reclassified a portion of the prior period amount within *other assets and liabilities* to the line item *realized gain on sale of equity securities* to conform with the current period presentation.

Use of Estimates

The preparation of our consolidated financial statements in accordance with GAAP requires our management to make estimates and assumptions that affect reported amounts of assets and liabilities at the date of our consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. We base our estimates on assumptions regarding historical experience, currently available information, and anticipated developments that we believe are reasonable and appropriate. However, because the use of estimates involves an inherent degree of uncertainty, actual results could differ from those estimates. Estimates are used for, but not limited to, revenue recognition, share-based compensation, determining the fair value of assets acquired and liabilities assumed in business combinations, marketable investments, fair value measurements (including those related to contingent consideration), inventory reserves, investments in privately-held companies, income taxes, goodwill and other intangible assets, and obligations related to our Supplemental Executive Retirement Plan.

Fair Value Measurements

Fair value is a market-based measurement, not an entity-specific measurement. The objective of a fair value measurement is to estimate the price to sell an asset or transfer a liability in an orderly transaction between market participants at the measurement date under current market conditions. Such transactions to sell an asset or transfer a liability are assumed to occur in the principal market for that asset or liability, or in the absence of the principal market, the most advantageous market for the asset or liability.

Assets and liabilities subject to fair value measurement disclosures are required to be classified according to a three-level fair value hierarchy with respect to the inputs (or assumptions) used to determine fair value. The level in which an asset or liability is disclosed within the fair value hierarchy is based on the lowest level input that is significant to the related fair value measurement in its entirety. The guidance under the fair value measurement framework applies to other existing accounting guidance in the Financial Accounting Standards Board (**FASB**) codification that requires or permits fair value measurements. Refer to related disclosures in Note 5—*Fair Value Measurements.*

Cash Equivalents

Cash equivalents consist of highly liquid investments with maturities of three months or less from the date of acquisition.

Marketable Investments

Our marketable investments are primarily debt securities that we classify as available-for-sale. If we have both the positive intent and the ability to hold the securities until maturity, the securities are classified as held-to-maturity. We determine the appropriate classification of the securities at the time they are acquired and evaluate the appropriateness of such classifications at each balance sheet date. Available-for-sale debt securities are recorded at fair value, with the portion of the unrealized gains and losses that are not credit-related included as a component of *accumulated other comprehensive income (loss)* in stockholders' equity, until realized. Held-to-maturity debt securities are recorded at amortized cost, adjusted for the amortization of discounts or premiums. Related discounts and premiums are amortized over the term of these securities as an adjustment to the yield using the effective interest method. Marketable investments are classified as either *current* or *non-current assets* in our consolidated balance sheets based on their contractual maturity dates.

We monitor our available-for-sale investments for impairment quarterly or more frequently if circumstances warrant. In the event that the carrying value of a debt security exceeds its fair value, we evaluate whether any impairment is a result of credit loss or other factors. For investments in an unrealized loss position, we determine whether a credit loss exists by considering information about the collectibility of the instrument, current market conditions, the investment issuer's financial condition and business outlook, and reasonable and supportable forecasts of economic conditions. An allowance for credit losses would be recorded in our consolidated statements of operations in the event the decline in the investment's fair value was a result of credit loss, and unrealized losses not related to credit losses would be recorded in *other comprehensive income (loss)*.

Our marketable investments also include investments in publicly-traded companies. The equity securities we own in these companies are recorded at fair value. Changes in the fair value of publicly-traded equity securities are recorded in our consolidated statements of operations within *other income, net*.

Inventories

Inventories are stated at the lower of cost (first-in, first-out method) or net realizable value and consist of the following, net of reserves (in millions):

	As of December 31,	
	2021	**2020**
Raw materials	$ 17.6	$ 18.4
Work-in-progress	31.9	29.5
Finished goods	44.3	38.6
Total inventories	$ 93.8	$ 86.5

Goodwill and Other Intangible Assets

The carrying amount of goodwill is not amortized but is subject to annual impairment testing. We conduct our impairment testing of goodwill annually during the fourth quarter, or more frequently if impairment indicators exist. Initially, we evaluate various pertinent qualitative factors to assess whether it is more likely than not that the fair value of a reporting unit to which goodwill has been assigned is less than its carrying value. Such qualitative factors can include, among others: (1) industry and market conditions; (2) present and anticipated sales and cost factors; and (3) overall financial performance. If we conclude based on our qualitative assessment that it is more likely than not that the fair value of a reporting unit is less than its carrying value, we then measure the fair value of the reporting unit and compare its fair value to its carrying value (Step 1 of the goodwill impairment test). Following adoption of ASU 2017-04 on January 1, 2020, we are no longer required to perform Step 2 of the goodwill impairment test. The impairment charge is limited to the amount of goodwill allocated to the reporting unit, thus, the new standard eliminates the requirement to calculate a goodwill impairment charge using Step 2. We performed a qualitative assessment for our goodwill impairment testing for 2021 and 2020. During the years ended December 31, 2021 and 2020, our evaluation of goodwill did not result in any impairment losses. During the year ended December 31, 2019, we wrote off $3.5 million of goodwill related to the deconsolidation of a variable interest entity, as discussed in Note 4—*Investments—Variable Interest Entities—Deconsolidation of a Variable Interest Entity.*

Indefinite-lived intangible assets are not amortized but are evaluated annually or more frequently for impairment if impairment indicators exist. Our indefinite-lived intangible assets include purchased in-process research and development (**IPR&D**) assets, which were measured at their estimated fair values as of their acquisition dates. During the year ended December 31, 2021, we recognized IPR&D impairment charges of $113.4 million related to our decision to discontinue the U.S. development of Trevyent® and our decision to discontinue our research and development efforts related to biomechanical lungs, described in footnotes 1 and 2, respectively, to the Goodwill table below. There were no impairment losses related to indefinite-lived intangible assets during the year ended December 31, 2020. During the year ended December 31, 2019, we recognized an impairment charge of $8.8 million related to an IPR&D asset associated with our terminated license agreement with a variable interest entity, as discussed in Note 4—*Investments—Variable Interest Entities—Deconsolidation of a Variable Interest Entity.*

Intangible assets subject to amortization are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an intangible asset may not be recoverable. Impairment losses are measured and recognized to the extent the carrying value of such assets exceeds their fair value. We recorded no impairment losses during the years ended December 31, 2021, 2020, and 2019 related to intangible assets subject to amortization.

Goodwill and other intangible assets comprise the following (in millions):

	As of December 31, 2021			As of December 31, 2020		
	Gross	Accumulated Amortization	Net	Gross	Accumulated Amortization	Net
Goodwill	$ 28.0	$ —	$ 28.0	$ 28.0	$ —	$ 28.0
Other intangible assets:						
Technology, patents, and trade names	6.7	(5.6)	1.1	6.7	(5.5)	1.2
In-process research and development[1][2]	15.5	—	15.5	128.9	—	128.9
Total	$ 50.2	$ (5.6)	$ 44.6	$ 163.6	$ (5.5)	$ 158.1

(1) In March 2021, we decided to discontinue the U.S. development of Trevyent due to written comments provided by the FDA in February 2021. The FDA provided these written comments following a meeting between us and the FDA to discuss our planned resubmission of our NDA for Trevyent in light of a complete response letter issued by the FDA in April 2020. We determined this decision to be a potential indicator of impairment of our IPR&D asset related to Trevyent, which had a carrying value of $107.3 million as of December 31, 2020. Based on our decision to discontinue the U.S. development of Trevyent, we fully impaired the IPR&D asset related to Trevyent during 2021. The $107.3 million impairment charge was recorded within *research and development* in our consolidated statements of operations.

(2) In January 2021, we decided to discontinue our research and development efforts related to biomechanical lungs. As a result of the decision, we fully impaired the IPR&D asset related to these efforts, which had a carrying value of $6.1 million, during 2021. The impairment charge was recorded within *research and development* in our consolidated statements of operations.

Related amortization expense for the years ended December 31, 2021, 2020, and 2019, was $0.1 million, $0.2 million, and $0.2 million, respectively. As of December 31, 2021, aggregate amortization expense related to definite-lived intangible assets for each of the five succeeding years and thereafter is estimated at less than $1.0 million per year.

Property, Plant, and Equipment

Property, plant, and equipment is recorded at cost and depreciated over its estimated useful life using the straight-line method. The estimated useful lives of property, plant, and equipment by major category are as follows:

Land improvements	15 Years
Buildings	25-39 Years
Building improvements	10-39 Years
Furniture, equipment, and vehicles	3-25 Years
Leasehold improvements	Remaining lease term, or the estimated useful life of the improvement, whichever is shorter

Property, plant, and equipment (**PP&E**) consists of the following (in millions):

	As of December 31,	
	2021	2020
Land and land improvements	$ 132.6	$ 74.9
Buildings, building improvements, and leasehold improvements	612.7	593.6
Buildings under construction	55.1	47.4
Furniture, equipment, and vehicles	322.9	325.0
Subtotal	1,123.3	1,040.9
Less—accumulated depreciation	(342.4)	(309.3)
Property, plant, and equipment, net	$ 780.9	$ 731.6

Depreciation expense for the years ended December 31, 2021, 2020, and 2019, was $49.8 million, $49.7 million, and $45.7 million, respectively.

Buildings under construction consists of direct costs related to our construction projects.

In 2019, we completed construction of a new cell culture and purification facility. During 2021, we decided to repurpose this facility to produce autologous cells that we intend to use to cellularize lung scaffolds for clinical studies. The decision to repurpose this facility was an indicator of impairment of the facility which we evaluated during 2021. Based on our impairment assessment, we recorded an $11.6 million impairment charge on equipment that was disposed of when we repurposed this facility during 2021. For the year ended December 31, 2021, we recorded $19.2 million of PP&E impairment charges in the aggregate, of which $16.7 million was recorded within *research and development* in our consolidated statements of operations and $2.5 million was recorded within *selling, general, and administrative* in our consolidated statements of operations. For the year ended December 31, 2020, we recorded a $5.4 million PP&E impairment charge, which was recorded within *selling, general, and administrative* in our consolidated statements of operations.

In October 2021, we acquired a 141,960 square foot commercial building located in Silver Spring, Maryland for future expansion. The total purchase price was $50.9 million, inclusive of taxes, closing costs, and other related expenses, the majority of which was capitalized as land and land improvements based on our intended use of the property.

Investments in Privately-Held Companies

We measure our non-controlling equity investments in privately-held companies using the measurement alternative because the fair values of these investments are not readily determinable. Under this alternative, the investments are measured at cost, less any impairment, adjusted for any observable price changes. We monitor these investments individually for any observable price changes or impairment indicators. We adjust the measurement of these investments for observable price changes in orderly transactions for the identical or a similar investment of the same issuer. We consider relevant transactions, including any potential funding opportunities, which occur on or before the balance sheet date in evaluating whether any observable price changes have occurred. When a relevant transaction is identified, a careful review of the attendant rights and obligations, such as voting rights, liquidation preferences, and protective provisions, is necessary to evaluate whether such transaction is deemed to be a similar or identical investment. When a transaction is identified as similar or identical to our investment, we assess the fair value of our investment using various inputs, such as the discount rate, time to a liquidation event, and volatility, in a valuation model or analysis. We include our investments in privately-held companies within *other non-current assets* in our consolidated balance sheets.

These investments are subject to a periodic impairment review and if impaired, the investment is measured and recorded at fair value in accordance with FASB Accounting Standards Codification (**ASC**) 820, *Fair Value Measurements*. At each reporting date, we review these investments individually for impairment by evaluating whether events or circumstances have occurred that may have a significant adverse effect on the fair value of the investments. If such events or circumstances have occurred, we will estimate the fair value of the investment. In such cases, we determine the estimated fair value of the investment using unobservable inputs including assumptions by the company's management.

Treasury Stock

Repurchased treasury stock is recorded at cost, including commissions and fees. The cost of treasury shares sold or reissued is determined using the first-in, first-out method. Related gains and losses on sales of treasury stock are recognized as adjustments to stockholders' equity.

Revenue Recognition

We determine revenue recognition for our contractual arrangements with customers based on the following five steps: (1) identify each contract with a customer; (2) identify the performance obligations in the contract; (3) determine the transaction price; (4) allocate the transaction price to our performance obligations in the contract; and (5) recognize revenue when (or as) we satisfy the relevant performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

Revenues are generated from the sale of our five commercially approved products: Tyvaso, Remodulin, Orenitram, Unituxin, and Adcirca. We recognize revenue when we transfer control of our product to our distributors, which is generally when the product is shipped or delivered to the distributor. Future revenue from delivery of our products will be based on purchase orders provided to us by our distributors.

See Note 13—*Segment Information*, for information on revenues disaggregated by commercial product, geographic area, and customer.

Gross-to-Net Deductions

As is customary in the pharmaceutical industry, our product sales are recorded net of various forms of gross-to-net deductions. These deductions vary the consideration to which we are entitled in exchange for the sale of our products to our distributors, and include reserves for: (1) rebates and chargebacks; (2) prompt payment discounts; (3) allowance for sales returns; and (4) distributor fees and other allowances. We estimate these reserves in the same period that we recognize revenue for product

sales to distributors. The net product sales amount recognized represents the amount we believe will not be subject to a significant future reversal of revenue.

Estimating gross-to-net deductions involves the use of significant assumptions and judgments, as well as information obtained from external sources. For our rebate and chargeback liabilities, in particular, the time lag experienced in the payment of the rebate or chargeback may result in revisions of these accruals in future periods. However, based on our significant history and experience estimating these accruals and our development of these accruals based on the expected value method, we do not believe there will be significant changes to our estimates recorded during the period of sale. We recognized an aggregate $2.1 million increase in our net product sales for the year ended December 31, 2021, an aggregate $0.5 million increase in our net product sales for the year ended December 31, 2020, and an aggregate $2.3 million decrease in our net product sales for the year ended December 31, 2019, related to revenue recognized from product sales in prior periods.

