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, 2016

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 001-37785

Reata Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its Charter)

DELAWARE	**11-3651945**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
2801 Gateway Dr, Suite 150 Irving, Texas	**75063**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (972) 865-2219

Securities registered pursuant to Section 12(b) of the Act: Class A Common Stock, Par Value $0.001 Per Share; listed on The NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act: None

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 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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit and post such files). YES ☒ NO ☐

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

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

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☒ (Do not check if a small reporting company)	Small reporting company	☐

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ☐ NO ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the shares of Class A Common Stock on The NASDAQ Stock Market on June 30, 2016, was $72,408,260.

The number of shares of Registrant's Common Stock outstanding as of February 28, 2017 was 13,888,645 shares of Class A Common Stock and 8,456,249 shares of Class B Common Stock.

Portions of the Registrant's Definitive Proxy Statement relating to the Annual Meeting of Shareholders, scheduled to be held on June 7, 2017, are incorporated by reference into Part III of this Report.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, or PSLRA, with the intention of obtaining the benefits of the "safe harbor" provisions of the PSLRA. In this Annual Report on Form 10-K, all statements other than statements of historical or present facts, including statements regarding our future financial condition, business strategy, and plans and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "believe," "will," "may," "estimate," "continue," "aim," "assume," "anticipate," "contemplate," "intend," "target," "project," "should," "plan," "expect," "predict," "could," "possible," "seek," "goal," "potential," "hypothesize," "likely," or the negative of these terms or other similar terms or expressions that concern our expectations, strategy, plans, or intentions. These forward-looking statements include, but are not limited to, statements about:

- the success, cost, and timing of our product development activities and clinical trials;
- our ability to advance our Nrf2 activators and other technologies;
- our ability to obtain and maintain regulatory approval of our product candidates, and limitations and warnings on the label of an approved product candidate;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- our plans to research, develop, and commercialize our product candidates;
- the commercialization of our product candidates, if approved;
- the rate and degree of market acceptance of our product candidates;
- the size and growth potential of the markets for our product candidates, and our ability to identify target patient populations and serve those markets, especially for diseases with small patient populations;
- the success of competing therapies that are or may become available;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates;
- the ability to license additional intellectual property relating to our product candidates and to comply with our existing license agreements;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our ability to attract collaborators with development, regulatory, and commercialization expertise;
- our ability to attract and retain key scientific or management personnel;
- our ability to grow our organization and increase the size of our facilities to meet our anticipated growth;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements, and needs for additional financing;
- regulatory developments in the United States and foreign countries; and
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act.

These risks are not exhaustive. Other sections of this Annual Report on Form 10-K include additional factors that could adversely affect our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the effects of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward- looking statements.

The forward-looking statements made in this Annual Report on Form 10-K are based on circumstances as of the date on which the statements are made. Except as required by law, we undertake no obligation to update or revise these forward-looking statements for any reason, whether as a result of new information, future events, or otherwise, or to conform these statements to actual results or to changes in our expectations.

This Annual Report on Form 10-K also contains estimates, projections, and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets and the incidence and prevalence of certain

medical conditions. Information that is based on estimates, forecasts, projections, market research, or similar methodologies is inherently subject to uncertainties, and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market, and other data from reports, research surveys, studies, and similar data prepared by market research firms and other third parties, industry, medical, and general publications, government data, and similar sources.

PART I

Item 1. Business.

Overview

We are a clinical stage biopharmaceutical company focused on identifying, developing, and commercializing product candidates to address rare and life-threatening diseases with few or no approved therapies by targeting molecular pathways that regulate cellular metabolism and inflammation. Our lead product candidates, bardoxolone methyl and omaveloxolone, are Nrf2 activators, previously referred to as antioxidant inflammation modulators, or AIMs, that target Nrf2, an important transcription factor, to restore mitochondrial function, reduce oxidative stress, and resolve inflammation. Bardoxolone methyl is currently being studied in a Phase 3 trial, known as CATALYST, for the treatment of pulmonary arterial hypertension, or PAH, associated with connective tissue disease, or CTD-PAH, as well as a Phase 2 trial known as LARIAT, for the treatment of pulmonary hypertension due to interstitial lung disease, or PH-ILD, and PAH, each of which are subsets of pulmonary hypertension, or PH. We began enrolling patients in CATALYST in October 2016. In addition, bardoxolone methyl is currently being studied in a single, pivotal Phase 2/3 trial, known as CARDINAL, for the treatment of chronic kidney disease, or CKD, caused by Alport syndrome. We began enrolling patients in CARDINAL on March 2, 2017. Omaveloxolone is being studied in separate two-part Phase 2 trials for the treatment of Friedreich's ataxia, or FA, and mitochondrial myopathies, or MM, known as MOXIe and MOTOR, respectively. We have completed enrollment of part one in MOXIe and are currently dosing patients in part one of MOTOR, which are dose ranging. Data from part two of each of the trials, if part one supports initiating part two, have the potential to be used for registration. Omaveloxolone is also being studied in a Phase 1b/2 trial for the treatment of metastatic melanoma, known as REVEAL. In addition to our lead product candidates, we are conducting a Phase 1 clinical trial of RTA 901. Beyond our clinical programs, we have additional promising preclinical development programs. We believe that our product candidates and preclinical programs have the potential to improve clinical outcomes in numerous underserved patient populations.

The foundational biology of Nrf2 activators underlies our two lead product candidates, bardoxolone methyl and omaveloxolone. Nrf2 activators bind to Keap1 and activate Nrf2, a transcription factor that promotes normal mitochondrial function by making reducing equivalents available for production of cellular energy, or ATP, and increases cellular antioxidant content. Nrf2 activation also reduces mitochondrial reactive oxygen species, or ROS, production and ROS-mediated activation of inflammatory signaling complexes. Nrf2 activators restore mitochondrial production of ATP, increase production of antioxidants, reduce oxidative stress, and reduce pro-inflammatory signaling. Mitochondrial dysfunction is directly implicated in a number of diseases and, in many diseases, is seen in conjunction with chronic inflammation. In a number of diseases, chronic inflammation can lead, in the longer term, to organ fibrosis and remodeling. Reducing this chronic inflammation may lead to reduction of fibrosis and remodeling.

Bardoxolone methyl is our most well characterized Nrf2 activator and is currently in Phase 3 development for CTD-PAH. In October 2016, the first patient was enrolled in CATALYST, an international, randomized, double-blind, placebo-controlled Phase 3 trial examining the safety, tolerability, and efficacy of bardoxolone methyl in patients with World Health Organization, or WHO, Group 1 CTD-PAH when added to standard-of-care vasodilator therapy. Patients will be on up to two background therapies and will be randomized 1:1 to bardoxolone methyl or placebo. Patients will be enrolled at approximately 100 sites in the U.S., Canada, Australia, Japan, Mexico, Europe, Israel, and South America, and the study drug will be administered once daily for 24 weeks. Patients randomized to bardoxolone methyl will start at 5 mg and will dose-escalate to 10 mg at Week 4 unless contraindicated clinically. The primary endpoint is the change from baseline in 6-minute walk distance, or 6MWD, relative to placebo at Week 24. Secondary endpoints include time to first clinical improvement as measured by improvement in WHO functional class, increase from baseline in 6MWD by at least 10%, or decrease from baseline in creatine kinase (as a surrogate biomarker for muscle injury and inflammation) by at least 10%. The trial will enroll between 130 and 200 patients. To determine the final sample size, a pre-specified, blinded sample size re-calculation based on 6MWD variability and baseline characteristics will be conducted after 100 patients have been enrolled in the trial. All patients who complete the treatment period are eligible to continue into an extension trial to evaluate the intermediate and long-term safety of bardoxolone methyl. Those patients who had been receiving placebo are converted to bardoxolone methyl in the extension trial. Data from CATALYST are expected to be available during the first half of 2018.

We have also tested bardoxolone methyl in PH patients in LARIAT, a randomized, placebo-controlled, double-blind, dose-escalation Phase 2 trial evaluating the safety and efficacy of once daily, orally administered bardoxolone methyl in PH patients with PAH or PH-ILD. The primary endpoint of the LARIAT trial is change in 6MWD during a 16 week treatment period. All patients who complete the treatment period are eligible to continue into an extension trial to evaluate the intermediate and long-term safety of bardoxolone methyl. Those patients who had been receiving placebo are converted to bardoxolone methyl in the extension trial. The initial treatment period for cohorts 1 and 2, which consisted of PAH patients, has been completed, and initial results from patients in these two LARIAT cohorts were presented at CHEST in October 2015. Initial data from cohort 3, which consisted of only CTD-PAH patients, also have been publicly announced. Because bardoxolone methyl was active in patients with CTD-PAH, a fibrotic disease, we believe that bardoxolone methyl may be effective in PH-ILD patients. We are enrolling patients with PH-ILD caused by CTD, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, and sarcoidosis in LARIAT cohorts 4a, 4b, 4c, and 4d, respectively. Data have not been presented from cohort 4. We anticipate that data from PH-ILD patients in the LARIAT trial will be available in the second half of 2017.