Rebates and chargebacks. Allowances for rebates include mandated discounts due to our participation in various government health care programs, contracted rebates to certain domestic distributors, and contracted discounts with commercial payers. We estimate our rebate liability on a product-by-product basis, considering actual revenue, contractual discount rates, expected utilization under each contract, and historical payment experience. We also consider changes in our product pricing and information regarding changes in program regulations and guidelines. Our chargebacks represent contractual discounts payable to distributors for the difference between the invoice price paid to us by the distributor for a particular product and the contracted price that the distributor's customer pays for that product. We estimate our chargeback liability on a product-by-product basis, primarily considering historical payment experience. Although we accrue a liability for rebates and chargebacks in the same period the product is sold, third-party reporting and payment of the rebate or chargeback amount occur on a time lag, with the majority of rebates and chargebacks paid within six months from date of sale. Our liability for rebates and chargebacks is included in accounts payable and accrued expenses in our consolidated balance sheets. At December 31, 2021 and 2020, our accrued rebates and chargebacks were $67.8 million and $65.3 million, respectively. In addition, during the years ended December 31, 2021, 2020, and 2019, we recognized $218.6 million, $195.9 million, and $178.7 million, respectively, in revenue deductions associated with rebates and chargebacks.

Prompt payment discounts. We offer prompt pay discounts to many of our distributors, typically for payments made within 30 days. Prompt pay discounts are estimated in the period of sale based on our experience with sales to eligible distributors. Our domestic distributors have routinely taken advantage of these discounts and we expect them to continue to do so. Prompt pay discounts are recorded as a deduction to the accounts receivable balance presented in our consolidated balance sheets.

Product returns. The sales terms for Adcirca and Unituxin include return rights that extend throughout the distribution channel. For Adcirca, we recognize an allowance for returns as customers have the right to return expired product for up to 12 months after the product's expiration date (generally 24 to 36 months after the initial sale). Returned product is destroyed. Regulatory exclusivity for Adcirca expired in May 2018, and generic versions of Adcirca became available for purchase beginning in the third quarter of 2018. Due to the availability of the generic versions, we have experienced a significant decline in Adcirca demand, which could result in inventory held by distributors and other downstream customers expiring unsold. Our allowance for product returns for Adcirca as of December 31, 2021 and 2020 is $6.3 million and $12.5 million, respectively. We record our allowance for product returns in *other current* and *non-current liabilities* in our consolidated balance sheets. We developed our returns liability as of December 31, 2021 and 2020, based on our estimate of the amount of Adcirca inventory in the downstream channel and the amount of that inventory that we expect will not be sold by distributors and other downstream customers. The estimates were developed using reports from our distributors and other third-party data, including estimates of Adcirca dispenses and the historical impact of generic entrants on other branded products that we deemed comparable to Adcirca. During the year ended December 31, 2021, we recognized a decrease of $3.9 million in revenue reductions associated with our allowance for product returns. During the year ended December 31, 2020, we recognized no change in revenue deductions associated with our allowance for product returns. During the year ended December 31, 2019, we recognized a decrease of $6.2 million in revenue deductions associated with our allowance for product returns.

For Unituxin, we ship product with expiration dates that are generally nine to 14 months after the initial sale. However, our historical returns have not been material and, therefore, we do not record a returns allowance for Unituxin. For sales of our other commercial products, we do not offer our customers a general right of return.

Distributor fees and other allowances. Distributor fees include distribution and other service fees paid to certain distributors. These fees are based on contractual amounts or rates applied to purchases of our product or units of service provided in a given period. Our liability for distributor fees is included in *accounts payable and accrued expenses* in our consolidated balance sheets.

Trade Receivables

We invoice and receive payment from our customers after we recognize revenue, resulting in receivables from our customers that are presented as *accounts receivable* in our consolidated balance sheets. Accounts receivable consist of short-term amounts due from our distributors (generally 30 to 90 days) and are stated at the amount we expect to collect. We establish an allowance for doubtful accounts, if deemed necessary, based on our assessment of the collectability of specific distributor accounts. We did not recognize any impairment losses for accounts receivable for each of the years ended December 31, 2021 and 2020. Changes in accounts receivable are primarily due to the timing and magnitude of orders of our products, the timing of when control of our products is transferred to our distributors, and the timing of cash collections.

Adcirca

Adcirca is manufactured for us by Lilly and distributed through its pharmaceutical wholesaler network on our behalf. Specifically, Lilly handles all of the administrative functions associated with the sale of Adcirca on our behalf, including the receipt and processing of customer purchase orders, shipment to customers, and invoicing and collection of customer payments. We recognize sales of Adcirca on a gross basis (net of reserves for gross-to-net deductions) based on our determination that we are acting as a principal due to our control of the product prior to its transfer to our customers. Our control is evidenced by our substantive ownership of product inventory, the fact that we bear all inventory risks, our primary responsibility for the acceptability of the product to our customers, and our ability to influence net product sales through our contracting decisions with commercial payers and participation in governmental-funded programs.

Research and Development

Research and development costs are expensed as incurred except for payments made in advance of services to be provided to us. Related expenses consist of internal labor and overhead, costs to acquire pharmaceutical products and product rights for development, materials used in clinical trials, amounts paid to third parties for services, and materials related to drug development and clinical trials.

As part of our business strategy, we may in-license the rights to develop and commercialize product candidates. For each in-license transaction, we evaluate whether we have acquired processes or activities along with inputs that would be sufficient to constitute a "business" as defined under GAAP. As defined under GAAP, a "business" consists of inputs and processes applied to those inputs that have the ability to create outputs. Although businesses usually have outputs, outputs are not required for an integrated set of activities to qualify as a business. When we determine that we have not acquired sufficient processes or activities to constitute a business, any up-front payments, as well as pre-commercial milestone payments, are immediately expensed as acquired IPR&D in the period in which they are incurred. Milestone payments made to third parties subsequent to regulatory approval are capitalized as intangible assets and amortized over the estimated remaining useful life of the related product.

We recognize the following costs, among others, as research and development expense in the period related costs are incurred:

- costs associated with in-house or contracted manufacturing activities prior to receiving FDA approval for such facilities, or for major unproven changes to our manufacturing processes;
- costs incurred in-licensing the rights to technologies in the research and development stage that have no alternative future use; and
- up-front payments made in connection with arrangements to obtain license and distribution rights to pharmaceutical product candidates prior to regulatory approval, absent any alternative future use.

Share-Based Compensation

Generally, the fair value of a stock option grant is measured on its grant date and related compensation expense is recognized ratably over the requisite service period. We issue new shares of our common stock upon the exercise of stock options. Additionally, certain executives sometimes have stock options with performance conditions that have vesting rights tied to achievement of specific targeted criteria. Share-based compensation expense for all awards is recorded ratably over their vesting period, depending on the specific terms of the award and achievement of the specified performance conditions. Forfeitures are recognized as they occur. Refer to Note 8—*Share-Based Compensation*.

We measure the fair value of restricted stock units using the stock price on the date of grant and related compensation expense is recognized ratably over the vesting period. Each restricted stock unit entitles the holder to receive one share of our common stock upon vesting. We issue new shares of our common stock upon the vesting of restricted stock units.

Awards under our share tracking awards plans require cash settlement upon exercise and are classified as a liability. Accordingly, the fair value of related cash-settled awards is re-measured at each reporting date until awards are exercised or are otherwise no longer outstanding. Related changes in the fair value of outstanding cash-settled awards at each financial reporting date are recognized as adjustments to share-based compensation expense.

We measure the fair value of stock to be purchased through our employee stock purchase plan at the beginning of an offering period, or grant date, and recognize related compensation expense ratably over the requisite service period (the offering period). We issue new shares of our common stock upon the end of each offering period, or exercise date.

Income Taxes

We account for income taxes in accordance with the asset and liability method. Under this method, we determine deferred tax assets and liabilities based on the difference between the financial statement carrying amounts and the tax bases of assets and liabilities, using enacted tax rates in effect for years in which the temporary differences are expected to reverse. We apply a valuation allowance against any net deferred tax asset if, based on the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

We recognize the benefit of an uncertain tax position that has been taken or that we expect to take on income tax returns only if such tax position is more likely than not to be sustained. We recognize the benefit in an amount equal to the largest amount that we determine has a greater than 50 percent likelihood of being realized upon settlement. The ultimate resolution of uncertain tax positions could result in amounts different from those recognized in our consolidated financial statements.

We have elected to account for the tax on Global Intangible Low-Taxed Income, enacted as part of the Tax Cuts and Jobs Act, as a component of tax expense in the period in which the tax is incurred.

Earnings per Share

Basic earnings (loss) per share is computed by dividing net income (loss) by the weighted average number of shares of common stock outstanding during the period. Diluted earnings (loss) per common share is computed by dividing net income (loss) by the weighted average number of shares of common stock outstanding during the period, plus the potential dilutive effect of other securities if such securities were converted or exercised. During periods in which we incur net losses, both basic and diluted loss per share are calculated by dividing the net loss by the weighted average shares outstanding. Potentially dilutive securities are excluded from the calculation because their effect would be anti-dilutive.

Concentration of Credit Risk

Financial instruments that are exposed to credit risk consist of cash, money market funds, certificates of deposit, marketable debt securities, and trade receivables. We maintain our cash and money market funds with financial institutions that are federally insured. While balances deposited in these institutions often exceed Federal Deposit Insurance Corporation limits, we have not experienced any losses on related accounts to date. Furthermore, we limit our risk exposure by maintaining funds in financial institutions that we believe are creditworthy and financially sound. Our investments in marketable debt securities have been issued by corporate entities and government-sponsored enterprises with high credit ratings. We mitigate investment risks by investing in highly-rated securities with relatively short maturities that we believe do not subject us to undue investment or credit risk. In addition, our investment policy does not provide for investments in complex or structured financial instruments. At any given time, our trade receivables are concentrated among a small number of principal customers. If any of these financial institutions, issuers, or customers fail to perform their obligations under the terms of these financial instruments, our maximum exposure to potential losses would be equal to amounts reported in our consolidated balance sheets.

3. Recently Issued Accounting Standards

Accounting Standards Adopted

In December 2019, the Financial Accounting Standards Board (**FASB**) issued Accounting Standards Update (**ASU**) No. 2019-12, *Simplifying the Accounting for Income Taxes* (**ASU 2019-12**), which simplifies the accounting for income taxes by removing certain exceptions to the general principles of Topic 740, Income Taxes, and also improves consistency of application by clarifying and amending existing guidance. ASU 2019-12 is effective for fiscal years beginning after December 15, 2020. We adopted the new standard on January 1, 2021, with no material impact on our financial statements.

In January 2020, the FASB issued ASU No. 2020-01, *Investments-Equity Securities (Topic 321), Investments–Equity Method and Joint Ventures (Topic 323), and Derivatives and Hedging (Topic 815)–Clarifying the Interactions between Topic 321, Topic 323, and Topic 815 (a consensus of the Emerging Issues Task Force)* (**ASU 2020-01**), which addresses the accounting for the transition into and out of the equity method and measuring certain purchased options and forward contracts to acquire investments. ASU 2020-01 is effective for fiscal years beginning after December 15, 2020. We adopted the new standard on January 1, 2021, with no material impact on our financial statements.

Accounting Standards Not Yet Adopted

In March 2020, the FASB issued ASU No. 2020-04, *Reference Rate Reform (Topic 848): Facilitation of the Effects of Reference Rate Reform on Financial Reporting* (**ASU 2020-04**), which provides optional expedients and exceptions to lessen the burden of accounting for contract modifications and hedging relationships that reference LIBOR or other reference rates that could be discontinued due to reference rate reform. ASU 2020-04 became effective immediately and may be applied through December 31, 2022. This guidance is applicable to our credit agreement, which references LIBOR. Refer to Note 7—*Debt* for more information on our credit agreement. The adoption of, and future elections under, this guidance are not expected to have a material impact on our consolidated financial statements as the guidance will ease, if warranted, the requirements for accounting for the future effects of the rate reform.

4. Investments

Marketable Investments

Available-for-Sale Debt Securities

Available-for-sale debt securities are recorded at fair value, with the portion of the unrealized gains and losses that are not credit-related included as a component of *accumulated other comprehensive loss* in stockholders' equity, until realized. Available-for-sale debt securities consisted of the following (in millions):

As of December 31, 2021	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. government and agency securities	$ 2,178.9	$ 2.0	$ (7.3)	$ 2,173.6
Corporate debt securities	482.5	0.6	(2.0)	481.1
Total	$ 2,661.4	$ 2.6	$ (9.3)	$ 2,654.7
Reported under the following captions in our consolidated balance sheets:				
Cash and cash equivalents				$ 39.3
Current marketable investments				965.5
Non-current marketable investments				1,649.9
Total				$ 2,654.7

As of December 31, 2020	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. government and agency securities	$ 1,902.4	$ 9.8	$ (0.1)	$ 1,912.1
Corporate debt securities	331.2	3.2	—	334.4
Total	$ 2,233.6	$ 13.0	$ (0.1)	$ 2,246.5
Reported under the following captions in our consolidated balance sheets:				
Cash and cash equivalents				$ 79.0
Current marketable investments				1,017.9
Non-current marketable investments				1,149.6
Total				$ 2,246.5

The following table summarizes the contractual maturities of available-for-sale debt securities (in millions). Actual maturities may differ from contractual maturities because the issuers of certain of these debt securities have the right to call the securities or prepay their obligations under the securities with or without penalties.

	As of December 31, 2021	
	Amortized Cost	Fair Value
Due within one year	$ 1,003.8	$ 1,004.8
Due in one to three years	1,657.6	1,649.9
Total	$ 2,661.4	$ 2,654.7

Investments in Equity Securities with Readily Determinable Fair Values

We held investments in equity securities with readily determinable fair values of $70.4 million and $78.4 million as of December 31, 2021 and 2020, respectively, which are included in *current marketable investments* in our consolidated balance sheets. One of the privately-held companies in which we invested became publicly traded in 2020 and another one became publicly traded in 2021. As a result, our investments in the equity securities of these companies are now recorded at fair value and included within *current marketable investments* in our consolidated balance sheets rather than measured as described below under *Investments in Privately-Held Companies*. Changes in the fair value of publicly-traded equity securities are recorded in our consolidated statements of operations within *other income, net*. Refer to Note 5—*Fair Value Measurements*.