We have initiated the Phase 2 portion of CARDINAL and enrolled the first patient on March 2, 2017. We designed the trial in collaboration with international key opinion leaders and the Alport Syndrome Foundation. Based on the guidance from the U.S. Food and Drug Administration, or FDA, the trial is an international, multi-center, double-blind, randomized, placebo-controlled trial that studies the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with Alport syndrome from age 12 to 60 at 50 to 60 sites. The Phase 2 portion of the trial is open-label and the primary endpoint will assess estimated glomerular filtration rate, or eGFR, change at 12 weeks. These patients will continue in the Phase 2 portion of the trial for two years and will not be included in the Phase 3 portion of the trial. The Phase 3 portion is designed to support registration. These patients are randomized 1:1 to either bardoxolone methyl or placebo. The eGFR change at one year will be measured after 48 weeks while the patient is on treatment, and after withdrawal of drug for four weeks (retained eGFR). After withdrawal, patients will be restarted on study drug with their original treatment assignments and will continue on study drug for a second year. The change from baseline in eGFR in bardoxolone methyl-treated patients relative to placebo will be measured again after two years. The eGFR change at two years will also be measured after 100 weeks while the patient is on treatment and after withdrawal of drug for four weeks (retained eGFR). If the trial is successful, the year one retained eGFR data could support accelerated approval under subpart H of the Federal Food, Drug, and Cosmetic Act, or the FD&C Act, and the year two retained eGFR data could support full approval under the FD&C Act. We expect to have Phase 2 data by the end of 2017. We expect to have the one year withdrawal data that could support accelerated approval in the first half of 2019.

Omaveloxolone is a close structural analog of bardoxolone methyl that was developed to improve tissue distribution, including blood-brain barrier penetration. In 2014, we met with the FDA to discuss our FA and MM programs. Based on discussions with the FDA, we designed MOXIe and MOTOR as two-part Phase 2 trials, each part of which is randomized, placebo-controlled, and double-blind. Part one of each trial is a dose-escalation portion to evaluate the safety and efficacy of omaveloxolone. We have completed enrollment of part one in MOXIe and are currently dosing patients in part one of MOTOR. Data from part two of each of the trials, if part one supports initiating part two, have the potential to be used for registration. There are no currently approved therapies for either FA or MM. Data from part one of MOXIe are expected in mid-year 2017, while we expect data from part one of MOTOR in the second half of 2017.

In addition to MOXIe and MOTOR, we are currently conducting an open-label, multi-center, dose-escalation Phase 1b/2 trial, known as REVEAL, to evaluate the safety, pharmacodynamics, and efficacy of omaveloxolone in combination with existing immunotherapies for the treatment of metastatic melanoma. Initial data from REVEAL are expected in the second half of 2017.

If beneficial effects are demonstrated in our ongoing PAH, PH-ILD, FA, or MM trials, this could indicate that our Nrf2 activator pharmacology may also provide therapeutic benefit for patients suffering from other diseases where mitochondrial dysfunction or chronic inflammation is implicated. In addition, if bardoxolone methyl is successful in treating CKD caused by Alport syndrome, this could indicate our pharmacology may also provide therapeutic benefit for patients suffering from other renal diseases.

In addition to our Nrf2 activators, we are pursuing clinical development of our Hsp90 inhibitors, including RTA 901, which are highly potent and selective C-terminal inhibitors of Hsp90. We observed favorable activity of RTA 901 in preclinical models of neurodegeneration and neuroprotection. In models of diabetic neuropathy and neural inflammation, RTA 901 has been observed to restore lost nerve function, restore thermal and mechanical sensitivity, and improve nerve conductance velocity and mitochondrial function. We are currently conducting a Phase 1 clinical trial of RTA 901 in healthy adults, which we expect to complete and report data in the second half of 2017.

We are also pursuing preclinical development of other non-Nrf2 activators, such as RORgT inhibitors for the treatment of a variety of autoimmune and inflammatory conditions.

The commercialization of our Nrf2 activator programs is subject to collaborations with AbbVie Ltd., or AbbVie, and Kyowa Hakko Kirin Co., Ltd., or KHK. Under the terms of our collaborations, we retain commercial rights to market and sell bardoxolone methyl in the United States. KHK has licensed from us the right to commercialize bardoxolone methyl in certain parts of Asia, and AbbVie has licensed from us the right to market and sell bardoxolone methyl in all non-KHK territories outside of the United States. We retain all U.S. commercial rights to market and sell omaveloxolone and have licensed to AbbVie commercialization rights to the rest of the world. We plan, either alone, with our strategic collaborators AbbVie and KHK, or with new collaboration partners, to devise global commercialization strategies for bardoxolone methyl and omaveloxolone if these product candidates are approved. We intend to market and sell these products, if approved, in the United States. Our non-Nrf2 activator programs are not subject to any collaborations and we retain worldwide rights with respect to these programs.

Our Approach

We seek to identify and select, for development and commercialization, small molecules with novel mechanisms of action that we believe have biological properties with broad applicability. Once we have selected a class of small molecules, we apply their biological properties to clinical settings with unmet needs, and we triage opportunities based on development timeline and cost, regulatory pathway, and commercial opportunity. Once we have identified suitable molecules for clinical development, we endeavor to run multiple clinical programs in parallel to maximize our probability of success.

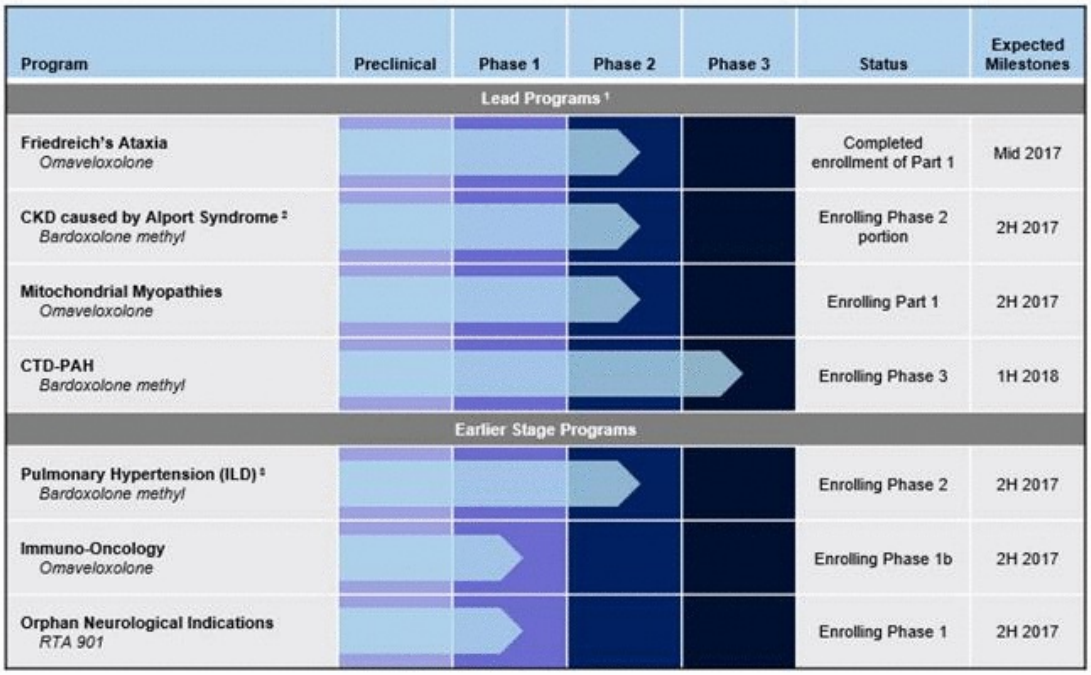
Our Strategy

Our goal is to become a leader in the discovery, development, and commercialization of small molecule therapies for the treatment of severe and life-threatening diseases. Our strategy is to mitigate development risk by maintaining a diversified and broad clinical pipeline, rapidly analyzing data to determine the potential of each program, and entering into development collaborations with industry-leading collaborators, and includes:

- ***Continuing to rapidly advance bardoxolone methyl.*** We are currently studying bardoxolone methyl in a Phase 3 clinical trial in CTD-PAH patients and in a Phase 2 clinical trial in PH-ILD and PAH patients. Our goal is to seek regulatory approval for the commercialization of bardoxolone methyl initially in CTD-PAH patients. We also intend to further pursue development and regulatory approval for the treatment of PH-ILD patients. In addition, we are currently studying bardoxolone methyl in chronic kidney disease caused by Alport syndrome, and, if successful, we intend to further pursue development and regulatory approval for the treatment of other renal diseases.
- ***Continuing to rapidly advance omaveloxolone.*** We believe that omaveloxolone has the potential to treat multiple indications, such as FA, MM, advanced solid tumors, and other diseases where mitochondrial dysfunction, oxidative stress, and inflammation are implicated. We plan to continue Phase 2 clinical development of omaveloxolone and to opportunistically advance this product candidate into registrational trials for the treatment of the most promising indications.
- ***Continuing to rapidly advance RTA 901.*** We believe that the neuroprotective and bioenergetic effects of Hsp90 inhibitors have the potential to benefit patients suffering from neurological indications, such as ALS, diabetic neuropathy, spinocerebellar ataxia, and spinal bulbar muscular atrophy. We are currently studying RTA 901 in a Phase 1 clinical trial in healthy adults, and, if successful, we plan to advance this product candidate into Phase 2 clinical development for the treatment of the most promising neurological indication.
- ***Advancing our preclinical programs into clinical development.*** We intend to advance our preclinical programs, including our RORgT inhibitors, through preclinical studies into clinical development. We believe that the anti-inflammatory effects of RORgT inhibitors may be promising for the treatment of a variety of autoimmune and inflammatory conditions.
- ***Leveraging our technologies to expand our development pipeline.*** We intend to leverage our multiple technologies by exploring preclinical and clinical proof of concept studies with multiple new molecules. We believe that our technologies may enable us to treat indications beyond those that we are currently exploring.
- ***Commercializing our lead product candidates in the United States.*** We retain U.S. commercial rights to our lead product candidates, bardoxolone methyl and omaveloxolone, and intend to commercialize these product candidates, if approved, in the United States. As we advance towards regulatory approvals for our lead product candidates, we intend to establish a specialty sales and marketing infrastructure and to contract with third parties for commercial scale manufacturing.
- ***Commercializing our lead product candidates outside of the United States.*** We plan to internationally commercialize our lead product candidates, bardoxolone methyl and omaveloxolone, subject to regulatory approvals, outside of the United States, either alone, with our strategic collaborators AbbVie and KHK, or with new collaboration partners. With the expansion of our product candidate pipeline, we may opportunistically seek additional strategic collaborations to maximize our commercial opportunities for these new product candidates outside of the United States.
- ***Using our expertise to identify promising novel molecules and technologies.*** Our management team collectively has over 200 years of experience in small molecule development, and we intend to use this expertise, together with our established drug selection and development methodology, to advance what we believe to be the most promising small molecules that we currently own and to opportunistically in-license additional small molecules for development.

Our Clinical Pipeline

The chart below is a summary of our clinical programs:



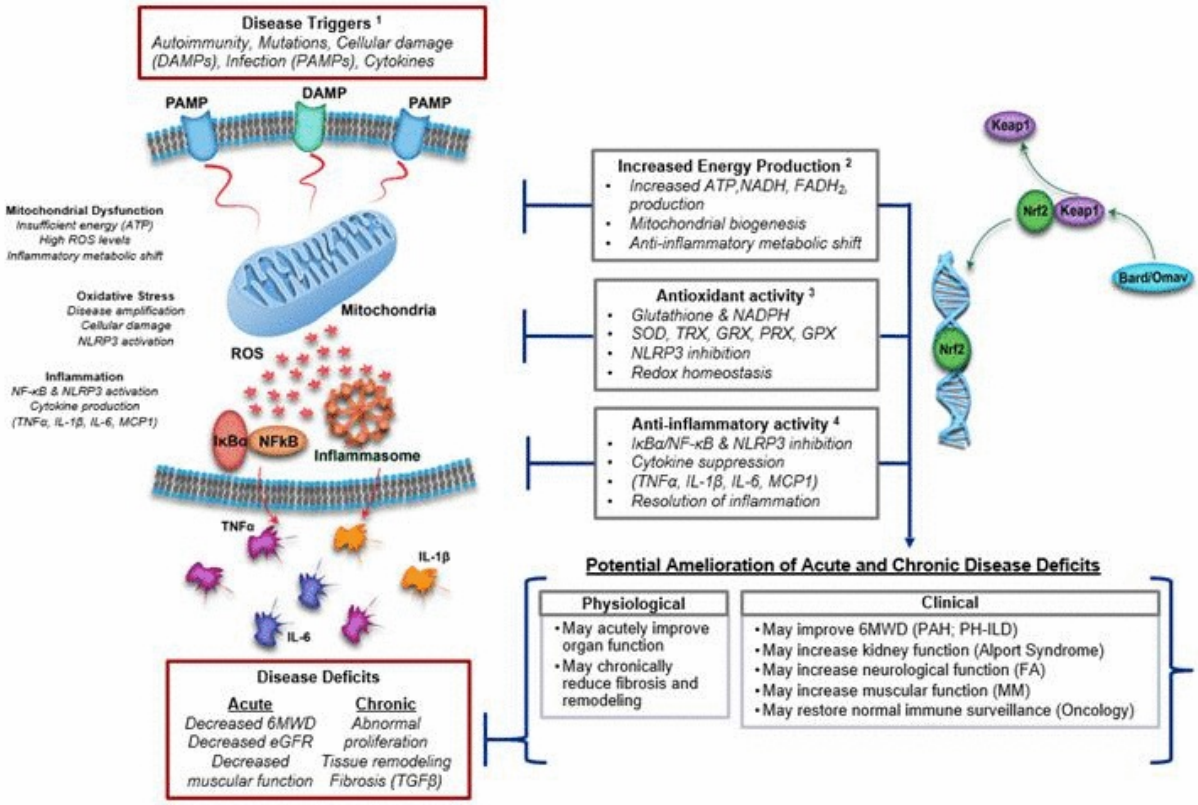
1 Our lead programs include programs for which we have received guidance from the FDA on registrational endpoints and trial design, and for which the ongoing trial may support registration.

2 We have initiated the Phase 2 portion of an integrated Phase 2/3 clinical trial in the first half of 2017, with Phase 2 data expected at the end of 2017. Additionally, the one year withdrawal data which could support accelerated approval are expected in the first half 2019.

3 We are studying bardoxolone methyl in a Phase 2 trial for patients with PH-ILD caused by CTD, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, and sarcoidosis.

The Foundational Biology of Nrf2 Activators

The foundational biology of Nrf2 activators underlies our two lead product candidates, bardoxolone methyl and omaveloxolone. Nrf2 activators bind to Keap1, a protein that coordinates the cellular response to ROS and other stimuli, each of which can cause cellular damage, which is generally referred to as oxidative stress. Binding to Keap1 activates Nrf2, a transcription factor that promotes normal mitochondrial function by making reducing equivalents available for ATP production and increases cellular antioxidant content. This reduces mitochondrial ROS production and ROS-mediated activation of inflammatory signaling complexes. Binding to Keap1, and activation of Nrf2, also inhibits NF-kB, the primary transcription factor producing proteins that promote inflammation and the production of ROS.



1 Multiple disease processes or external stimuli can initiate cellular responses leading to mitochondrial dysfunction, oxidative stress, and inflammation. Specific triggers can include an autoimmune response, genetic mutations, cellular damage (generating damage-associated molecular patterns, or DAMPs), infections (generating pathogen-associated molecular patterns, or PAMPs), or cytokine production.

2 Electrons are carried in the electron transport chain by NADH and FADH2, which are reducing equivalents that transfer electrons for the production of energy in the form of ATP. NADH is the reduced form of nicotinamide adenine dinucleotide, and FADH2 is the reduced form of flavin adenine dinucleotide. Reactive oxygen species (ROS) are generated during the production of ATP; an excess of ROS leads to oxidative stress. Reducing equivalents within the cell can either be consumed to produce energy via ATP, or consumed to defend against oxidative stress (ROS). Nrf2 activation is also associated with an increase in the number of mitochondria within cells (mitochondrial biogenesis).

3 Glutathione, SOD (superoxide dismutase), TRX (thioredoxin), GRX (glutaredoxin), PRX (peroxiredoxins), and GPX (glutathione peroxidase) are all antioxidants which convert ROS, reactive nitrogen species, and other harmful reactive molecules into less harmful molecules. Nrf2 activation leads to increased production of these antioxidants, which augments the ability of the cell to defend against oxidative stress, thereby allowing more reducing equivalents to be used for energy production.

4 A key component of inflammatory signaling is the NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome. NLRP3 can be activated by a number of stimuli, including mitochondrial ROS. NLRP3 activation, together with IκBα/Nf-κB signaling, leads to the production of multiple proteins involved in pro-inflammatory signaling, including IL-1β (interleukin 1-beta), IL-6 (interleukin 6), MCP1 (monocyte chemotactic protein-1), and TNFα (tumor necrosis factor-alpha). IκBα is a negative regulator of the Nf-κB pathway.

Nrf2 activators restore mitochondrial production of ATP, increase production of antioxidants, reduce oxidative stress, and reduce pro-inflammatory signaling. Since mitochondrial dysfunction, oxidative stress, and inflammation are features of many diseases, Nrf2 activators have many potential clinical applications and have been the subject of more than 200 peer-reviewed scientific papers. Mitochondrial dysfunction is directly implicated in a number of diseases and, in many diseases, is seen in conjunction with chronic inflammation. In a number

of diseases, chronic inflammation can lead, in the longer term, to organ fibrosis and remodeling. Reducing this chronic inflammation may lead to reduction of fibrosis and remodeling. The effects of Nrf2 activators are described below in more detail.

Promoting Energy Metabolism and Mitochondrial Function

Mitochondria are often described as the power plants of the cell because they generate energy through the production of ATP, the primary unit of cellular energy. Mitochondrial dysfunction, which is manifested through decreased cellular energy production and increased production of ROS, is a feature of many diseases, including many chronic inflammatory diseases. Nrf2 activation reduces mitochondrial ROS, promotes the availability of fatty acids and glucose for mitochondrial ATP production, and increases mitochondrial biogenesis. Genetic activation of Nrf2 has been shown to increase ATP production *in vitro* and *in vivo* and has been shown to increase physical activity in mice.

- **ATP production.** ROS are produced in the mitochondria as a byproduct of ATP production. Nrf2 activation improves mitochondrial efficiency by making antioxidant enzymes available to reduce or neutralize ROS. The management of these reducing equivalents is a constant and critical balancing act within the mitochondria. Disease processes that increase ROS deplete reducing equivalents available for ATP production. Accordingly, the induction of antioxidant proteins through Nrf2 activation augments mitochondrial ATP production.
- **Efficient consumption of fats and sugars.** Nrf2 activation promotes the transport of fatty acids to the mitochondria where they are converted into reducing equivalents used to produce ATP. Nrf2 also promotes the transport of glucose from the bloodstream into the cells where it is converted into reducing equivalents used to produce ATP. Nrf2 activators have been shown to promote glucose uptake and oxygen consumption in animal models of diet-induced obesity and diabetes.
- **Mitochondrial biogenesis.** PGC1a is a protein that increases the number of mitochondria in a cell. Activation of Nrf2 has been shown to increase PGC1a expression in skeletal muscle, which may increase ATP production.

Reducing Oxidative Stress, Inflammatory Signaling, and Inflammation

Inflammation is a protective response of the body to harmful stimuli such as invading pathogens, damaged cells, or irritants. It evolved to neutralize the initial cause of injury, eliminate dead cells, and initiate repair of damaged tissues. A central feature of inflammation is mitochondrial dysfunction and the production of ROS, which promotes activation of inflammatory pathways. In many diseases, inflammation does not resolve normally and is associated with chronic excessive ROS, organ fibrosis, remodeling or other tissue damage, and impaired ATP production.

- **Reactive oxygen species.** ROS are chemically reactive molecules that contain oxygen and have important roles in cell signaling and balancing cellular systems. ROS are formed during mitochondrial ATP production and by a variety of other cellular processes. ROS increase inflammatory signaling, and excessive ROS can cause cellular damage to tissues in critical organs including the muscles, lung, heart, liver, brain, and eyes. Excessive ROS and chronic inflammation have been shown to be the cause of cellular damage in many diseases. Nrf2 activation increases the cellular antioxidant content, which makes reducing equivalents available to neutralize ROS. This suppresses the pro-inflammatory signaling effects of ROS and protects tissues from the damaging effects of excessive ROS.
- **Inhibition of inflammatory signaling.** Mitochondrial ROS and NF-kB are important activators of the inflammatory response. Nrf2 activators, through reduction of ROS and inhibition of NF-kB, suppress production of TNFa, IL-6, IL-1, and other inflammatory cytokines, or cellular messengers. The suppression of these inflammatory cytokines inhibits their downstream proinflammatory signaling pathways.
- **Reduction of proteins associated with fibrosis and tissue remodeling.** Tissue remodeling and fibrosis can be caused by chronic inflammation due to deposition of excess collagen and other factors. In a variety of models and settings, suppression of ROS and inhibition of NF-kB has been observed to reduce the expression of enzymes associated with tissue remodeling that are implicated in the progression of PH, certain types of kidney disease, cancer, arthritis, and many other diseases.
- **Inhibition of cellular proliferative pathways.** Inhibition of NF-kB by Nrf2 activators can prevent cellular proliferation, or harmful excessive cellular growth, the prevention of which is known as anti-proliferative effects, as demonstrated by the fact that Nrf2 activators have been shown to inhibit cancer cell replication in *in vitro* and *in vivo* model systems.

Bardoxolone Methyl for the Treatment of PAH, PH-ILD, and Chronic Kidney Disease Caused by Alport Syndrome

Bardoxolone methyl is currently being tested in a Phase 3 trial in CTD-PAH, a Phase 2 trial in several forms of PH-ILD and PAH, and a single, pivotal Phase 2/3 trial in CKD caused by Alport syndrome. CTD-PAH and CKD caused by Alport syndrome are our most advanced indications with bardoxolone methyl. Although CTD-PAH and CKD caused by Alport syndrome have different causes and inflammatory stimuli, at a molecular level, mitochondrial dysfunction, inflammation, and proliferative signaling are common to the pathophysiology of both diseases. The anti-inflammatory and anti-fibrotic properties of bardoxolone methyl may therefore be relevant to preventing remodeling of the

pulmonary vasculature in CTD-PAH as well as inhibiting structural alterations and glomerulosclerosis, or fibrosis of the glomerulus in the kidney, in Alport syndrome.

PAH and PH-ILD

We are currently focused on the treatment of PAH associated with CTD and PH-ILD. PAH results in a progressive increase in pulmonary vascular resistance, which ultimately leads to right ventricular heart failure and death. Female PAH patients outnumber males by a factor of 2:1, and the onset of PAH generally occurs between the ages of 40 and 60, with the average age of onset being 53. CTD-PAH represents approximately 30% of the overall PAH population. CTD-PAH is a late and often fatal manifestation of many types of autoimmune disease, including systemic sclerosis (scleroderma), systemic lupus erythematosus, mixed connective tissue disease, and others. Patients with CTD-PAH are generally less responsive to existing therapies and have a worse prognosis than patients with other forms of PAH. In comparison to patients with idiopathic PAH, or I-PAH, patients with CTD-PAH have a higher occurrence of small vessel fibrosis and greater incidence of pulmonary veno-obstructive diseases. In the United States, the five-year survival rate for CTD-PAH patients is approximately 44% compared to I-PAH patients, who have a 68% five-year survival rate. Additionally, CTD-PAH patients make up 10-15% of patients with scleroderma or lupus erythematosus, and scleroderma patients without CTD-PAH have a five-year survival rate of approximately 85%, compared to a five-year survival rate of 10% for scleroderma patients with CTD-PAH.

Interstitial lung disease, or ILD, patients experience extensive pulmonary vascular remodeling, which ultimately leads to PH-ILD in approximately 30% to 40% of ILD patients. We are initially targeting the use of bardoxolone methyl in the subsets of ILD patients with idiopathic pulmonary fibrosis, CTD that has affected the lung tissue, and idiopathic interstitial pneumonia, as well as sarcoidosis. PH-ILD patients have a one-year survival rate of approximately 63%, as compared to approximately 92% for ILD patients without PH. Recent studies have demonstrated that mitochondrial abnormalities are key contributors to PH-ILD.

Limitations of Current Therapies for PAH and PH-ILD

Pulmonary Arterial Hypertension Therapies

Three classes of drugs are currently used to treat all etiologies of PAH: endothelin receptor antagonists, or ERAs, such as Tracleer® and Letairis®; nitric oxide pathway modulators, including Revatio®, Adcirca® and Adempas®; and prostacyclins pathway agonists, such as Ventavis®, Uptravi® and Remodulin®. There are also additional therapies in late-stage clinical development. These agents are all systemic vasodilators that directly modulate vasoconstrictive and vasodilatory pathways, which have limited ability to mitigate the synergistic effects of vasoconstriction, thrombosis, fibrosis, and vascular remodeling within the pulmonary arterial system, and do not address the role of mitochondrial dysfunction and inflammation in PAH.

All three classes of existing therapies are not specific to the pulmonary vasculature and have effects on blood pressure, vascular resistance, and cardiac output. These systemic hemodynamic effects can result in hypotension and syncope, or fainting, which generally limit their clinical dosages. These hemodynamic effects can be exacerbated when a patient is prescribed multiple vasodilators. In addition, clinically significant drug-drug interactions have been observed that can further limit the ability to deliver effective drug combinations.

Vasodilators approved for PAH also generally do not yield significant functional improvements in CTD-PAH patients, likely because vasoconstriction is not as prominent a feature in these patients as it is in other PAH patients. Further, the efficacy of currently approved therapies is impacted by the number of other PAH therapies being administered to a patient, with each new therapy yielding lower marginal return.

In addition, most patients in North America and certain other regions are generally managed more closely than their counterparts outside of North America and certain other regions, are treated with a higher number of background therapies, and receive less incremental improvement from an additional therapy. Accordingly, the treatment effect observed in some registrational trials for new PAH therapies is primarily driven by improvements seen in patients outside of North America and certain other regions, who are generally on fewer existing therapies.