During the years ended December 31, 2021, 2020, and 2019, we received $111.5 million, $27.3 million, and $20.5 million, respectively, in cash from the sale of these equity securities. During 2021, we sold our investments in two publicly-traded companies and realized a gain of $92.6 million. During 2020 and 2019, we sold our investment in one publicly-traded company and realized a gain of $3.4 million and $2.6 million, respectively. The gains were recorded within *other income, net* in our consolidated statements of operations for the years ended December 31, 2021, 2020, and 2019.

Investments in Privately-Held Companies

As of December 31, 2021 and 2020, we maintained non-controlling equity investments in privately-held companies of $31.1 million and $84.8 million, respectively, in the aggregate. We made payments of $8.0 million for investments in privately-held companies during the year ended December 31, 2019. No such payments were made during the years ended December 31, 2021 and 2020.

When an observable price transaction occurs that is identified as similar or identical to our investment, we perform a valuation analysis to assess the fair value of our investment using various inputs, such as the discount rate, time to a liquidation event, and price volatility of peer company stocks. We adjust the fair value of our investment based on the valuation analysis and recognize the gain or loss in the period in which the observable price change occurred. During the years ended December 31, 2021, 2020, and 2019, we recorded an aggregate increase of zero, $25.5 million, and $1.2 million, respectively, in the value of our investments. These gains were recorded within *other income, net* in our consolidated statements of operations.

During 2021, we observed an indicator of impairment for our investments in two of the private companies in which we invested, which caused us to recognize aggregate impairment charges of $2.3 million. During the years ended December 31, 2020 and 2019, we recorded $9.1 million and zero, respectively, of impairment charges related to our investments in privately-held companies. These impairment charges were recorded within *impairments of investments in privately-held companies* in our consolidated statements of operations.

Cumulative impairments and downward fair value adjustments on non-controlling equity investments in privately-held companies and cumulative upward fair value adjustments in privately-held companies were $4.1 million and $1.9 million, respectively, as of December 31, 2021.

Variable Interest Entities

We evaluate our interests in variable interest entities (**VIEs**) and will consolidate any VIE in which we have a controlling financial interest and are deemed to be the primary beneficiary. A controlling financial interest has both of the following characteristics: (1) the power to direct the activities of the VIE that most significantly impact its economic performance; and (2) the obligation to absorb losses of the VIE that could potentially be significant to the VIE or the right to receive benefits from the VIE that could be significant to the VIE. If both of the characteristics are met, we are considered to be the primary beneficiary and therefore will consolidate that VIE into our consolidated financial statements.

Unconsolidated Variable Interest Entity

In November 2019, we entered into a supply agreement with an affiliate of DEKA Research & Development Corporation (**DEKA**) to manufacture and supply the Remunity® Pump to us. Under the terms of the supply agreement, we reimburse all of the affiliate's costs to manufacture and supply the Remunity Pump. We determined that the affiliate is a VIE as we are currently the only customer of the affiliate and the affiliate currently relies on our reimbursement of its costs to sustain its operations. We have determined we are not the primary beneficiary of the affiliate as we do not have the power to direct or control its significant activities related to the manufacturing of medical devices. Accordingly, we have not consolidated the affiliate's results of operations and financial position with ours. As of December 31, 2021 and 2020, our consolidated balance sheets included $10.6 million and $11.7 million of assets, respectively, related to the supply agreement. As of December 31, 2021 and 2020, our consolidated balance sheets included a $2.0 million and $24.0 million liability, respectively, for our obligation to reimburse costs related to the supply agreement. While the terms of the supply agreement expose us to various future risks of loss given our responsibility to reimburse all costs incurred by the affiliate to manufacture and supply the Remunity Pump, we believe that our maximum exposure to loss as of December 31, 2021 as a result of our involvement with the affiliate is $10.6 million, the amount of assets related to the supply agreement noted above.

Consolidation of a Variable Interest Entity

In August 2019, we entered into an operating agreement and trust agreement related to the contribution of an asset to a newly created trust of which we are the beneficiary. The trust was created for legal and administrative purposes and is not expected to make future purchases. As the operator of the asset, we are required to incur all future expenses related to the operation and maintenance of the asset. Accordingly, the trust is deemed a VIE because it relies on our capital to sustain future operating expenses. We are deemed the primary beneficiary of the VIE because we are the sole provider of financial support and can unilaterally remove the trustee without cause. Accordingly, we consolidate the VIE's balance sheet and results of operations.

As of December 31, 2021, our consolidated balance sheets included a $49.3 million asset due to the consolidation of this VIE included within *property, plant, and equipment, net*. Upon consolidating the VIE, which was not deemed a business as defined in ASC 805, *Business Combinations*, no gain or loss was recognized. This VIE has no recourse against our assets and general credit, and the VIE assets cannot be used to settle the VIE liabilities. Our total risk of loss is the $49.3 million asset we contributed, as noted above.

Deconsolidation of a Variable Interest Entity

In April 2017, we made a $7.5 million minority equity investment in a privately-held company. In addition to our investment, we entered into an exclusive license, development, and commercialization agreement (the **License Agreement**) with this company. The License Agreement entitled us to control rights sufficient to require us to regard the company as a VIE and to consolidate the company's balance sheet and results of operations as the primary beneficiary of this company.

In June 2019, we elected to terminate the License Agreement. The termination of the License Agreement caused us to impair an associated IPR&D asset during 2019 and recognize an impairment charge of $8.8 million, which is included within *research and development* in our consolidated statements of operations. Upon effectiveness of the termination of the License Agreement in 2019, we no longer have the power to direct the entity's activities. Consequently, we deconsolidated the entity in 2019. Our deconsolidation of the entity's balance sheet, which included $3.5 million of goodwill and $8.4 million of temporary equity, resulted in a net deconsolidation loss of $2.0 million. We have no further obligations to fund the entity. In 2021, we recognized an impairment charge equal to the entire value of our equity investment in this privately-held company of $1.3 million and recorded the impairment charge within *impairments of investments in privately-held companies* in our consolidated statements of operations.

5. Fair Value Measurements

Assets and liabilities subject to fair value measurements are required to be disclosed within a fair value hierarchy. The fair value hierarchy ranks the quality and reliability of inputs used to determine fair value. Accordingly, assets and liabilities carried at, or permitted to be carried at, fair value are classified within the fair value hierarchy in one of the following categories based on the lowest level input that is significant in measuring fair value:

Level 1—Fair value is determined by using unadjusted quoted prices that are available in active markets for identical assets and liabilities.

Level 2—Fair value is determined by using inputs other than Level 1 quoted prices that are directly or indirectly observable. Inputs can include quoted prices for similar assets and liabilities in active markets or quoted prices for identical assets and liabilities in inactive markets. Related inputs can also include those used in valuation or other pricing models such as interest rates and yield curves that can be corroborated by observable market data.

Level 3—Fair value is determined by using inputs that are unobservable and not corroborated by market data. Use of these inputs involves significant and subjective judgment.

We account for certain assets and liabilities at fair value and classify these assets and liabilities within the fair value hierarchy. Our *other current assets* and *other current liabilities* have fair values that approximate their carrying values. Assets and liabilities subject to fair value measurements are as follows (in millions):

	As of December 31, 2021			
	Level 1	**Level 2**	**Level 3**	**Balance**
Assets				
Money market funds[1]	$ 516.7	$ —	$ —	$ 516.7
U.S. government and agency securities[2]	—	2,173.6	—	2,173.6
Corporate debt securities[2]	—	481.1	—	481.1
Equity securities[3]	70.4	—	—	70.4
Contingent consideration[4]	—	—	1.2	1.2
Total assets	$ 587.1	$ 2,654.7	$ 1.2	$ 3,243.0
Liabilities				
Contingent consideration[5]	—	—	20.8	20.8
Total liabilities	$ —	$ —	$ 20.8	$ 20.8

	As of December 31, 2020			
	Level 1	**Level 2**	**Level 3**	**Balance**
Assets				
Money market funds[1]	$ 323.1	$ —	$ —	$ 323.1
U.S. government and agency securities[2]	—	1,912.1	—	1,912.1
Corporate debt securities[2]	—	334.4	—	334.4
Equity securities[3]	78.4	—	—	78.4
Contingent consideration[4]	—	—	4.1	4.1
Total assets	$ 401.5	$ 2,246.5	$ 4.1	$ 2,652.1
Liabilities				
Contingent consideration[5]	—	—	17.1	17.1
Total liabilities	$ —	$ —	$ 17.1	$ 17.1

(1) Included in *cash and cash equivalents* in our consolidated balance sheets.

(2) Included in *cash and cash equivalents* and *current* and *non-current marketable investments* in our consolidated balance sheets. Refer to Note 4 —*Investments—Marketable Investments—Available-for-Sale Debt Securities* for further information. The fair value of these securities is principally measured or corroborated by trade data for identical securities for which related trading activity is not sufficiently frequent to be considered a Level 1 input or comparable securities that are more actively traded.

(3) Included in *current marketable investments* in our consolidated balance sheets. The fair value of these securities is based on quoted market prices for identical instruments in active markets. During the years ended December 31, 2021 and 2020, we recognized $50.8 million and $25.1 million of net unrealized and realized gains, respectively, on these securities. We recorded these gains and losses in our consolidated statements of operations within *other income, net*. Refer to Note 4—*Investments—Marketable Investments—Investments in Equity Securities with Readily Determinable Fair Values*.

(4) Included in *other non-current assets* in our consolidated balance sheet as of December 31, 2021 and in *other currents assets* and *other non-current assets* in our consolidated balance sheet as of December 31, 2020. We estimated the fair value of contingent consideration using a Monte Carlo simulation. The Monte Carlo simulation incorporates Level 3 inputs including price volatility of peer company stocks and the probability of completing certain milestones during a specified period of time. The fair value of our contingent consideration assets decreased by $2.9 million from December 31, 2020 to December 31, 2021. The loss was recorded within *other income, net* in our consolidated statements of operations.

(5) Included in *other non-current liabilities* in our consolidated balance sheets. The fair value of our contingent consideration obligations has been estimated using probability-weighted discounted cash flow models (**DCFs**). The DCFs incorporate Level 3 inputs including estimated discount rates that we believe that market participants would consider relevant in pricing and the projected timing and amount of cash flows, which are estimated and developed, in part, based on the requirements specific to each acquisition agreement. The fair value of our contingent consideration liabilities increased by $3.7 million from December 31, 2020 to December 31, 2021. The loss was recorded within *research and development* in our consolidated statements of operations.

Fair Value of Financial Instruments

The carrying amounts of cash and cash equivalents, accounts receivable, accounts payable, and accrued expenses approximate fair value because of their short maturities. The fair values of our marketable investments and contingent consideration are reported above within the fair value hierarchy. Refer to Note 4—*Investments*. The carrying value of our debt is a reasonable estimate of the fair value of the outstanding debt based on the variable interest rate of the debt.

6. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following by major categories (in millions):

	As of December 31,	
	2021	2020
Accounts payable	$ 3.8	$ 4.1
Accrued expenses:		
Sales-related (royalties, rebates, and fees)	85.3	84.5
Payroll-related	53.6	47.9
Research and development-related	19.0	27.8
Other	12.9	22.7
Total accrued expenses	$ 170.8	$ 182.9
Total accounts payable and accrued expenses	$ 174.6	$ 187.0

7. Debt

Credit Agreement

In June 2018, we entered into a credit agreement (the **Credit Agreement**) with Wells Fargo Bank, National Association (**Wells Fargo**), as administrative agent and a swingline lender, and various other lender parties, providing for: (1) an unsecured revolving credit facility of up to $1.0 billion; and (2) a second unsecured revolving credit facility of up to $500.0 million (which facilities may, at our request, be increased by up to $300.0 million in the aggregate subject to obtaining commitments from existing or new lenders for such increase and other conditions). In December 2020, we extended the maturity date of the Credit Agreement by one year, to December 2025.

At our option, amounts borrowed under the Credit Agreement bear interest at either the LIBOR rate or a fluctuating base rate, in each case, plus an applicable margin determined on a quarterly basis based in our consolidated ratio of total indebtedness to earnings before interest, taxes, depreciation, and amortization (as calculated in accordance with the Credit Agreement). To date, we have elected to calculate interest on the outstanding balance at LIBOR plus an applicable margin. As of December 31, 2021 and 2020, our outstanding aggregate principal balance under the Credit Agreement was $800.0 million, all of which was classified as a non-current liability because we do not intend to repay any portion of this amount within one year.

The Credit Agreement contains customary events of default and customary affirmative and negative covenants. As of December 31, 2021, we were in compliance with these covenants. Lung Biotechnology PBC is our only subsidiary that guarantees our obligations under the Credit Agreement though, from time to time, one or more of our other subsidiaries may be required to guarantee our obligations.

In connection with the Credit Agreement, we capitalized debt issuance costs, which are being amortized to interest expense over the contractual term of the Credit Agreement. As of December 31, 2021, $2.4 million was recorded in *other current assets* and $6.9 million in *other non-current assets* in our consolidated balance sheets.

The interest expense reported in our consolidated statements of operations for each of the years ended December 31, 2021, 2020, and 2019, related to our borrowings under the Credit Agreement.

8. Share-Based Compensation

As of December 31, 2021, we have two shareholder-approved equity incentive plans: the United Therapeutics Corporation Amended and Restated Equity Incentive Plan (the **1999 Plan**) and the United Therapeutics Corporation Amended and Restated 2015 Stock Incentive Plan (as amended to date, the **2015 Plan**). The 2015 Plan provides for the issuance of up to 11,000,000 shares of our common stock pursuant to awards granted under the 2015 Plan, which includes the 1,000,000 shares added pursuant to an amendment and restatement of the 2015 Plan approved by our shareholders in June 2021. No further awards will be granted under the 1999 Plan. We also have one equity incentive plan, the United Therapeutics Corporation 2019 Inducement Stock Incentive Plan (the **2019 Inducement Plan**), that has not been approved by our shareholders, as permitted by the Nasdaq Stock Market rules. The 2019 Inducement Plan was approved by our Board of Directors in February 2019 and provides for the issuance of up to 99,000 shares of our common stock under awards granted to newly-hired employees. Currently, we grant equity-based awards to employees and members of our Board of Directors in the form of stock options and restricted stock units (**RSUs**) under the 2015 Plan, and we grant RSUs to newly-hired employees under the 2019 Inducement Plan. Refer to the sections entitled *Stock Options* and RSUs below.

We previously issued awards under the United Therapeutics Corporation Share Tracking Awards Plan (**2008 STAP**) and the United Therapeutics Corporation 2011 Share Tracking Awards Plan (**2011 STAP**). We refer to the 2008 STAP and the 2011 STAP collectively as the **STAP** and awards outstanding under either of these plans as **STAP awards**. Refer to the section entitled *Share Tracking Awards Plans* below. We discontinued the issuance of STAP awards in June 2015.

In 2012, our shareholders approved the United Therapeutics Corporation Employee Stock Purchase Plan (**ESPP**), which is structured to comply with Section 423 of the Internal Revenue Code. Refer to the section entitled *Employee Stock Purchase Plan* below.

The following table reflects the components of share-based compensation expense recognized in our consolidated statements of operations (in millions):

	Year Ended December 31,		
	2021	**2020**	**2019**
Stock options	$ 25.4	$ 44.0	$ 70.5
RSUs	24.7	20.5	13.3
STAP awards	86.6	97.8	(39.7)
Employee stock purchase plan	1.8	1.5	1.3
Total share-based compensation expense before tax	$ 138.5	$ 163.8	$ 45.4
Share-based compensation capitalized as part of inventory	$ 1.0	$ 1.0	$ 0.7

Stock Options

We estimate the fair value of stock options using the Black-Scholes-Merton valuation model, which requires us to make certain assumptions that can materially impact the estimation of fair value and related compensation expense. The assumptions used to estimate fair value include the price of our common stock, the expected volatility of our common stock, the risk-free interest rate, the expected term of stock option awards, and the expected dividend yield.

In March 2017 and March 2018, we issued stock options with performance conditions to certain executives with vesting conditions tied to the achievement of specified performance criteria, which had target performance levels that span from one to three years. Upon the conclusion of the performance period, the performance level achieved was measured and the ultimate number of shares that may vest was determined. Share-based compensation expense for these awards was recorded ratably over their vesting periods, depending on the specific terms of the award and anticipated achievement of the specified performance criteria. As of December 31, 2021, the performance period for these awards had ended, and the awards granted in March 2017 and March 2018 had vested. During 2021 and 2020, we did not grant stock options with performance vesting conditions.

A description of the key inputs, requiring estimates, used in determining the fair value of stock options are provided below:

Expected term—The expected term reflects the estimated time period we expect an award to remain outstanding. For the years ended December 31, 2021, 2020, and 2019, we used the simplified approach to develop this input for our stock options as we do not have sufficient historical data related to stock option exercises. Under the simplified approach, the expected term reflects the weighted average midpoint between the vesting date and the expiration date of the awards. For the expected term input related to our STAP awards, refer to the *Share Tracking Awards Plans* section below.

Expected volatility—Volatility is a measure of the amount the price of our common stock has fluctuated (historical volatility) or is expected to fluctuate (expected volatility) during a period. We use historical volatility based on weekly price observations of our common stock during the period immediately preceding an award that is equal to its expected term up to a maximum period of five years. We believe that the volatility in the price of our common stock over the preceding five years generally provides a reliable projection of future long-term volatility.

Risk-free interest rate—The risk-free interest rate is the average interest rate consistent with the yield available on a U.S. Treasury note with a term equal to the expected term of an award.

Expected dividend yield—We do not pay cash dividends on our common stock and do not expect to do so in the future. Therefore, the dividend yield is zero.

The following weighted average assumptions were used in estimating the fair value of stock options granted to employees during the twelve months ended December 31, 2021, 2020, and 2019:

	Year Ended December 31,		
	2021	2020	2019
Expected term of awards (in years)	5.7	5.6	5.8
Expected volatility	32.5 %	33.4 %	33.8 %
Risk-free interest rate	1.0 %	0.5 %	2.4 %
Expected dividend yield	0.0 %	0.0 %	0.0 %

A summary of the activity and status of stock options under our equity incentive plans is presented below:

	Number of Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value (in millions)
Outstanding at January 1, 2021	7,680,194	$ 126.27		
Granted	43,653	177.33		
Exercised	(405,536)	123.47		
Forfeited	(333)	146.03		
Outstanding at December 31, 2021	7,317,978	$ 126.73	4.6	$ 653.9
Exercisable at December 31, 2021	5,592,698	$ 125.92	4.4	$ 504.2
Unvested at December 31, 2021	1,725,280	$ 129.34	5.3	$ 149.7

The weighted average fair value of a stock option granted during each of the years in the three-year period ended December 31, 2021, was $56.69, $34.56, and $39.63, respectively. The total fair value of stock options that vested for each of the years in the three-year period ended December 31, 2021, was $50.4 million, $73.5 million, and $37.4 million, respectively.

Total share-based compensation expense related to stock options is recorded as follows (in millions):

	Year Ended December 31,		
	2021	2020	2019
Cost of product sales	$ 0.1	$ 0.5	$ 0.8
Research and development	0.5	2.0	3.7
Selling, general, and administrative	24.8	41.5	66.0
Share-based compensation expense before taxes	25.4	44.0	70.5
Related income tax benefit	(0.8)	(3.1)	(16.0)
Share-based compensation expense, net of taxes	$ 24.6	$ 40.9	$ 54.5

As of December 31, 2021, unrecognized compensation cost relating to stock options was $25.7 million. Unvested outstanding stock options as of December 31, 2021 had a weighted average remaining vesting period of 1.2 years.

Stock option exercise data is summarized below (dollars in millions):

	Year Ended December 31,		
	2021	2020	2019
Number of options exercised	405,536	466,731	191,508
Cash received from options exercised	$ 50.0	$ 33.8	$ 9.9
Total intrinsic value of options exercised	$ 26.6	$ 22.9	$ 11.5
Tax benefits realized from options exercised[(1)]	$ 5.3	$ 5.4	$ 2.6

(1) We recognize these tax benefits in our consolidated statements of operations within income tax (expense) benefit.

RSUs

In June 2016, we began issuing RSUs to our non-employee directors. In October 2017, we also began issuing RSUs to our employees. Each RSU entitles the recipient to one share of our common stock upon vesting. We measure the fair value of RSUs using the stock price on the date of grant. Share-based compensation expense for the RSUs is recorded ratably over their vesting period.

A summary of the activity with respect to, and status of, RSUs during year ended December 31, 2021 is presented below:

	Number of RSUs	Weighted Average Grant Date Fair Value
Unvested at January 1, 2021	440,528	$ 102.40
Granted	188,378	166.19
Vested	(210,676)	106.23
Forfeited/canceled	(27,691)	121.33
Unvested at December 31, 2021	390,539	$ 129.76

Total share-based compensation expense relating to RSUs is recorded as follows (in millions):

	Year Ended December 31,		
	2021	2020	2019
Cost of product sales	$ 2.1	$ 1.6	$ 1.0
Research and development	8.2	7.0	4.4
Selling, general, and administrative	14.4	11.9	7.9
Share-based compensation expense before taxes	24.7	20.5	13.3
Related income tax benefit	(5.9)	(4.8)	(3.0)
Share-based compensation expense, net of taxes	$ 18.8	$ 15.7	$ 10.3

As of December 31, 2021, unrecognized compensation cost related to the grant of RSUs was $31.5 million. Unvested outstanding RSUs as of December 31, 2021 had a weighted average remaining vesting period of 1.8 years.

Share Tracking Awards Plans

STAP awards convey the right to receive in cash an amount equal to the appreciation of our common stock, which is measured as the increase in the closing price of our common stock between the dates of grant and exercise. STAP awards expire on the tenth anniversary of the grant date, and in most cases they vest in equal increments on each anniversary of the grant date over a four-year period.

The aggregate STAP liability balance was $102.4 million and $96.8 million at December 31, 2021 and 2020, respectively, all of which was classified as a current liability in our consolidated balance sheets.

Estimating the fair value of STAP awards requires the use of certain inputs that can materially impact the determination of fair value and the amount of compensation expense (benefit) we recognize. Inputs used in estimating fair value include the price of our common stock, the expected volatility of the price of our common stock, the risk-free interest rate, the expected term of STAP awards, and the expected dividend yield. The fair value of the STAP awards is measured at the end of each financial reporting period because the awards are settled in cash. Refer to the descriptions of these key inputs, requiring estimates, used in determining the fair value of the awards in the *Stock Options* section above. A description of the expected term input for STAP awards is provided below:

Expected term—The expected term reflects the estimated time period we expect an award to remain outstanding. We use the weighted average midpoint of the remaining contractual term to calculate the expected term of outstanding STAP awards.

The table below includes the weighted-average assumptions used to measure the fair value of the outstanding STAP awards:

	As of December 31,		
	2021	2020	2019
Expected term of awards (in years)	1.3	1.7	2.0
Expected volatility	30.0 %	34.8 %	29.1 %
Risk-free interest rate	0.4 %	0.1 %	1.6 %
Expected dividend yield	0.0 %	0.0 %	0.0 %

The closing price of our common stock was $216.08, $151.79, and $88.08 on December 31, 2021, 2020, and 2019, respectively.

A summary of the activity and status of STAP awards during the year ended December 31, 2021 is presented below:

	Number of Awards	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value (in millions)
Outstanding at January 1, 2021	2,121,860	$ 118.48		
Granted	—	—		
Exercised	(1,027,738)	112.72		
Forfeited	(562)	145.30		
Outstanding at December 31, 2021	1,093,560	$ 123.89	2.5	$ 100.8
Exercisable at December 31, 2021	1,083,560	$ 124.55	2.6	$ 99.2
Unvested at December 31, 2021	10,000	$ 52.57	0.9	$ 1.6

Share-based compensation expense (benefit) recognized in connection with STAP awards is as follows (in millions):

	Year Ended December 31,		
	2021	2020	2019
Cost of product sales	$ 3.5	$ 4.9	$ (1.7)
Research and development	15.0	19.9	(8.2)
Selling, general, and administrative	68.1	73.0	(29.8)
Share-based compensation expense (benefit) before taxes	86.6	97.8	(39.7)
Related income tax (benefit) expense	(14.7)	(19.3)	9.0
Share-based compensation expense (benefit), net of taxes	$ 71.9	$ 78.5	$ (30.7)

Cash paid to settle STAP exercises during the years ended December 31, 2021, 2020, and 2019 was $81.1 million, $26.1 million, and $7.6 million, respectively.

Employee Stock Purchase Plan

In June 2012, our shareholders approved the ESPP, which is structured to comply with Section 423 of the Internal Revenue Code. The ESPP provides eligible employees with the right to purchase shares of our common stock at a discount through elective accumulated payroll deductions at the end of each offering period. Offering periods, which began in 2012, occur in consecutive six-month periods commencing on September 5th and March 5th of each year. Eligible employees may contribute up to 15 percent of their base salary, subject to certain annual limitations as defined in the ESPP. The purchase price of the shares is equal to the lower of 85 percent of the closing price of our common stock on either the first or last trading day of a given offering period. In addition, the ESPP provides that no eligible employee may purchase more than 4,000 shares during any offering period. The ESPP has a 20-year term and limits the aggregate number of shares that can be issued under the ESPP to 3.0 million.

9. Stockholders' Equity

Earnings Per Common Share

Basic earnings (loss) per common share is computed by dividing net income (loss) by the weighted average number of shares of common stock outstanding during the period. Diluted earnings (loss) per common share is computed by dividing net income (loss) by the weighted average number of shares of common stock outstanding during the period, adjusted for the potential dilutive effect of our outstanding stock options, RSUs, and shares issuable under the ESPP, as if they were vested and exercised.

The components of basic and diluted earnings (loss) per common share comprised the following (in millions, except per share amounts):

	Year Ended December 31,		
	2021	2020	2019
Numerator:			
Net income (loss)	$ 475.8	$ 514.8	$ (104.5)
Denominator:			
Weighted average outstanding shares — basic	44.9	44.2	43.8
Effect of dilutive securities[1]:			
Stock options, RSUs, and employee stock purchase plan	2.4	0.4	—
Weighted average shares — diluted[2]	47.3	44.6	43.8
Net income (loss) per common share:			
Basic	$ 10.60	$ 11.65	$ (2.39)
Diluted	$ 10.06	$ 11.54	$ (2.39)
Stock options and RSUs excluded from calculation[2]	0.1	6.6	7.2

(1) Calculated using the treasury stock method.

(2) The common shares underlying certain stock options and RSUs have been excluded from the computation of diluted earnings per share because their impact would be anti-dilutive. For the year ended December 31, 2019, we had a net loss, and as such, all outstanding stock options, RSUs, and shares issuable under the ESPP were excluded from our calculation of diluted earnings per share.

Accumulated Other Comprehensive Loss

The following table includes changes in accumulated other comprehensive loss by component, net of tax (in millions):

	Defined Benefit Pension Plan[1]	Foreign Currency Translation Losses	Unrealized Gains and (Losses) on Available-for-Sale Securities	Total
Balance, January 1, 2021	$ (6.7)	$ (17.9)	$ 10.4	$ (14.2)
Other comprehensive (loss) income before reclassifications	5.6	—	(15.0)	(9.4)
Amounts reclassified from accumulated other comprehensive loss	0.6	—	—	0.6
Net current-period other comprehensive (loss) income	6.2	—	(15.0)	(8.8)
Balance, December 31, 2021	$ (0.5)	$ (17.9)	$ (4.6)	$ (23.0)

	Defined Benefit Pension Plan[1]	Foreign Currency Translation Losses	Unrealized Gains and (Losses) on Available-for-Sale Securities	Total
Balance, January 1, 2020	$ —	$ (17.9)	$ 3.7	$ (14.2)
Other comprehensive (loss) income before reclassifications	(8.0)	—	6.7	(1.3)
Amounts reclassified from accumulated other comprehensive loss	1.3	—	—	1.3
Net current-period other comprehensive (loss) income	(6.7)	—	6.7	—
Balance, December 31, 2020	$ (6.7)	$ (17.9)	$ 10.4	$ (14.2)

(1) Refer to Note 11—*Employee Benefit Plans—Supplemental Executive Retirement Plan*, which identifies the captions within our consolidated statements of operations where reclassification adjustments were recognized and their associated tax impact.