Within PAH, the subset of CTD-PAH represents a population with a significant unmet medical need. A recently published meta-analysis of the response of CTD-PAH patients to vasodilator therapy in 11 registrational trials comprised of more than 2,700 PAH patients demonstrated that CTD-PAH patients respond less well than I-PAH patients to approved vasodilator therapies in both clinical worsening and improvements in 6MWD from baseline, with response in CTD-PAH patients (9.6 meters) approximately one-third of the response in I-PAH patients (30 meters). The meta-analysis also demonstrated that I-PAH patients were more hemodynamically impaired than CTD-PAH patients, which likely explains why vasodilator therapy is more effective in I-PAH patients. This difference also explains why CTD-PAH patients respond less well to vasodilator therapy, as their disease process is less hemodynamic and involves systemic fibrotic processes caused by the patients' underlying autoimmune diseases, such as scleroderma, lupus, or mixed connective tissue disease.

Pulmonary Hypertension in Interstitial Lung Disease Therapies

Currently, there are no approved therapies for PH-ILD patients. While approved vasodilators are sometimes used off-label, given the degree of remodeling and fibrosis present in the lung tissue and vasculature of PH-ILD patients, they are minimally effective. Several current PAH therapies have been tested in PH-ILD patients and have resulted in little to no reproducible clinical improvement.

Bardoxolone Methyl in PAH and PH-ILD

Bardoxolone methyl directly targets the bioenergetic and inflammatory components of PAH. PAH patients experience mitochondrial dysfunction, increased production of NF-kB and related inflammatory pathways involved in ROS signaling, cellular proliferation, and fibrosis. Bardoxolone methyl, through the combined effect of Nrf2 activation and NF-kB suppression, has the potential to inhibit inflammatory and proliferative signaling, suppress ROS production and signaling, reduce the production of enzymes related to fibrosis and tissue remodeling, and increase ATP production and cellular respiration. By addressing a novel pathway in PAH, we believe that bardoxolone methyl may provide additional benefits beyond current PAH therapies, including:

- **Increased functional capacity.** We believe the bioenergetic effects of bardoxolone methyl may result in increased functional capacity, the ability to perform everyday functions, for PAH patients due to its effects on energy production and cellular respiration, as have been characterized in preclinical studies with bardoxolone methyl and other Nrf2 activators.
- **Potential effects beyond functional improvements**. Bardoxolone methyl has potential anti-inflammatory, anti-proliferative, and anti-fibrotic effects and targets multiple cell types relevant to PAH, including endothelial cells, smooth muscle cells, and macrophages. We believe that bardoxolone methyl may, over an extended period of time, affect the synergistic effects of vasoconstriction, thrombosis, fibrosis, and vascular remodeling within the pulmonary arterial system, potentially improving patient outcomes.
- **Broader applicability.** Bardoxolone methyl may be useful in treating CTD-PAH patients, earlier stage PAH patients, and PH-ILD patients, all of whom are underserved by existing PAH therapies, likely because vasoconstriction is a less prominent feature in these patients as it is in idiopathic and other PAH patients. In addition, lack of embryofetal toxicity may allow for the use of bardoxolone methyl in pregnant women, who are currently limited to prostacyclins.
- **Potential as a combination therapy.** To date, it has been observed that bardoxolone methyl does not have systemic hemodynamic effects or drug-drug interactions in PAH patients. This may provide clinicians with greater flexibility in dosing, ultimately result in a more favorable safety profile, and allow for use in combination with other therapies with a greater incremental effect than an additional vasodilator.

Market Opportunity for Bardoxolone Methyl in PAH and PH-ILD

Pulmonary Arterial Hypertension Market

We believe there is significant opportunity for once-daily, orally administered bardoxolone methyl to address the PAH market currently served only by the existing vasodilator therapies. In 2015, global sales of approved PAH treatments were approximately $4.7 billion. In addition, recently approved treatments such as Opsumit® and Adempas® have shown rapid uptake in the PAH market and, based on industry reports, Opsumit® is projected to reach between $1 and $2 billion in annual sales within seven years from launch. Based on literature and proprietary research, we believe there are approximately 12,000 CTD-PAH patients in the United States and 50,000 worldwide. Furthermore, CTD-PAH represents approximately 30% of the overall PAH population, which is estimated to be growing globally at an annual rate of 10 to 15 patients per million of population each year.

Pulmonary Hypertension in Interstitial Lung Diseases Market

There are no therapies currently approved for PH-ILD. Based on literature and proprietary research, we believe there are approximately 60,000 patients in the United States and 160,000 worldwide with the forms of PH-ILD that we are targeting. Further, PH-ILD may be underdiagnosed because the current standard for diagnosis is heavily focused on the characteristics of PAH patients, while PH-ILD patients have different hemodynamics and lung function. We believe that with the emergence of an effective therapy, identification of patients with this subset of PH may increase.

Clinical Development for Bardoxolone Methyl in PAH and PH-ILD

Phase 3 CATALYST Trial

In October 2016, the first patient was enrolled in CATALYST, an international, randomized, double-blind, placebo-controlled Phase 3 trial examining the safety, tolerability, and efficacy of bardoxolone methyl in patients with CTD-PAH when added to standard-of-care vasodilator therapy. Patients will be on up to two background therapies and will be randomized 1:1 to bardoxolone methyl or placebo. Patients

will be enrolled at approximately 100 sites in the U.S., Canada, Australia, Japan, Mexico, Europe, Israel, and South America, and the study drug will be administered once daily for 24 weeks. Patients randomized to bardoxolone methyl will start at 5 mg and will dose-escalate to 10 mg at Week 4 unless contraindicated clinically. The primary endpoint is the change from baseline in 6MWD relative to placebo at Week 24. Secondary endpoints include time to first clinical improvement as measured by improvement in World Health Organization/New York Heart Association, or WHO/NYHA, functional class, increase from baseline in 6MWD by at least 10%, or decrease from baseline in creatine kinase (as a surrogate biomarker for muscle injury and inflammation) by at least 10%. The trial will enroll between 130 and 200 patients. To determine the final sample size, a pre-specified, blinded sample size re-calculation based on 6MWD variability and baseline characteristics will be conducted after 100 patients have been enrolled in the trial. All patients who complete the treatment period are eligible to continue into an extension trial to evaluate the intermediate and long-term safety of bardoxolone methyl. Those patients who had been receiving placebo are converted to bardoxolone methyl in the extension trial. Data from CATALYST are expected to be available during the first half of 2018.

During our interaction with the FDA in October 2015, the FDA concurred with our design of the Phase 3 trial and noted that CATALYST, together with the Phase 2 data from our LARIAT trial in PAH patients and prior clinical trials with bardoxolone methyl, would provide adequate data for a New Drug Application, or NDA, review of the safety profile of bardoxolone methyl. Prior to this meeting, we had completed a series of clinical pharmacology studies, including a Thorough QT study, hepatic impairment study, food effect study, mass balance study, and three drug-drug interaction studies. The FDA recommended conducting a single additional clinical drug-drug interaction study and otherwise had no clinical trial, clinical pharmacology, or preclinical study requests.

We presented initial results from cohorts 1 and 2 of LARIAT, our Phase 2 PAH trial in patients with PAH and PH-ILD, at the CHEST World Congress during October 2015. Cohorts 1 and 2 included patients with both I-PAH and CTD-PAH. Cohorts 1 and 2 of the trial enrolled only U.S. patients on approved vasodilator therapy with most patients receiving two background therapies upon study entry. The data demonstrated that administration of bardoxolone methyl significantly improved the function of patients when compared to placebo as assessed by 6MWD. A result is considered to be statistically significant when the probability of the result occurring by random chance, rather than from the efficacy of the treatment, is sufficiently low. The conventional method for measuring the statistical significance of a result is known as the "p-value," which represents the probability that random chance caused the result. For example, a p-value of 0.001 means that there is a 0.1% or less probability that the difference between the control group and the treatment group is purely due to random chance. A p-value of 0.05 is a commonly used criterion for statistical significance, and may be supportive of a finding of efficacy by regulatory authorities. However, regulatory authorities, including the FDA, do not rely on strict statistical significance thresholds as criteria for marketing approval and maintain the flexibility to evaluate the overall risks and benefits of a treatment. Accordingly, treatments may receive marketing approval from the FDA even if the p-value of the primary endpoint is greater than 0.05, or may fail to receive marketing approval from the FDA even if the p-value of the primary endpoint is less than 0.05. The primary efficacy analysis was the time-averaged change through 16 weeks of treatment using all available 6MWD values post-randomization. The placebo-corrected change in time averaged 6MWD was 21.4 meters with a p-value of 0.037. Additionally, no clinically meaningful differences were noted in safety variables including vital signs and laboratory data, and bardoxolone methyl was combined with approved vasodilator therapies without increasing the risk of hypotensive events or exacerbating their adverse event profile.

An important finding from cohort 1 of LARIAT was that bardoxolone methyl provided the greatest improvement in 6MWD to CTD-PAH patients. In cohort 1 of LARIAT, six CTD-PAH patients treated with bardoxolone methyl had time-averaged 6MWD improvements from baseline of 30.3 meters with a p-value of 0.05 and increases in 6MWD from baseline at Week 16 of 38.3 meters with a p-value of 0.01. In response to these initial data, we expanded LARIAT to include cohort 3a, a cohort of additional CTD-PAH patients, in order to further test the planned titration design and expand the available data set in advance of enrolling CATALYST.