10. Income Taxes

Components of income tax expense (benefit) consist of the following (in millions):

	Year Ended December 31,		
	2021	2020	2019
Current:			
Federal	$ 112.3	$ 114.6	$ 63.1
State	24.6	20.0	9.4
Total current	136.9	134.6	72.5
Deferred			
Federal	(10.1)	1.6	(120.1)
State	(8.7)	(12.1)	(12.9)
Total deferred	(18.8)	(10.5)	(133.0)
Total income tax expense (benefit)	$ 118.1	$ 124.1	$ (60.5)

Presented below is a reconciliation of income tax expense (benefit) computed at the statutory federal tax rate of 21 percent in 2021, 2020, and 2019 to income tax expense (benefit) as reported (in millions):

	Year Ended December 31,		
	2021	2020	2019
Federal taxes at the statutory rate	$ 124.7	$ 134.2	$ (34.7)
Change in valuation allowance	(18.7)	(3.1)	(5.7)
State taxes, net of federal benefit	14.6	7.0	(3.1)
Nondeductible compensation	11.8	11.5	6.3
General business credits	(11.5)	(24.0)	(21.3)
Deduction for foreign-derived intangible income	(2.8)	(2.2)	(3.3)
Uncertain tax positions	(1.0)	4.8	(0.3)
Other	1.0	(4.1)	(1.6)
Foreign income adjustment	—	—	5.1
Deconsolidation of VIE	—	—	(1.9)
Total income tax expense (benefit)	$ 118.1	$ 124.1	$ (60.5)
Effective tax rate	20 %	19 %	37 %

Components of the net deferred tax assets are as follows (in millions):

	As of December 31,	
	2021	2020
Deferred tax assets:		
Intangible assets	$ 186.1	$ 176.0
Share-based compensation	73.4	73.1
Reserves and accrued liabilities	18.3	18.8
SERP	10.9	10.9
NOLs	8.3	9.7
Basis differences in investments	1.4	7.4
Other	5.0	5.6
Total deferred tax assets	303.4	301.5
Less: Valuation allowance	(11.5)	(35.5)
Total net deferred tax assets	291.9	266.0
Deferred tax liabilities:		
Plant and equipment principally due to differences in depreciation	(28.2)	(26.1)
Other	(1.8)	(1.3)
Total deferred tax liabilities	(30.0)	(27.4)
Total deferred tax assets, net	$ 261.9	$ 238.6

At December 31, 2021, we had gross federal, foreign, and state net operating loss carryforwards of zero, $4.3 million, and $131.3 million, respectively, which either expire at various dates beginning in 2030 or have no expiration date. We expect that a significant amount of these carryforwards will expire unused, so we have established valuation allowances for the related deferred tax assets.

We are subject to federal and state taxation in the United States and various foreign jurisdictions. We are no longer subject to income tax examinations by the Internal Revenue Service and all other major jurisdictions for tax years prior to 2013.

As of December 31, 2021 and 2020, we had $3.6 million and $4.5 million of unrecognized tax benefits, excluding interest and penalties, that would impact our effective tax rate if recognized. The total amount of unrecognized tax benefits relating to our tax positions is subject to change based on future events including, but not limited to, the settlements of ongoing tax audits and assessments and the expiration of applicable statutes of limitations. Given the uncertainty of potential adjustments from examination, it is reasonably possible that the balance of unrecognized tax benefits could change significantly over the next 12 months. However, due to the number of years remaining that are subject to examination, we are unable to estimate the full range of possible adjustments to the balance of gross unrecognized tax benefits.

The following table represents a reconciliation of the total unrecognized tax benefit liability, excluding interest and penalties, for the years ended December 31, 2021, 2020, and 2019 (in millions):

	Year Ended December 31,		
	2021	2020	2019
Unrecognized tax benefits, beginning of the period	$ 4.5	$ —	$ 0.5
Gross decreases related to prior period tax positions	(0.1)	—	(0.5)
Gross increases related to prior period tax positions	—	3.8	—
Gross increases related to current period tax positions	0.7	0.7	—
Gross decreases as a result of settlements during the current period	(1.5)	—	—
Unrecognized tax benefits, end of the period	$ 3.6	$ 4.5	$ —

We record interest and penalties related to uncertain tax positions as a component of income tax expense. As of December 31, 2021 and 2020, our liability for unrecognized tax benefits included approximately $0.3 million and $0.4 million, respectively, for the accrual of interest and penalties. As of December 31, 2021 and 2020, we recorded approximately $0.1 million benefit and $0.3 million expense, respectively, for the accrual of interest and penalties in our consolidated statement of operations.

As of December 31, 2021 and 2020, we had a total liability for unrecognized tax benefits, including related interest and penalties, of approximately $3.9 million and $4.9 million, respectively. As of December 31, 2019, we did not have any unrecognized tax benefits.

Beginning in 2022, the Tax Cuts and Jobs Act of 2017 eliminates the option to deduct research and development expenditures in the period they are incurred and requires taxpayers to amortize them over five or fifteen years pursuant to Internal Revenue Code Section 174. Although Congress is considering legislation that would defer the amortization requirement to later years, we have no assurance that the requirement to amortize will be repealed or otherwise modified. If the requirement is not repealed or delayed, it will increase our cash paid for income taxes beginning in 2022.

11. Employee Benefit Plans

Supplemental Executive Retirement Plan

We maintain the United Therapeutics Corporation Supplemental Executive Retirement Plan (**SERP**) to provide retirement benefits to certain senior members of our management team.

Participants who retire at age 60 or older are eligible to receive either monthly payments or a lump sum payment based on an average of their total gross base salary over the last 36 months of active employment, subject to certain adjustments. Related benefit payments commence on the first day of the sixth month after retirement. Participants who elect to receive monthly payments will continue to receive payments through the remainder of their life. Alternatively, participants who elect to receive a lump sum distribution will receive a payment equal to the present value of the estimated monthly payments that would have been received upon retirement. As of December 31, 2021 and 2020, all SERP participants had elected to receive a lump sum distribution. Participants who terminate employment for any reason other than death, disability, or change in control prior to age 60 will not be entitled to receive any benefits under the SERP.

Because we do not fund the SERP, we recognize a liability equal to the projected benefit obligation as measured at the end of each fiscal year.

A reconciliation of the beginning and ending balances of the projected benefit obligation is presented below (in millions):

	Year Ended December 31,	
	2021	2020
Projected benefit obligation at the beginning of the year	$ 68.6	$ 56.1
Service cost	3.4	2.8
Interest cost	0.9	1.3
Benefits paid	—	—
Net actuarial (gain) loss	(5.8)	8.4
Projected benefit obligation at the end of the year	$ 67.1	$ 68.6
Amount included in Other current liabilities[(1)]	$ 18.2	$ 19.1
Amount included in Other non-current liabilities	$ 48.9	$ 49.5

(1) This amount represents the benefit obligation due to participants who are eligible to retire and whose benefit payments could commence within one year of the respective balance sheet date.

The following weighted average assumptions were used to measure the SERP obligation:

	Year Ended December 31,	
	2021	2020
Discount rate	2.05 %	1.49 %
Salary increases	4.00 %	4.00 %
Lump-sum interest rate	2.75 %	2.25 %

The increases in the discount rate and lump-sum interest rate for the year ended December 31, 2021, as compared to the same period in 2020, resulted in a decrease in the projected benefit obligation of $1.3 million and $4.0 million, respectively, at December 31, 2021.

The components of net periodic pension cost recognized in our consolidated statements of operations consisted of the following (in millions):

	Year Ended December 31,		
	2021	2020	2019
Service cost	$ 3.4	$ 2.8	$ 2.2
Interest cost	0.9	1.3	1.4
Amortization of prior service cost	0.7	1.3	1.5
Amortization of net actuarial gain	—	—	(2.2)
Settlement	—	—	(1.9)
Total	$ 5.0	$ 5.4	$ 1.0

The service cost component is reported within *operating expenses* and the other components are reported in *other income, net* in our consolidated statements of operations.

Amounts related to the SERP that have been recognized in other comprehensive (loss) income are as follows (in millions):

	Year Ended December 31,		
	2021	2020	2019
Net actuarial gain (loss)	$ 5.8	$ (8.4)	$ (12.9)
Prior service cost	0.7	1.3	1.5
Settlement	—	—	(1.9)
Total recognized in other comprehensive (loss) income	6.5	(7.1)	(13.3)
Tax (expense) benefit	(0.3)	0.4	1.0
Total, net of tax	$ 6.2	$ (6.7)	$ (12.3)

The table below presents amounts related to the SERP included in accumulated other comprehensive loss that have not yet been recognized as a component of net periodic pension cost in our consolidated statements of operations (in millions):

	Year Ended December 31,		
	2021	2020	2019
Net actuarial (gain) loss	$ (2.0)	$ 3.8	$ (4.5)
Prior service cost	1.3	2.0	3.3
Total included in accumulated other comprehensive loss	(0.7)	5.8	(1.2)
Tax expense	1.2	0.9	1.2
Total, net of tax	$ 0.5	$ 6.7	$ —

The accumulated benefit obligation, a measure that does not consider future increases in participants' salaries, was $59.1 million and $58.7 million at December 31, 2021 and 2020, respectively.

Future estimated benefit payments, based on current assumptions, including election of lump-sum distributions and expected future service, are as follows (in millions):

Year Ended December 31,	
2022	$ 18.2
2023	6.3
2024	16.5
2025	6.8
2026	—
Thereafter	38.9
Total	$ 86.7

Employee Retirement Plan

We maintain a Section 401(k) Salary Reduction Plan which is open to all eligible full-time employees. Under the 401(k) Plan, eligible employees can make pre-tax or after-tax contributions up to statutory limits. Currently, we make discretionary matching contributions to the 401(k) Plan equal to 40 percent of a participant's elected salary deferral. Matching contributions vest immediately for participants who have been employed for three-years; otherwise, matching contributions vest annually, in one-third increments over a three-year period until the three-year employment requirement has been met.

12. Commitments and Contingencies

Leases

We lease facilities and equipment under operating lease arrangements that have terms expiring at various dates through 2031. Certain lease arrangements include renewal options and escalation clauses. In addition, various lease agreements to which we are party require that we comply with certain customary covenants throughout the term of these leases. If we are unable to comply with these covenants and cannot reach a satisfactory resolution in the event of noncompliance, these agreements could terminate.

Future minimum lease payments under non-cancelable operating leases as of December 31, 2021, are as follows (in millions):

Year Ending December 31,		
2022	$	3.1
2023		2.7
2024		2.4
2025		1.7
2026		1.8
Thereafter		7.2
Total	$	18.9

Total operating lease expense was $3.6 million, $3.5 million, and $4.9 million for the years ended December 31, 2021, 2020, and 2019, respectively. The amounts recorded in operating lease expense include short-term leases, which are immaterial.

In August 2021, we entered into a commercial supply agreement (**Supply Agreement**) with MannKind Corporation (**MannKind**), which was later amended in October 2021. Pursuant to the Supply Agreement, MannKind is responsible for manufacturing and supplying Tyvaso DPI to us on a cost-plus basis. Unless earlier terminated, the initial term of the Supply Agreement continues until December 31, 2031 and will thereafter be renewed automatically for additional, successive two-year terms unless either party provides notice of non-renewal. We determined that the Supply Agreement contains certain lease components and have elected the expedient to combine lease and non-lease components as a single lease component. All payment obligations are variable in nature and costs of $9.6 million were incurred during the year ended December 31, 2021.

Milestone Payments and Royalty Obligations

We are party to certain license agreements pursuant to which we have in-licensed or acquired intellectual property rights covering our commercial and/or development-stage products. Generally, these agreements require that we make milestone payments in cash upon the achievement of certain product development and commercialization goals and payments of royalties upon commercial sales. The following table outlines our financial obligations under certain of these agreements:

Counterparty	Relevant Product	Our Financial Obligation
Supernus Pharmaceuticals, Inc.	Orenitram	Single-digit royalty on net product sales of Orenitram, through the second quarter of 2026
Lilly	Adcirca	Ten percent royalty on net sales, plus milestone payments of $325,000 for each $1,000,000 in net product sales
The Scripps Research Institute	Unituxin	One percent royalty on net product sales of Unituxin
DEKA Research & Development Corp.	Remunity Pump	Product fees and single-digit royalty on net product sales of the Remunity Pump and on net sales of Remodulin for use with the system; reimbursement of DEKA's development and manufacturing costs
MannKind Corporation	Tyvaso DPI	Low double-digit royalty on net product sales of Tyvaso DPI and up to $50.0 million in developmental milestone payments (all of which have already been paid)
Arena	Ralinepag	Low double-digit, tiered royalty on net product sales of ralinepag (any route of administration); a one-time payment of $250.0 million upon FDA approval of an inhaled formulation of ralinepag to treat PAH; and a one-time payment of $150.0 million upon approval in certain non-U.S. jurisdictions of an oral version of ralinepag to treat any indication

13. Segment Information

We operate as one operating segment with a focus on the development and commercialization of products to address the unmet needs of patients with chronic and life-threatening conditions. Our Chief Executive Officer, as our chief operating decision maker, manages and allocates resources to the operations of our company on a consolidated basis. This enables our Chief Executive Officer to assess our overall level of available resources and determine how best to deploy these resources across functions, therapeutic areas, and research and development projects in line with our long-term company-wide strategic goals.

Net product sales, cost of product sales, and gross profit for each of our commercial products were as follows (in millions):

Year Ended December 31, 2021	Tyvaso[(1)]	Remodulin[(1)]	Orenitram	Unituxin	Adcirca	Total
Net product sales	$ 607.5	$ 513.7	$ 306.1	$ 202.3	$ 55.9	$ 1,685.5
Cost of product sales	26.8	37.9	19.7	14.2	23.9	122.5
Gross profit	$ 580.7	$ 475.8	$ 286.4	$ 188.1	$ 32.0	$ 1,563.0
Year Ended December 31, 2020						
Net product sales	$ 483.3	$ 516.7	$ 293.1	$ 122.9	$ 67.3	$ 1,483.3
Cost of product sales	24.5	23.2	18.7	12.6	29.1	108.1
Gross profit	$ 458.8	$ 493.5	$ 274.4	$ 110.3	$ 38.2	$ 1,375.2
Year Ended December 31, 2019						
Net product sales	$ 415.6	$ 587.0	$ 225.3	$ 113.7	$ 107.2	$ 1,448.8
Cost of product sales	19.6	21.1	15.0	15.7	46.2	117.6
Gross profit	$ 396.0	$ 565.9	$ 210.3	$ 98.0	$ 61.0	$ 1,331.2

(1) Net product sales and cost of product sales include sales of delivery devices for the respective product, including, with respect to Remodulin, the Remunity Pump.

Geographic revenues are determined based on the country in which our customers (distributors) are located. Total revenues from external customers by geographic area are as follows (in millions):

Year Ended December 31,	2021	2020	2019
United States	$ 1,564.2	$ 1,412.1	$ 1,323.2
Rest-of-World	121.3	71.2	125.6
Total	$ 1,685.5	$ 1,483.3	$ 1,448.8

We recorded revenue from three distributors in the United States that exceeded ten percent of total revenues. Revenue from these three distributors as a percentage of total revenues is as follows:

Year Ended December 31,	2021	2020	2019
Distributor 1	50 %	55 %	54 %
Distributor 2	29 %	28 %	22 %
Distributor 3	11 %	8 %	8 %

Long-lived assets (property, plant, and equipment) located by geographic area are as follows (in millions):

Year Ended December 31,	2021	2020	2019
United States	$ 768.1	$ 717.3	$ 723.1
Rest-of-World	12.8	14.3	15.4
Total	$ 780.9	$ 731.6	$ 738.5

14. Litigation

Sandoz Antitrust Litigation

On April 16, 2019, Sandoz Inc. (**Sandoz**) and its marketing partner RareGen, LLC (now known as Liquidia PAH, LLC, a subsidiary of Liquidia Corporation) (**RareGen**), filed a complaint in the U.S. District Court for the District of New Jersey against us and Smiths Medical ASD, Inc. (**Smiths Medical**), alleging that we and Smiths Medical engaged in anticompetitive conduct in connection with plaintiffs' efforts to launch their generic version of Remodulin. In particular, the complaint alleges that we and Smiths Medical unlawfully impeded competition by entering into an agreement to produce CADD-MS®3 cartridges specifically for the delivery of subcutaneous Remodulin, without making these cartridges available for the delivery of Sandoz's generic version of Remodulin. The parties completed expedited discovery in anticipation of a motion filed by the plaintiffs on October 4, 2019, seeking preliminary injunctive relief. We and Smiths Medical filed a motion to dismiss the complaint, and we filed our opposition to plaintiffs' motion for a preliminary injunction on October 25, 2019. On January 29, 2020, the court issued a decision denying the request for preliminary injunction sought by Sandoz and RareGen. According to the court, "[Sandoz and RareGen] have not met their burden of demonstrating a reasonable probability of eventual success in the litigation." The court also denied our and Smiths Medical's motion to dismiss the entire action. Plaintiffs declined to appeal the court's denial of their motion for preliminary injunction. On March 30, 2020, the plaintiffs filed an amended complaint to add a count alleging that we breached our earlier patent settlement agreement with Sandoz by refusing to grant Sandoz access to cartridges. The parties have substantially completed discovery, and Sandoz and United Therapeutics have briefed motions for summary judgment on a variety of issues. We are waiting for the court's decision on these motions, and no trial date has been set. We do not anticipate a trial before mid-2022 at the earliest.

Smiths Medical was dismissed from the case on November 13, 2020, based on a settlement resolving the disputes between the plaintiffs and Smiths Medical. As part of this settlement, Smiths Medical paid the plaintiffs $4.25 million, disclosed and made available to the plaintiffs certain specifications and other information related to the MS-3 cartridges, and granted to the plaintiffs a non-exclusive, royalty-free license in the United States to Smiths Medical's patents and copyrights associated with the MS-3 cartridges and certain other information related to the MS-3 pumps and cartridges.

We believe that plaintiffs' claims are meritless and intend to vigorously defend the litigation. However, due to the uncertainty inherent in any litigation, we cannot guarantee that an adverse outcome will not result. Any litigation of this nature could involve substantial cost, and an adverse outcome could result in substantial monetary damages and/or injunctive relief adverse to our business. We currently are not able to reasonably estimate a range of potential losses due to the early stage of the litigation and the inherent unpredictability of any outcome at trial.

Litigation with Liquidia Technologies, Inc.

On March 30, 2020, Liquidia Technologies, Inc. (**Liquidia**) filed two petitions for *inter partes* review (**IPR**) with the Patent Trial and Appeal Board (**PTAB**) of the U.S. Patent and Trademark Office (**USPTO**). In its petitions, Liquidia seeks to invalidate U.S. Patent Nos. 9,604,901 (the **'901 patent**) and 9,593,066 (the **'066 patent**), both of which relate to a method of making treprostinil, the active pharmaceutical ingredient in Tyvaso, Tyvaso DPI, Remodulin, and Orenitram. These patents were issued in March 2017 and are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations publication, also known as the Orange Book, for Tyvaso, Remodulin, and Orenitram. In July 2020, we filed preliminary responses to the petitions. On October 13, 2020, the PTAB declined to institute IPR proceedings on the '066 patent because Liquidia failed to establish a reasonable likelihood of prevailing on any claim relating to the '066 patent. Also on October 13, 2020, the PTAB instituted IPR proceedings on the '901 patent. We received a final written decision from the PTAB on October 8, 2021. The final written decision found that Liquidia had proven the invalidity of seven of the claims of the '901 patent, but failed to prove the invalidity of two other claims. Each party has the right to appeal this decision, and no cancelation of claims takes effect until resolution of any appeals. The PTAB is currently addressing post-decision issues, and the time for appeal has not yet commenced.

In January 2020, Liquidia submitted an NDA to the FDA for approval of Yutrepia, a dry powder inhalation formulation of treprostinil, to treat PAH. This NDA was submitted under the 505(b)(2) regulatory pathway with Tyvaso as the reference listed drug. In November 2021, the FDA granted tentative approval for Liquidia's NDA.

In April 2020, we received a Paragraph IV Certification Notice Letter (**Notice Letter**) from Liquidia, stating that it intends to market Yutrepia before the expiration of all patents listed in the Orange Book for Tyvaso. The Notice Letter states that Liquidia's NDA for Yutrepia contains a Paragraph IV certification alleging that these patents are not valid, not enforceable, and/or will not be infringed by the commercial manufacture, use or sale of Yutrepia.

On June 4, 2020, we filed a lawsuit in the U.S. District Court for the District of Delaware against Liquidia for infringement of the '901 patent and the '066 patent, both of which expire in December 2028. We filed our lawsuit within 45 days of receipt of notice from Liquidia of its NDA filing. As a result, under the Hatch-Waxman Act, the FDA is precluded by regulation from approving Liquidia's NDA for up to 30 months or until the resolution of the litigation, whichever occurs first. On July 16, 2020, Liquidia filed an answer to our complaint that included counterclaims alleging, among other things, that the patents at issue in the litigation are not valid and will not be infringed by the commercial manufacture, use or sale of Yutrepia.

On July 21, 2020, the USPTO issued a new patent to us related to Tyvaso. The new patent, U.S. Patent No. 10,716,793 (the **'793 patent**), expires May 14, 2027, and is listed in the Orange Book for Tyvaso. On July 22, 2020, we filed an amended complaint against Liquidia to include a claim for infringement of the '793 patent. The '793 patent relates to a method of administering treprostinil via inhalation and includes claims covering the dosing regimen used to administer Tyvaso. On August 5, 2020, Liquidia filed an answer to our amended complaint that repeated its defenses and counterclaims and added new defenses and counterclaims related to the '793 patent. On August 26, 2020, we filed a motion to dismiss Liquidia's invalidity defenses with respect to the '793 patent based on assignor estoppel. The court denied our motion, finding that it is too early in the case to conclusively resolve the issue given the fact-intensive inquiry that is necessary. We can continue to assert an assignor estoppel defense and raise it for resolution later in the case, whether at trial or in a dispositive pre-trial motion. On December 28, 2021, we filed a stipulation that the '901 patent is not infringed by Liquidia based on the court's claim construction ruling. That stipulation is subject to our right to appeal the court's claim construction at the appropriate time. On January 7, 2022, Liquidia filed a motion for summary judgment arguing that the '901 and '066 patents are invalid based on collateral estoppel in view of an earlier decision invalidating a related patent, U.S. Patent No. 8,497,393. The parties are currently briefing that motion, and no hearing date has been set. The case is set for trial commencing on March 28, 2022.

On January 7, 2021, Liquidia filed another petition for IPR with the PTAB. In its petition, Liquidia seeks to invalidate the '793 patent. On August 11, 2021, the PTAB issued a decision instituting review. The parties are currently submitting evidence and argument according to the case schedule, and the PTAB's deadline to issue a final written decision regarding the '793 patent will be in August 2022. Any appeals of the PTAB's final written decision would delay any final outcome.

On June 4, 2021, we filed a motion in the District of Delaware patent case to file an amended complaint adding trade secret misappropriation claims against Liquidia and a former Liquidia employee, Dr. Robert Roscigno. The court denied the motion based on a finding that adding the additional claims would impact the case schedule. Thus, we filed those claims as a separate case against Liquidia and Robert Roscigno in North Carolina state court. Liquidia and Roscigno removed those claims to the U.S. District Court for the Middle District of North Carolina. The parties are currently briefing whether the case should be litigated in state or federal court.

We plan to vigorously enforce our intellectual property rights related to Tyvaso.

MSP Recovery Litigation

On July 27, 2020, MSP Recovery Claims, Series LLC; MSPA Claims 1, LLC; and Series PMPI, a designated series of MAO-MSO Recovery II, LLC (**Plaintiffs**) filed a "Class Action Complaint" (the **Complaint**) against Caring Voices Coalition, Inc. (**CVC**) and us in the U.S. District Court for the District of Massachusetts. The Complaint alleges that we violated the federal Racketeer Influenced and Corrupt Organizations act and various state laws by coordinating with CVC when making donations to a pulmonary arterial hypertension fund so that those donations would go towards copayment obligations for Medicare patients taking drugs manufactured and marketed by us. Plaintiffs claim to have received assignments from various Medicare Advantage health plans and other insurance entities that allow them to bring this lawsuit on behalf of those entities to recover allegedly inflated amounts they paid for our drugs. On April 6, 2021, the court granted our motion to transfer the case to the U.S. District Court for the Southern District of Florida. Two members of the putative class, Humana Inc. and UnitedHealthcare Insurance Company, have informed us that they may bring claims directly against us to recover alleged overpayments.

On October 15, 2021, we filed a motion for judgment on the pleadings, seeking to dismiss plaintiffs' claims in this litigation. On that same day, plaintiffs filed an amended complaint (the **Amended Complaint**) that includes state antitrust claims based on alleged facts similar to those raised by Sandoz and RareGen in the matter described above. The Amended Complaint added MSP Recovery Claims Series 44, LLC as a plaintiff and Smiths Medical ASD and CVC as defendants. As a result of the Amended Complaint, the court ruled that our motion for judgment on the pleadings was moot. On December 15, 2021, we filed a motion to dismiss all of Plaintiffs' claims in the Amended Complaint, including the new antitrust claims. The motion to dismiss remains pending. The court has set a case schedule with trial commencing in June 2024.

We intend to vigorously defend against this lawsuit.

Patent Litigation with ANI Pharmaceuticals, Inc.

In February 2021, we received a Paragraph IV certification notice letter from ANI indicating that ANI submitted an abbreviated new drug application (**ANDA**) to the FDA to market a generic version of Orenitram before the expiration of the following patents:

U.S. Patent No.	Expiration Date
8,252,839	May 2024
9,050,311	May 2024
9,278,901	May 2024
7,544,713	July 2024
7,417,070	July 2026
8,497,393	December 2028
9,604,901	December 2028
9,592,066	December 2028
8,747,897	October 2029
8,410,169	February 2030
8,349,892	January 2031

ANI's notice letter states that the ANDA contains a Paragraph IV certification alleging that these patents are not valid, not enforceable, and/or will not be infringed by the commercial manufacture, use or sale of the proposed product described in ANI's ANDA submission. We responded to the ANI notice letter by filing a lawsuit against ANI on April 1, 2021 in the U.S. District Court for the District of Delaware alleging infringement of each of the patents noted above. Under the Hatch-Waxman Act, the FDA is automatically precluded from approving ANI's ANDA for up to 30 months from receipt of ANI's notice letter or until the entry by a U.S. District Court of a final judgment that is adverse to us on all patents that form the basis of the stay, whichever occurs first. The court has set a schedule for the case with trial set to start on May 8, 2023, and the parties are currently engaged in discovery and addressing claim construction.

We previously settled litigation with Actavis Laboratories FL, Inc. (**Actavis**) related to its ANDA submitted to the FDA to market a generic version of Orenitram. Under our settlement agreement, Actavis is permitted to market its generic version of Orenitram in June 2027. If ANI is successful in the pending litigation, it could potentially accelerate Actavis' launch date. We do not know whether Actavis obtained and, if so, retained, 180 days of exclusivity from other generic competition based on its first-to-file status.

We intend to vigorously enforce our intellectual property rights relating to Orenitram.

340B Program Litigation

We participate in the Public Health Service's 340B drug pricing program (the **340B program**), through which we sell our products at discounted prices to covered entities, including through pharmacies that have contracts with such covered entities (**340B contract pharmacies**). Increasing use of 340B contract pharmacies, coupled with a lack of oversight and transparency, has resulted in increased risks of 340B statutory violations related to the diversion of 340B-purchased drugs to individuals who are not patients of the 340B covered entity, and to prohibited "duplicate discounts" when 340B-purchased drugs are also billed to Medicaid. On November 13, 2020, we notified the U.S. Health Resources and Services Administration (**HRSA**) that we would begin implementing narrowly-tailored 340B contract pharmacy policies with the goal of stemming abuses of the 340B program without upsetting the status quo or creating hardship for covered entities or their patients. At around the same time, a number of other manufacturers also announced their own policies aimed at stemming 340B program abuses.

On December 30, 2020, the U.S. Department of Health and Human Services (**HHS**) General Counsel issued a non-binding Advisory Opinion (the **Advisory Opinion**) concluding that, among other things, pharmaceutical manufacturers are obligated to sell their drugs at the 340B discounted price to an unlimited number of 340B contract pharmacies. On May 17, 2021, HRSA sent a letter to us stating that our 340B contract pharmacy policies violated the 340B statute. HRSA also sent materially similar letters to five other pharmaceutical manufacturers. We responded to that letter by clarifying our policies and requesting additional information from HRSA. To date, HRSA has not responded.