In advance of the initiation of CATALYST, we analyzed data for all CTD-PAH patients treated with doses of up to 10 mg who had completed the 16-week treatment period (or terminated early) in the ongoing LARIAT trial. A total of 22 CTD-PAH patients, including patients from cohorts 1, 2, and 3a, which are discussed below, met these criteria, with 15 randomized to bardoxolone methyl and seven randomized to placebo. Baseline characteristics of the 22 CTD-PAH patients can be found in the table below.

Baseline Characteristics for CTD-PAH Patients in LARIAT

	Bard	Placebo
N	15	7
Mean Age (years)	56.4	52.4
Female/Male	80%/20%	100%/0%
Mean Weight (kg)	75.5	68.2
Mean BMI (kg/m^2)	27.5	26.3
WHO Functional Class:		
II	9 (60%)	4 (57%)
III	6 (40%)	3 (43%)
Mean Time Since Diagnosis (years)	2.9	3.0
Mean Baseline 6MWD (m)	381	396

The LARIAT statistical analysis plan defined the treatment effect as the time-averaged change from baseline in 6MWD values using a longitudinal model to assess the average of all available 6MWD timepoints, improving the study's sensitivity to detect a significant difference between the active drug and placebo groups. Change from baseline in 6MWD at Weeks 4, 8, 12, and 16 were analyzed using a mixed-model repeated measures, or MMRM, analysis to compare the difference between the active drug and placebo groups. The analysis showed that patients treated with bardoxolone methyl demonstrated a statistically significant mean time-averaged increase in 6MWD compared to baseline of 26.7 meters (p=0.001). Placebo-treated patients had a non-significant time-averaged mean change from baseline in 6MWD of 0.6 meters (p=0.96). The placebo-corrected time-averaged change in 6MWD was 26.1 meters (p=0.06).

Patients with moderate to severe anemia, which represents a small percentage of the patient population, will be excluded from CATALYST because treatment with iron supplementation or erythropoietin can affect 6MWD values independent of study drug effect. Three CTD-PAH patients enrolled in LARIAT and included in the above analysis were anemic at screening (as defined by low hemoglobin values), and two of these patients, both randomized to placebo, received post-randomization anemia treatments. An analysis was conducted excluding patients with anemia at screening to estimate the treatment effect in patients who meet the final CATALYST eligibility criteria. MMRM analysis showed that CATALYST-eligible patients treated with bardoxolone methyl in LARIAT demonstrated a statistically significant mean time-averaged increase in 6MWD compared to baseline of 30.2 meters (p<0.001), and placebo-treated patients had a non-significant mean change from baseline in 6MWD of -10.1 meters (p=0.39) for a placebo-corrected change of 40.3 meters (p=0.009). The pooled standard deviation of change of 6MWD was 34.1 meters. The time-averaged change in 6MWD is shown in the table below.

Summary of Time-Averaged 6MWD Changes for CTD-PAH Patients in LARIAT

	All Patients			CATALYST-Eligible Patients		
Treatment	N	Change from Baseline (m)	Placebo-corrected (m)	N	Change from Baseline (m)	Placebo-corrected (m)
Placebo	7	0.6 p=0.96	—	5	-10.1 p=0.39	—
Bardoxolone Methyl	15	26.1 p=0.001	26.1 p=0.06	14	30.2 p < 0.001	40.3 p=0.009

The method of statistical analysis for the CATALYST primary endpoint is the placebo-corrected change from baseline in 6MWD to the end-of-treatment at 24 weeks. This method allows for greater separation in 6MWD values between active and placebo groups assuming improved efficacy over time. We performed an analysis applying the MMRM statistical analysis method for CATALYST to the available end-of-treatment change in 6MWD data from CTD-PAH patients in LARIAT. Patients treated with bardoxolone methyl demonstrated a statistically significant mean increase of 38.2 meters with a p-value of less than 0.001. Placebo-treated patients had a non-significant mean change from baseline in 6MWD of 9.8 meters with a p-value of 0.44. The placebo-corrected change in 6MWD at Week 16 was 28.4 meters with a p-value of 0.07. Excluding patients with moderate to severe anemia at screening, the patients treated with bardoxolone methyl demonstrated a statistically significant mean increase in 6MWD compared to baseline of 42.7 meters with a p-value of less than 0.001. Placebo-treated patients had a non-significant mean change from baseline in 6MWD of -5.8 meters with a p-value of 0.68. The placebo-corrected change in 6MWD at Week 16 was 48.5 meters with a p-value of 0.005. The end-of-treatment change in 6MWD is shown in the table below.

Summary of End-of-Treatment 6MWD Changes for CTD-PAH Patients in LARIAT

Treatment	All Patients			CATALYST Eligible Patients		
	N	Change from Baseline (m)	Placebo-corrected (m)	N	Change from Baseline	Placebo-corrected
Placebo	7	9.8 p=0.44	—	5	-5.8 p=0.68	—
Bardoxolone Methyl	15	38.2 p <0.001	28.4 p=0.07	14	42.7 p < 0.001	48.5 p=0.005

With respect to safety, bardoxolone methyl was well-tolerated in CTD-PAH patients. None of the 15 bardoxolone methyl treated patients discontinued early, whereas one of the seven placebo treated patients discontinued prematurely. The expanded data set shows no clinically meaningful differences in safety variables including vital signs and laboratory data. Bardoxolone methyl was combined with approved vasodilator therapies without increasing the risk of hypotensive events or exacerbating their adverse event profile.

CATALYST is designed to detect a minimum treatment effect of 12.5 meters versus placebo assuming a standard deviation of 50 meters. The observed treatment effect in the LARIAT CTD-PAH subgroup analyses, both with and without the anemic patients included, is meaningfully larger than the minimally detectable treatment effect in CATALYST. Further, the standard deviation observed in LARIAT of 37 meters is lower than the estimated standard deviation of 50 meters in CATALYST.

Phase 2 LARIAT Trial

We first proposed entering into a Phase 2 trial of bardoxolone methyl in patients with PAH in September 2013, at which time we met with the FDA to discuss our proposed trial design and the analysis performed following the BEACON trial, which is discussed below. Our trial design incorporated FDA feedback, which included the selection of 6MWD as the primary efficacy endpoint and the exclusion of patients with significant renal disease, a prior history of left-sided heart disease or heart failure, or with elevated baseline brain natriuretic peptide, or BNP, levels in order to mitigate risk. We filed an investigational new drug, or IND, application with the FDA in November 2013, for which we served as sponsor. In September 2015, we expanded our development program to include PH-ILD patients under our existing IND for PAH. The protocol for the LARIAT trial was amended to include four separate, independently randomized cohorts for four different etiologies of PH-ILD patients and was submitted to the FDA in September 2015. Both cohorts 3 and 4 continue to enroll. In March 2015, the FDA granted our request for orphan drug designation for the treatment of PAH.

Phase 2 LARIAT Trial Design

The LARIAT trial is a randomized, placebo-controlled, double-blinded, dose-escalation Phase 2 trial evaluating the safety and efficacy of once daily, orally administered bardoxolone methyl in up to 486 patients with PAH or PH-ILD. LARIAT is comprised of four separate cohort groups, all of which include patients classified as WHO/NYHA, Functional Class II and III. Functional Class II patients are comfortable at rest, but ordinary physical activity results in breathlessness, fatigue, or palpitations. Functional Class III patients are comfortable at rest, but less than ordinary physical activity results in breathlessness, fatigue, or palpitations.

The primary endpoint of the LARIAT trial is change in 6MWD during a 16 week treatment period. All patients who complete the treatment period are eligible to continue into an extension trial to evaluate the intermediate and long-term safety of bardoxolone methyl. Those patients who had been receiving placebo are converted to bardoxolone methyl in the extension trial. The initial treatment period for cohorts 1 and 2 has been completed and, as discussed above, initial data from cohorts 1 and 2 and initial data from cohort 3 have been publicly presented.

Because bardoxolone methyl was active in patients with CTD-PAH, a fibrotic disease, we believe that bardoxolone methyl may be effective in PH-ILD patients. We have also begun enrolling patients with PH-ILD caused by CTD, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, and sarcoidosis in LARIAT cohorts 4a, 4b, 4c, and 4d, respectively. Data have not been presented from cohort 4. We anticipate that data from PH-ILD patients in the LARIAT trial will be available in the second half of 2017.

The cohorts from the LARIAT trial are described below.

- **Cohort 1.** The first cohort began enrolling in May 2014 and consists of PAH patients in the United States. Eligible patients must have had a baseline 6MWD of greater than or equal to 150 meters but less than or equal to 450 meters and were randomized 3:1 in each dose group to either bardoxolone methyl at doses of 2.5 mg, 5 mg, 10 mg, or 20 mg, or placebo.
- **Cohort 2.** The second cohort began enrolling in January 2015 and consists of PAH patients in the United States. Eligible patients must have had a baseline 6MWD of greater than 450 meters and were randomized 3:1 in each dose group to bardoxolone methyl at doses of 5 mg or 20 mg, or placebo.

- **Cohort 3.** The third cohort began enrolling in November 2015, and consists of PAH patients in the United States and other countries, and is comprised of two sub-cohorts for CTD-PAH (cohort 3a) patients and non-CTD-PAH (cohort 3b) patients. Eligible patients must have a baseline 6MWD of greater than or equal to 150 meters and are randomized 2:1 to bardoxolone methyl or placebo. Patients in the treatment group are titrated from 5 mg to 10 mg doses based on tolerability.
- **Cohort 4.** The fourth cohort began enrolling in December 2015, and consists of PH-ILD patients in the United States and potentially other countries, and is comprised of four sub-cohorts based on the patient's underlying type of ILD: (a) PH-ILD caused by CTD, such as scleroderma and lupus, or CTD-PH-ILD; (b) PH-ILD caused by idiopathic pulmonary fibrosis, or IPF-PH-ILD; (c) PH-ILD caused by idiopathic interstitial pneumonia, or IIP-PH-ILD; and (d) PH-ILD caused by sarcoidosis, or SA-PH-ILD. Eligible patients must have a baseline 6MWD of greater than or equal to 150 meters. There are no therapies approved for any of the four groups of PH-ILD patients. Patients are randomized 2:1 to bardoxolone methyl or placebo. Patients in the treatment group are titrated from 5 mg to 10 mg doses based on tolerability.

Phase 2 LARIAT Trial Safety and Tolerability

We have observed no significant tolerability issues in LARIAT to date. A higher incidence of AEs related to mild, transient nausea has been observed in patients at the 20 mg dose of bardoxolone methyl. Due to the observed nausea at the 20 mg dose and the fact that signs of activity have been observed at lower dose levels, the titration design in cohorts 3 and 4 utilizes 2.5 mg, 5 mg, and 10 mg doses. In the PAH patients in this trial, all of whom receive background vasodilator therapies, there have been no observed increases in the incidence of AEs typically associated with vasodilation, such as headache or jaw pain. We have also begun enrolling patients with PH-ILD caused by CTD, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, and sarcoidosis in LARIAT cohorts 4a, 4b, 4c, and 4d, respectively.

PAH and PH-ILD are serious progressive diseases that ultimately lead to right ventricular heart failure and death. Patients with these diseases can develop serious comorbidities such as syncope, chest pain, palpitations, fluid retention, and hypoxemia. The trial utilizes a protocol safety review committee, or PSRC, that reviews all data, including SAE and AE data, on an unblinded basis to assess safety. The PSRC has not reported any safety concerns to date.

Chronic Kidney Disease Caused by Alport Syndrome

Alport syndrome is a rare and serious hereditary disease that affects approximately 12,000 children and adults in the United States and 40,000 globally. It is caused by mutations in the genes encoding type IV collagen, a major structural component of the glomerular basement membrane, or GBM, in the kidney. The abnormal expression of type IV collagen causes loss of GBM integrity, abnormal leakage of proteins through the GBM, and excessive reabsorption of protein in the proximal tubules of the kidney. As in other forms of CKD, excessive reabsorption of protein in the tubules induces oxidative stress, renal interstitial inflammation, and fibrosis.

Patients with Alport syndrome are normally diagnosed with the disease in childhood to early adulthood and have average glomerular filtration rate, or GFR, declines of 4.0 mL/min/1.73 m^2 per year. The progressive decline of GFR in Alport syndrome inexorably leads to renal failure and end-stage renal disease, or ESRD, with a median survival of approximately 55 years. Fifty percent of males with the most prevalent subtype of Alport syndrome require dialysis or kidney transplant by age 25. The incidence of renal failure in these patients increases to 90% by age 40 and nearly 100% by age 60. Similar to patients with other forms of CKD, Alport syndrome patients receiving dialysis are at increased risk for cardiovascular disease and infections, which are the most common causes of death in these patients.

The pathogenic role of inflammatory processes in Alport syndrome disease progression and declining renal function is similar to that of other chronic kidney diseases. The GBM defects and leaked proteins in Alport syndrome, the hyperglycemia in diabetes, and hypertension in cardiovascular disease all activate pro-inflammatory signaling pathways. These signals induce mitochondrial dysfunction in which ATP is impaired in favor of production of pro-inflammatory ROS. ROS is a central feature of inflammation and activates pro-inflammatory signaling complexes including NF-kB and the NLRP3 complex referred to as the inflammasome. ROS-mediated activation of NF-kB and the inflammasome produce cytokines that promote inflammation in glomerular endothelial cells, mesangial cells, and podocytes while also recruiting activated macrophages and other inflammatory effector cells to the renal interstitium.

Chronic activation of pro-inflammatory pathways in kidney cells promotes GFR loss by at least three mechanisms. First, inflammation-associated ROS reduce the amount of nitric oxide available to the endothelial cells in the blood vessels of the glomerulus. This results in a decrease of the overall surface area of the glomerulus that is available for filtration, and thus decreases GFR. Second, inflammation-associated ROS cause contraction of mesangial cells in the kidney. The primary function of these cells is to remove debris and protein from the glomerular basement membrane, or GBM, allowing proper filtration to occur. Mesangial cell contraction reduces their function, and thus reduces GFR. Third, inflammation-associated ROS lead to fibrosis, which changes the structure of the mesangial cell layer and causes thickening of the GBM, contributing to decline of GFR.

No Current Therapies for Alport Syndrome

There are no currently approved therapies for the treatment of CKD caused by Alport syndrome. The goal of current disease management is to slow the progression of CKD, beginning with anti-hypertensives, such as angiotensin converting enzyme, or ACE, inhibitors or angiotensin receptor blockers, or ARBs, aldosterone, and diuretics, all of which are intended to reduce the levels of protein found in patient urine. Once patients reach ESRD, they require dialysis and, in severe cases, renal transplantation.

Bardoxolone Methyl in Chronic Kidney Disease Caused by Alport Syndrome

Bardoxolone methyl has the potential to address the causes of GFR loss in Alport syndrome patients because it activates molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting ROS-mediated pro-inflammatory signaling. Bardoxolone methyl binds to Keap1 and activates Nrf2, a transcription factor that increases cellular antioxidant content and promotes normal mitochondrial function by making reducing equivalents available for ATP production. This reduces mitochondrial ROS production and ROS-mediated activation of inflammatory signaling complexes. Through these effects, bardoxolone methyl restores mitochondrial production of ATP, increases production of antioxidants, reduces oxidative stress, and reduces pro-inflammatory signaling.

In the kidney, the first stage of the blood filtering process takes place in the glomerulus, which consists of a small tuft of capillaries containing endothelial cells, between which are large pores, and mesangial cells which are modified smooth muscle cells that lie between the capillaries. Tight coordination between these cell types is necessary for proper filtration. The pores between the endothelial cells allow for the free filtration of fluid, plasma solutes, and protein. When endothelial cells become dysfunctional, due to oxidative stress or other reasons, the pores can become more permeable and increase spillage of protein, which can drive further inflammatory signaling and oxidative stress. The mesangial cells regulate blood flow by their contractile activity, and contraction of the cells reduces surface area for filtration of the blood. Mesangial cells also remove proteins and other molecules trapped in the glomerular basement membrane, or filtration barrier.

In preclinical models, bardoxolone methyl reverses endothelial dysfunction and chronic, disease related, mesangial cell contraction, resulting in increased surface area of the glomerulus and increased GFR. Additionally, bardoxolone methyl inhibits activation of inflammatory and pro-fibrotic pathways that lead to structural remodeling and glomerulosclerosis.

As a result, bardoxolone methyl and closely related structural analogs have been shown to improve renal function, reduce inflammation, and prevent injury, remodeling, and fibrosis, or the thickening and scarring of connective tissue, in a number of animal models of renal injury and disease as seen in the table below. Specifically, bardoxolone methyl and analogs reverse endothelial dysfunction and mesangial cell contraction in response to angiotensin II, a hormone that causes vasoconstriction and subsequent increase in blood pressure, thereby increasing the surface area of the glomerulus and increasing GFR. Further, data from animal models relevant to chronic renal disease demonstrate that the compounds are anti-fibrotic and have protective effects on the renal interstitium, part of the extravascular space of the kidney responsible for modulating exchange among the tubular and vascular elements of the organ, in response to high protein, as well as pressure overload in the setting of hyperfiltration, or increased kidney filtration driven by higher blood pressure in the organ, and dyslipidemia, or an abnormal amount of lipids in the blood. These effects are summarized in the table below.