The federal government's pronouncements regarding the use of 340B contract pharmacies have triggered a variety of litigation. In one of those cases, the court concluded that the Advisory Opinion was "legally flawed," and in response HHS withdrew the Advisory Opinion. Notwithstanding the withdrawal of the Advisory Opinion, HRSA has made clear that it is not withdrawing its May 17, 2021 letter to us and the threat of enforcement action.

On June 23, 2021, we commenced litigation against HRSA and HHS in the U.S. District Court for the District of Columbia seeking to vindicate the lawfulness of our 340B program contract pharmacy policies. Despite the litigation, on September 22, 2021, HRSA sent to us, along with the other manufacturers challenging HRSA's 340B interpretation, letters stating that HRSA is referring "this issue to the HHS Office of the Inspector General (**OIG**)" for potential enforcement action. We have not received any communication from the OIG regarding our 340B contract pharmacy policy. Meanwhile, the parties submitted and fully briefed

cross-motions for summary judgment, and the court heard oral argument on those motions, and also similar motions in a related case involving Novartis, on October 12, 2021. On November 5, 2021, the court granted our motion for summary judgment in part, and issued a decision holding that the HRSA letters threatening enforcement action "contain legal reasoning that rests upon an erroneous reading of Section 340B." The court explained that "[t]he statute's plain language, purpose, and structure do not *prohibit* drug manufacturers from attaching any conditions to the sales of covered drugs through contract pharmacies. Nor do they *permit* all conditions. Accordingly, any future enforcement action must rest on a new statutory provision, a new legislative rule, or a well-developed legal theory that Section 340B precludes the specific conditions at issue here." HRSA and HSS appealed to the U.S. Court of Appeals for the District of Columbia Circuit on December 28, 2021, and the appeal is pending.

Litigation involving other manufacturers is also moving forward in parallel with our case, and decisions issued in those cases have reached different conclusions regarding HRSA's and HHS's interpretation of the 340B statute.

We intend to vigorously defend our 340B program contract pharmacy policies.

15. Arena License Agreement

On November 15, 2018, we entered into an exclusive license agreement with Arena related to ralinepag, a next-generation, oral, selective, and potent prostacyclin receptor agonist being developed for treatment of PAH. On January 24, 2019, in connection with the closing of the transactions contemplated by the license agreement: (1) Arena granted to us perpetual, irrevocable, and exclusive rights throughout the universe to develop, manufacture, and commercialize ralinepag; (2) Arena transferred to us certain other assets related to ralinepag, including, among others, related domain names and trademarks, permits, certain contracts, inventory, regulatory documentation, Investigational New Drug (**IND**) Application No. 109021 (related to ralinepag), and nonclinical, preclinical, and clinical trial data; (3) we assumed certain limited liabilities from Arena, including, among others, all obligations arising after the closing under the assumed contracts and the IND described above; and (4) we paid Arena an upfront payment of $800.0 million, which was expensed as acquired in-process research and development and included within research and development expenses in our consolidated statements of operations in the first quarter of 2019. We will also pay Arena: (1) a one-time payment of $250.0 million for the first, if any, marketing approval we receive in the United States for an inhaled version of ralinepag to treat PAH; (2) a one-time payment of $150.0 million for the first, if any, marketing approval we receive in any of Japan, France, Italy, the United Kingdom, Spain, or Germany for an oral version of ralinepag to treat any indication; and (3) low double-digit, tiered royalties on net sales of any pharmaceutical product containing ralinepag as an active ingredient, subject to certain adjustments for third-party license payments.

16. Priority Review Voucher

On December 28, 2020, we entered into an agreement to acquire a rare pediatric disease priority review voucher for $105.0 million. On January 21, 2021, we closed the transaction and expensed the $105.0 million within *research and development* in our consolidated statements of operations for the year ended December 31, 2021. We redeemed the voucher in connection with our submission of the NDA for Tyvaso DPI in April 2021.

Schedule II—Valuation and Qualifying Accounts
Years Ended December 31, 2021, 2020, and 2019
(In millions)

	Valuation Allowance on Deferred Tax Assets				
	Balance at Beginning of Year	Additions Charged to Expense	Other Additions	Deductions	Balance at End of Year
Year Ended December 31, 2021[1]	$ 35.5	$ 4.4	$ —	$ (28.4)	$ 11.5
Year Ended December 31, 2020[2]	$ 36.6	$ —	$ 3.0	$ (4.1)	$ 35.5
Year Ended December 31, 2019[3]	$ 42.6	$ 1.9	$ 0.9	$ (8.8)	$ 36.6

(1) Deductions relate to changes in capital investments and our investment in a foreign entity.

(2) Other Additions relate to changes in our investment in a foreign entity. Deductions relate primarily to changes in capital investments and state net operating losses.

(3) Other Additions relate to changes in our investment in a foreign entity. Deductions relate to changes in capital investments and the acquisition of a foreign entity.

	Inventory Reserves			
	Balance at Beginning of Year	Additions Charged to Expense	Deductions	Balance at End of Year
Year Ended December 31, 2021	$ 16.8	$ 10.0	$ (11.1)	$ 15.7
Year Ended December 31, 2020	$ 20.9	$ 7.7	$ (11.8)	$ 16.8
Year Ended December 31, 2019	$ 26.0	$ 8.4	$ (13.5)	$ 20.9

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with participation of our Chairperson and Chief Executive Officer and Chief Financial Officer and Treasurer, has evaluated the effectiveness of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) of the Securities Exchange Act of 1934, as of December 31, 2021. Based on that evaluation, our Chairperson and Chief Executive Officer and Chief Financial Officer and Treasurer concluded that our disclosure controls and procedures were effective as of December 31, 2021.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934, as amended). Our internal control over financial reporting was designed to provide reasonable assurance to our management and Board of Directors regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. All internal controls over financial reporting, no matter how well designed, have inherent limitations. As a result of these inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those internal controls determined to be effective can provide only reasonable assurance with respect to the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2021, based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control—Integrated Framework (2013)*. Management's assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on this assessment, our management concluded that, as of December 31, 2021, our internal control over financial reporting was effective.

Ernst & Young LLP, an independent registered public accounting firm, has issued an attestation report on our internal control over financial reporting. The report of Ernst & Young LLP is contained in *Item 8* of this Report.

Attestation of Independent Registered Public Accounting Firm

The attestation report of our independent registered public accounting firm regarding internal control over financial reporting is set forth in *Item 8* of this Report under the caption "Report of Independent Registered Public Accounting Firm" and incorporated herein by reference.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

Information as to the individuals serving on our board of directors is set forth below under the heading *Board of Directors*. Additional information required by Item 10 regarding nominees and directors appearing under *Proposal No. 1: Election of Directors* in our definitive proxy statement for our 2022 annual meeting of shareholders currently scheduled for June 27, 2022 (the **2022 Proxy Statement**) is hereby incorporated herein by reference. Information regarding our executive officers appears in *Item 1* of this Report under the heading *Information about our Executive Officers*. Information regarding our Audit Committee and our Audit Committee's financial expert appearing under the heading *Committees of our Board of Directors—Audit Committee* in our 2022 Proxy Statement is hereby incorporated herein by reference.

Information appearing under the heading *Delinquent Section 16(a) Reports* in our 2022 Proxy Statement is hereby incorporated herein by reference.

We have a written Code of Conduct and Business Ethics that applies to our principal executive officer, principal financial officer and our principal accounting officer and every other director, officer and employee of United Therapeutics. The Code of Conduct and Business Ethics is available on our Internet website at *http://ir.unither.com/corporate-governance*. A copy of the Code of Conduct and Business Ethics will be provided free of charge by making a written request and mailing it to our corporate headquarters offices to the attention of the Investor Relations Department. If any amendment to, or a waiver from, a provision of the Code of Conduct and Business Ethics that applies to the principal executive officer, principal financial officer and principal accounting officer is made, we intend to post such information on our Internet website within four business days at *www.unither.com*.

Board of Directors

Christopher Causey, M.B.A.

Former Consultant and Healthcare Executive

Raymond Dwek, C.B.E., F.R.S.

Emeritus Director Oxford Glycobiology Institute, Oxford University

Richard Giltner

Former Portfolio Manager at Lyxor Asset Management, an asset management group at Société Générale, S.A.

Katherine Klein, Ph.D.

Vice-Dean and Professor, The Wharton School of the University of Pennsylvania

Ray Kurzweil

Director of Engineering, Google Inc.

Linda Maxwell, M.D., M.B.A.

Head and Neck Surgeon; Founding Executive Director, the Biomedical Zone (Canada)

Nilda Mesa, J.D.

Adjunct Professor and Director of the Urban Sustainability and Equity Planning Program, Columbia University

Judy D. Olian, Ph.D.

President, Quinnipiac University

Christopher Patusky, J.D., M.G.A.

Founding Principal, Patusky Associates, LLC

Martine Rothblatt, Ph.D., J.D., M.B.A.

Chairperson and Chief Executive Officer of United Therapeutics

Louis Sullivan, M.D.

Former Secretary, U.S. Department of Health and Human Services

Tommy Thompson, J.D.

Interim President, University of Wisconsin System; Former Secretary, U.S. Department of Health and Human Services

Item 11. Executive Compensation

Information concerning executive compensation required by Item 11 will appear under the headings *Director Compensation*, *Compensation Discussion and Analysis, and Executive Compensation Data* in our 2022 Proxy Statement and is incorporated herein by reference.

Information concerning the Compensation Committee required by Item 11 will appear under the heading *Compensation Committee Report* in our 2022 Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information regarding beneficial ownership of our common stock required by Item 12 will appear under *Beneficial Ownership of Common Stock* in our 2022 Proxy Statement and is incorporated herein by reference.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table presents information as of December 31, 2021, regarding our securities authorized for issuance under equity compensation plans:

Plan category	Number of securities to be issued upon exercise of outstanding options and RSUs (a)[3]		Weighted average exercise price of outstanding options (b)[4]	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a)) (c)[5]
Equity compensation plan approved by security holders[1]	7,701,852	$	126.73	5,964,775
Equity compensation plan not approved by security holders[2]	6,665		—	75,768
Total	7,708,517	$	126.73	6,040,543

(1) All outstanding stock options were issued under our two equity incentive plans approved by security holders in 1999 and 2015. The majority of outstanding RSUs were issued under the 2015 Plan. In addition, our employees have outstanding rights to purchase our common stock at a discount as part of our ESPP, which was approved by security holders in 2011. No further awards will be issued under the 1999 Plan. Information regarding these plans is contained in Note 8—*Share-Based Compensation* to our consolidated financial statements.

(2) We have one equity incentive plan, the 2019 Inducement Stock Incentive Plan, that has not been approved by our shareholders, as permitted by the Nasdaq Stock Market rules. The 2019 Inducement Plan was approved by our Board of Directors in February 2019 and provides for the issuance of up to 99,000 shares of our common stock in the aggregate under awards granted to newly-hired employees. Currently, we grant only RSUs to newly-hired employees under the 2019 Inducement Plan. Information regarding this plan is contained in Note 8—*Share-Based Compensation* to our consolidated financial statements.

(3) Column (a) includes 7,317,978 shares of our common stock issuable upon the exercise of outstanding stock options issued under the 1999 and 2015 Plan; 383,874 shares issuable upon the vesting of outstanding RSUs issued under the 2015 Plan; and 6,665 shares issuable upon the vesting of outstanding RSUs issued under the 2019 Inducement Plan. The 2015 Plan and 2019 Inducement Plan use a share counting formula for determining the number of shares available for issuance under the plans. In accordance with this formula, each option issued under the 2015 Plan counts as one share, while each RSU issued under the 2015 Plan and the 2019 Inducement Plan counts as 1.35 shares and 2.14 shares, respectively. The number under column (a) represents the actual number of shares issuable under our outstanding awards without giving effect to the share counting formula.

(4) Column (b) represents the weighted average exercise price of the outstanding stock options only. The outstanding RSUs are not included in this calculation because they do not have an exercise price.

(5) Column (c) includes 2,581,300, 3,383,475, and 75,768 of shares available for future issuance under the ESPP, the 2015 Plan, and the 2019 Inducement Plan, respectively. Under the ESPP, employees may purchase shares based upon a six-month offering period at an amount equal to the lesser of (1) 85 percent of the closing market price of the Common Stock on the first day of the offering period; or (2) 85 percent of the closing market price of the Common Stock on the last day of the offering period. Refer to Note 8—*Share-Based Compensation—Employee Stock Purchase Plan* for more information. The number under column (c) assumes that all 390,539 outstanding RSUs included in column (a) vest. Each RSU is only counted as one share in column (a) because only one share is issuable upon vesting. However, if any RSU does not vest, the number of shares available for future issuance will increase by 1.35 and 2.14, under the 2015 Plan and 2019 Inducement Plan, respectively, because of the share counting formula described in note (3) above.

Item 13. Certain Relationships and Related Transactions, and Director Independence

Information concerning related party transactions and director independence required by Item 13 will appear under the headings *Other Matters—Certain Relationships and Related Party Transactions, Our Corporate Governance—Board of Directors and Nominees—Director Independence, and Our Corporate Governance—Board Structure—Committees of Our Board of Directors* in our 2022 Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services

Information required by Item 14 concerning the principal accounting fees paid by the Registrant and the Audit Committee's pre-approval policies and procedures, will appear under the heading *Audit Matters* in our 2022 Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

In reviewing the agreements included or incorporated by reference as exhibits to this Report, it is important to note that they are included to provide investors with information regarding their terms, and are not intended to provide any other facts or disclose any other information about United Therapeutics or the other parties to the agreements. The agreements contain representations and warranties made by each of the parties to the applicable agreement. These representations and warranties have been made solely for the benefit of the other parties to the applicable agreement, and: (1) should not be treated as categorical statements of fact, but rather as a way of allocating risk between the parties; (2) have in some cases been qualified by disclosures that were made to the other party in connection with the negotiation of the applicable agreement, which disclosures are not necessarily reflected in the agreement; (3) may apply standards of materiality in a way that is different from what may be material to investors; and (4) were made only as of the date of the applicable agreement or such other date or dates as may be specified in the agreement and are subject to more recent developments.

Accordingly, these representations and warranties may not describe the actual state of affairs as of the date they were made or at any other time. Additional information about United Therapeutics may be found elsewhere in this Report and our other public filings, which are available without charge through the SEC's website at *http://www.sec.gov*.

(a)(1)	Our financial statements filed as part of this report on Form 10-K are set forth in the Index to Consolidated Financial Statements under Part II, Item 8 of this Form 10-K.
(a)(2)	The Schedule II—Valuation and Qualifying Accounts is filed as part of this Form 10-K. All other schedules are omitted because they are not applicable or not required, or because the required information is included in our consolidated statements or notes thereto.
(a)(3)	Exhibits filed as a part of this Form 10-K are listed on the Exhibit Index, which is incorporated by reference herein.

Certain exhibits to this report have been included only with the copies of this report filed with the Securities and Exchange Commission. Copies of individual exhibits will be furnished to shareholders upon written request to United Therapeutics and payment of a reasonable fee (covering the expense of furnishing copies). Shareholders may request exhibit copies by contacting: United Therapeutics Corporation, Attn: Investor Relations, 1040 Spring Street, Silver Spring, Maryland 20910.

Exhibit Index

Exhibit No.	Description
2.1*	Exclusive License Agreement, dated as of November 15, 2018, by and between Arena Pharmaceuticals, Inc. and the Registrant, incorporated by reference to Exhibit 2.1 to the Registrant's Current Report on Form 8-K filed January 25, 2019.
3.1	Restated Certificate of Incorporation of the Registrant, incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K filed October 1, 2021.

3.2	Ninth Amended and Restated Bylaws of the Registrant, incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K filed February 5, 2021.
4.1	Reference is made to Exhibits 3.1 and 3.2.
4.2***	Description of Securities Registered under Section 12 of the Exchange Act.
10.1	Form of Indemnification Agreement between the Registrant and each of its Directors and Executive Officers, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed October 1, 2021.
10.2**	Amended and Restated Executive Employment Agreement dated as of January 1, 2009, between the Registrant and Martine Rothblatt, incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2009.
10.3**	Amendment to Amended and Restated Executive Employment Agreement between the Registrant and Martine Rothblatt, Ph.D., dated as of January 1, 2015, incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K filed December 17, 2014.
10.4**	Employment Agreement, dated as of June 26, 2016, between the Registrant and Michael Benkowitz, incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed June 22, 2016.
10.5**	Change in Control Severance Agreement between the Registrant and Michael Benkowitz, dated as of February 14, 2012, incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed April 28, 2016.
10.6**	Employment Agreement, dated as of March 13, 2015, between the Registrant and James Edgemond, incorporated by reference to Exhibit 10.55 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014.
10.7**	Amendment to Employment Agreement, dated as of October 25, 2016, between the Registrant and James Edgemond, incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2016.
10.8**	Change in Control Severance Agreement between the Registrant and James Edgemond, dated as of November 12, 2014, incorporated by reference to Exhibit 10.56 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014.
10.9**	Employment Agreement dated as of June 16, 2001 between the Registrant and Paul Mahon, incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2002.
10.10**	Amendment dated December 11, 2002 to Employment Agreement between the Registrant and Paul Mahon, incorporated by reference to Exhibit 10.43 of the Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2002.
10.11**	Amendment dated December 29, 2004 to Employment Agreement between Paul A. Mahon and the Registrant dated June 16, 2001, as previously amended, incorporated by reference to Exhibit 10.4 of the Registrant's Current Report on Form 8-K filed on December 29, 2004.
10.12**	Amendment, dated as of July 31, 2006, to amended Employment Agreement, dated June 16, 2001, between Paul Mahon and the Registrant, incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K filed on August 4, 2006.
10.13**	Form of Amendment to Employment Agreement between the Registrant and Paul Mahon, dated as of January 1, 2009, incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2009.
10.14**	Form of Amendment to Employment Agreement between the Registrant and Paul Mahon, dated as of February 22, 2010, incorporated by reference to Exhibit 10.46 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2009.
10.15**	United Therapeutics Corporation Amended and Restated Equity Incentive Plan, as amended effective as of September 24, 2004, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2004.
10.16**	First Amendment to the United Therapeutics Corporation Amended and Restated Equity Incentive Plan, effective as of June 2, 2015, incorporated by reference to Exhibit 10.6 to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015.
10.17**	Form of terms and conditions for awards granted to Employees by the Registrant under the Amended and Restated Equity Incentive Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on December 17, 2004.
10.18**	Form of terms and conditions for awards granted to Non-Employees by the Registrant under the Amended and Restated Equity Incentive Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on December 17, 2004.
10.19**	United Therapeutics Corporation Supplemental Executive Retirement Plan, effective as of July 1, 2006, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on May 4, 2006.
10.20	United Therapeutics Corporation Supplemental Executive Retirement Plan Rabbi Trust Document entered into on December 28, 2007, by and between the Registrant and Wilmington Trust Company, as trustee, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on December 28, 2007.

Exhibit No.	Description
10.21**	United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.22**	First Amendment to the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on September 18, 2009.
10.23**	Second Amendment to the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on February 6, 2012.
10.24**	Form of terms and conditions for awards granted to non-employees by the Registrant under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.25**	Form of terms and conditions for awards granted to employees by the Registrant prior to January 1, 2010, under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.26**	Form of terms and conditions for awards granted to employees by the Registrant on or after January 1, 2010, under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.48 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2009.
10.27**	Form of terms and conditions for awards granted to employees on or after March 15, 2011 under the United Therapeutics Corporation 2011 Share Tracking Awards Plan and the United Therapeutics Corporation 2008 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of Registrant's Registration Statement on Form S-8 (Registration No. 333-173858) filed on May 2, 2011.
10.28**	Form of grant letter used by Registrant under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.29	Stipulation of Settlement, dated October 25, 2010, among the parties to a derivative lawsuit against the directors and officers of the Registrant identified therein, incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2010.
10.30**	United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.31**	First Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on February 6, 2012.
10.32**	Second Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2012.
10.33**	Third Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on February 4, 2013.
10.34**	Fourth Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on January 31, 2014.
10.35**	Form of terms and conditions for awards granted to non-employees by the Registrant on or after March 15, 2011 under the United Therapeutics Corporation Share Tracking Awards Plan or the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.36**	Form of grant letter used by Registrant under the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.4 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.37**	United Therapeutics Corporation Employee Stock Purchase Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012.
10.38**	United Therapeutics Corporation Amended and Restated 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed June 25, 2021.
10.39**	Form of Grant Notice and Standard Terms and Conditions for Non-Qualified Stock Options Granted to Non-Employee Directors under the United Therapeutics Corporation 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed June 29, 2015.
10.40**	Form of Grant Notice and Standard Terms and Conditions for Non-Qualified Stock Options Granted to Certain Executives under the United Therapeutics Corporation 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K filed June 29, 2015.

Exhibit No.	Description
10.41**	Form of Grant Notice and Standard Terms and Conditions for Non-Qualified Stock Options Granted to Employees under the United Therapeutics Corporation 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.4 of the Registrant's Current Report on Form 8-K filed June 29, 2015.
10.42**	Form of Grant Notice and Standard Terms and Conditions for Restricted Stock Units Granted to Non-Employee Directors under the United Therapeutics Corporation 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2016.
10.43**	Form of Grant Notice and Standard Terms and Conditions for Non-Qualified Stock Options Granted to Employees (Performance Vesting) under the United Therapeutics Corporation 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.59 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016.
10.44**	Form of Grant Notice and Standard Terms and Conditions for Restricted Stock Units Granted to Employees under the United Therapeutics Corporation 2015 Stock Incentive Plan, incorporated by reference to Exhibit 10.45 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017.
10.45**	Form of Grant Notice and Standard Terms and Conditions for Stock Options Granted to Certain Executives under the United Therapeutics Corporation Amended and Restated 2015 Stock Incentive Plan (applicable to 2019-2022 Stock Options), incorporated by reference to Exhibit 10.45 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018.
10.46**	United Therapeutics Corporation 2019 Inducement Stock Incentive Plan, incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed March 1, 2019.
10.47**	Form of Restricted Stock Unit Grant Notice and Terms and Conditions under the 2019 Inducement Stock Incentive Plan, incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed March 1, 2019.
10.48*	Wholesale Product Purchase Agreement, dated January 1, 2018, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.51 to the Registrant's Quarterly Report on Form 10-K for the year ended December 31, 2017.
10.49	First Amendment to Wholesale Product Purchase Agreement, dated November 27, 2018, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.47 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018.
10.50	Second Amendment to Wholesale Product Purchase Agreement, dated February 1, 2019, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.48 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018.
10.51*	Third Amendment to Wholesale Product Purchase Agreement, dated as of March 1, 2019, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.49 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018.
10.52+	Fourth Amendment to Wholesale Product Purchase Agreement, dated as of September 18, 2019, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.52 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019.
10.53+	Fifth Amendment to Wholesale Product Purchase Agreement, dated as of November 13, 2019, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.59 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019.
10.54+	Sixth Amendment to Wholesale Product Purchase Agreement, dated as of March 1, 2020, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, for the quarter ended March 31, 2020.
10.55+	Seventh Amendment to Wholesale Product Purchase Agreement, dated as of May 12, 2020, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, for the quarter ended June 30, 2020.
10.56	Eighth Amendment to Wholesale Product Purchase Agreement, dated as of May 13, 2020, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant, incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q, for the quarter ended June 30, 2020.
10.57+***	Ninth Amendment to Wholesale Product Purchase Agreement, dated as of October 6, 2021, by and between Priority Healthcare Distribution, Inc., doing business as CuraScript SD Specialty Distribution, and the Registrant.

Exhibit No.	Description
10.58	Specialty Pharmacy Network Agreement, dated as of January 1, 2018, between the Registrant and Accredo Health Group, Inc., incorporated by reference to Exhibit 10.52 to the Registrant's Quarterly Report on Form 10-K for the year ended December 31, 2017.
10.59	Credit Agreement, dated as of June 27, 2018, among the Registrant, certain of its subsidiaries party thereto, as guarantors, the lenders referred to therein and Wells Fargo Bank, National Association, as administrative agent and swingline lender, incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on June 28, 2018.
10.60	First Amendment to Credit Agreement, dated as of November 2, 2018, among the Registrant, certain of its subsidiaries party thereto, as guarantors, the lenders referred to therein and Wells Fargo Bank, National Association, as administrative agent and swingline lender, incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed December 2, 2020.
10.61	Second Amendment to Credit Agreement, dated as of December 1, 2020, among the Registrant, certain of its subsidiaries party thereto, as guarantors, the lenders referred to therein and Wells Fargo Bank, National Association, as administrative agent and swingline lender, incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed December 2, 2020.
10.62	Settlement Agreement, dated December 19, 2017, among the United States of America, acting through the United States Department of Justice and on behalf of the Office of Inspector General of the Department of Health and Human Services, and the Registrant, incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 20, 2017.
10.63	Corporate Integrity Agreement, dated December 18, 2017, between the Registrant and the Office of Inspector General of the Department of Health and Human Services, incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on December 20, 2017.
21***	Subsidiaries of the Registrant.
23.1***	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
31.1***	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934.
31.2***	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934.
32.1***	Certification of Principal Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2***	Certification of Principal Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101***	The following financial information from our Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on February 24, 2022, formatted in Inline Extensible Business Reporting Language (iXBRL): (1) our Consolidated Balance Sheets as of December 31, 2021 and 2020, (2) our Consolidated Statements of Operations for each of three years in the period ended December 31, 2021, (3) our Consolidated Statements of Comprehensive Income for each of the three years in the period ended December 31, 2021, (4) our Consolidated Statements of Stockholders' Equity for each of the three years in the period ended December 31, 2021, (5) our Consolidated Statements of Cash Flows for each of the three years in the period ended December 31, 2021, and (6) the Notes to our Consolidated Financial Statements.
104***	Cover Page Interactive Data File (embedded within the iXBRL document)

+ Certain identified information has been omitted from this exhibit because it is both (1) not material and (2i) would be competitively harmful if publicly disclosed.

* Confidential treatment has been granted with respect to certain portions of this exhibit pursuant to Rule 406 of the Securities Act of 1933, as amended or Rule 24b-2 of the Securities Act of 1934, as amended. The omitted portions of this document have been filed with the Securities and Exchange Commission.

** Designates management contracts and compensation plans.

*** Filed herewith.

Note: Except as otherwise noted above, all exhibits incorporated by reference to the Registrant's previously filed reports with the Securities and Exchange Commission are filed under File No. 000-26301.

Item 16. Form 10-K Summary

None.

Signatures

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereto duly authorized.

UNITED THERAPEUTICS CORPORATION

By: /s/ MARTINE ROTHBLATT
Martine Rothblatt, Ph.D.
Chairperson and Chief Executive Officer

February 24, 2022

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ MARTINE ROTHBLATT Martine Rothblatt	Chairperson, Chief Executive Officer and Director (Principal Executive Officer)	February 24, 2022
/s/ JAMES C. EDGEMOND James C. Edgemond	Chief Financial Officer and Treasurer (Principal Financial Officer and Principal Accounting Officer)	February 24, 2022
/s/ CHRISTOPHER CAUSEY Christopher Causey	Director	February 24, 2022
/s/ RAYMOND DWEK Raymond Dwek	Director	February 24, 2022
/s/ RICHARD GILTNER Richard Giltner	Director	February 24, 2022
/s/ KATHERINE KLEIN Katherine Klein	Director	February 24, 2022
/s/ RAYMOND KURZWEIL Raymond Kurzweil	Director	February 24, 2022
/s/ LINDA MAXWELL Linda Maxwell	Director	February 24, 2022
/s/ NILDA MESA Nilda Mesa	Director	February 24, 2022
/s/ JUDY D. OLIAN Judy D. Olian	Director	February 24, 2022
/s/ CHRISTOPHER PATUSKY Christopher Patusky	Director	February 24, 2022
/s/ LOUIS W. SULLIVAN Louis W. Sullivan	Director	February 24, 2022
/s/ TOMMY G. THOMPSON Tommy Thompson	Director	February 24, 2022