Model	General Findings
Protein overload [1]	— Reduced oxidative/nitrosative stress, interstitial inflammation, and fibrogenic mediators including TGF-ß and a-SMA — Decreased proteinuria and tubular damage
Angiotensin II-induced GFR decline [2]	— Increased inulin clearance by increasing Kf without affecting BP or renal plasma flow — Reduced whole glomeruli and mesangial cell contraction due to angiotensin II
5/6 nephrectomy [3]	— Reversed endothelial dysfunction in arterial tissue — Ameliorated hyperfiltration-induced glomerulosclerosis and tubular injury — Suppressed renal inflammation and infiltration of lymphocytes and macrophages — Mitigated systolic blood pressure increase caused by chronic renal failure
12-month monkey safety study [4]	— Improved kidney function for 12 months without adverse renal histological effects — Induced renal Nrf2 targets and suppressed megalin
High-fat (HF) diet-induced CKD [5]	— Prevented HF diet-induced development of structural changes in the heart and kidneys — Prevented HF diet-induced renal corpuscle hypertrophy
Lupus nephritis [6]	— Attenuated renal disease and reduced glomerulonephritis in 3 different models of lupus nephritis — Decreased proteinuria and BUN
Ischemic-reperfusion [7]	— Prevented structural injury from ischemia acute kidney injury — Pre-treatment preserved renal function following ischemic surgery
FeNTA-iuduced acute kidney injury [8]	— Prevented acute kidney injury and preserved renal function — Reduced severity of proximal tubule degeneration and necrosis
Cisplatin-induced acute kidney injury [9]	— Protected against cisplatin-induced renal toxicity — Reduced proximal tubule degeneration, apoptosis, necrosis, and inflammation

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6 Wu T, Ye Y, Min SY, et al. Targeting multiple signaling axes and oxidative stress using a synthetic triterpenoid prevents murine lupus nephritis. Arthritis Rheumatol 2014;66:3129-3139.

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8 Tanaka Y, Aleksunes LM, Goedken MJ, et al. Coordinated induction of Nrf2 target genes protects against iron nitrilotriacetate (FeNTA)-induced nephrotoxicity. Toxicol Appl Pharmacol 2008;231:364-373.

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Previous Renal Findings in Clinical Trials of Bardoxolone Methyl

Prior to initiating the current clinical development programs in PH and CKD caused by Alport syndrome, bardoxolone methyl was evaluated in multiple trials, enrolling approximately 3,100 people, of which approximately 1,900 received bardoxolone methyl, including patients with CKD caused by diabetes, patients with solid tumors or lymphoma, and healthy volunteers.

We conducted six Phase 1 and 2 studies that demonstrated significant improvements in renal function evidenced by increases in eGFR and creatinine clearance as well as reductions in uremic solutes, such as blood urea nitrogen, or BUN, uric acid, and phosphate, in inverse correlation with eGFR. These trials included the BEAM trial, a randomized, placebo-controlled 52-week Phase 2 trial in patients with CKD

caused by diabetes. BEAM enrolled primarily patients with moderate or Stage 3 CKD caused by diabetes and demonstrated that eGFR improvements were sustained for 52 weeks on treatment and that eGFR at week 56, four weeks after withdrawal of drug, was greater than both baseline and placebo eGFR values. The BEAM data demonstrated that a portion of the on treatment eGFR improvement was retained after withdrawal of drug and suggested that bardoxolone methyl had disease-modifying activity in CKD caused by diabetes.

On the basis of the Phase 2 results, we conducted BEACON, a large, multinational Phase 3 trial in patients with severe or Stage 4 CKD caused by diabetes. During October 2012, BEACON was terminated early in response to the independent data monitoring committee's recommendation to stop the trial for safety concerns when data trends indicated a statistically significant increase in heart failure events and a non-statistically significant increase in mortality in the treatment arm. At the time, nothing was known about the cause or timing of the safety events or whether these events might worsen. After the trial was terminated, analysis revealed that there was a small but significant imbalance in heart failure events of 5.0% on placebo and 8.8% on active drug but no statistical difference in mortality. The primary reason for the increase in heart failure events was fluid overload that occurred in the first four weeks after randomization. Patients with fluid overload events who were treated with intravenous diuretics resolved their symptoms, and there was no increase in risk for fluid overload, as compared to placebo, after the first four weeks of treatment.

Further investigation, including additional preclinical studies, indicated that bardoxolone methyl modulates the endothelin pathway. In patients with Stage 4 and 5 CKD caused by diabetes, the endothelin pathway is dysregulated and, under certain circumstances, activation of this pathway can put these patients at greater risk for fluid retention. Patients who have less compromised renal function do not have dysregulation of this pathway, and their kidneys are able to excrete excess fluid. Similar fluid overload events had been observed previously in patients with late-stage CKD caused by diabetes treated with other therapies, including ERAs, which are vasodilating agents that are currently approved for the treatment of PAH. This review of data from PAH trials prompted our interest in the applicability of the pharmacology of Nrf2 activators, particularly their mitochondrial and anti-inflammatory effects, to PAH.

Post-hoc analysis from BEACON identified three major risk factors as predictors of fluid overload events: Stage 4 CKD caused by diabetes, prior hospitalization for heart failure, and baseline elevation in B-type natriuretic peptide or BNP, a clinical chemistry measure of fluid status. Patients without these risk factors showed no imbalance in heart failure events or mortality, which is consistent with the Phase 2 trials conducted by us that primarily enrolled in patients with Stage 3 CKD caused by diabetes and did not show a risk of fluid overload. There were no other significant adverse safety findings from the BEACON trial, and patients in the treatment arm had fewer kidney and liver-related SAEs than patients in the placebo arm. Having identified risk factors for fluid overload, we communicated our analysis to the Division of Cardiovascular and Renal Products of the FDA, the division that oversaw the IND application for CKD caused by diabetes, and provided them with our analysis datasets from the BEACON trial so that they could replicate our analyses. We also proposed entering into a Phase 2 trial with bardoxolone methyl in patients with PAH and filed a new IND with the Division of Cardiovascular and Renal Products of the FDA. The FDA communicated in November 2013 that the trial could proceed.

We subsequently initiated the Phase 2 LARIAT trial in PAH patients. As part of this trial, risk mitigation procedures include exclusion of patients with significant renal disease, prior history of left-sided heart disease or heart failure, or with elevated baseline BNP levels. These risk mitigation procedures have been used in all trials since BEACON, including the TSUBAKI trial conducted by KHK discussed below. Results, to date, of the LARIAT trial were discussed above. We have since initiated the Phase 3 CATALYST trial in CTD-PAH and the Phase 2/3 CARDINAL trial in CKD caused by Alport syndrome.

In April 2014, a paper in the *American Journal of Nephrology* was published that described the mechanisms contributing to the adverse events described above in the BEACON trial. In June 2014, we gave a presentation at the *European Renal Association-European Dialysis and Transplant Association* on the investigation of serious adverse events in bardoxolone methyl patients in BEACON and in December 2014, a paper in the *Journal of Cardiac Failure* was published describing the risk factors discussed above.

In addition, our Asian development partner, KHK, reviewed the BEACON data with the Japanese Pharmaceuticals and Medical Devices Agency and subsequently initiated a Phase 2 trial, named TSUBAKI, with bardoxolone methyl in patients in Stage 3 CKD caused by diabetes. In May 2016, KHK announced interim results from TSUBAKI showing that bardoxolone methyl treatment resulted in a significant improvement in measured GFR, as assessed by inulin clearance, after 16 weeks of treatment compared to placebo. Inulin clearance is the most rigorous technique to determine measured GFR. Moreover, the increase in inulin clearance is similar in magnitude to the changes in eGFR reported in other studies with bardoxolone methyl. KHK has recently expanded the trial to include patients in Stage 4 CKD caused by diabetes. No results from these patients have been released.

In previous trials performed by us in patients with CKD caused by diabetes, bardoxolone methyl significantly increased creatinine clearance, significantly reduced uremic solutes, such as BUN, uric acid, and phosphate, in inverse correlation to eGFR increases, and numerically reduced renal SAEs and ESRD events. These data, taken together with the KHK data, support that the increases in eGFR observed in the seven trials in patients with CKD caused by diabetes of bardoxolone methyl treatment reflect actual increases in GFR and support the use of eGFR as a reliable marker of renal function. Below is an overview of renal improvements that have been shown in clinical trials with bardoxolone.

Overview of Bardoxolone Methyl Studies Demonstrating Improvements in Renal Function

Study	Phase/Country	Patient Population	Mean Placebo-corrected D eGFR (mL/min/1.73m2) 1
402-C-0903 (BEACON)	3/Global	CKD/Diabetes	6.4 (p<0.001 vs PBO) 3
402-C-0804 (BEAM)	2/US	CKD/Diabetes	8.6 (p<0.001 vs PBO)
RTA402-005 (TSUBAKI)	2/Japan	CKD/Diabetes	Data not yet publicly disclosed
402-C-0902	2/US	CKD/Diabetes	6.5 (p<0.001) 2
402-C-0801 (Stratum 1)	2a/US	CKD/Diabetes	6.7 (p<0.001) 2
402-C-0801 (Stratum 2)	2b/US	CKD/Diabetes	7.2 (p<0.001) 2,3
402-C-1102	1/US	CKD/Diabetes	9.0 (p<0.05) 2
402-C-0501	1/US	Cancer	18.2 (p<0.0001) 2
402-C-0702	1/2/US	Cancer	32.2 (p=0.001) 2
402-C-1302 (LARIAT)	2/US	Pulmonary hypertension	14.7 (p<0.001 vs PBO)

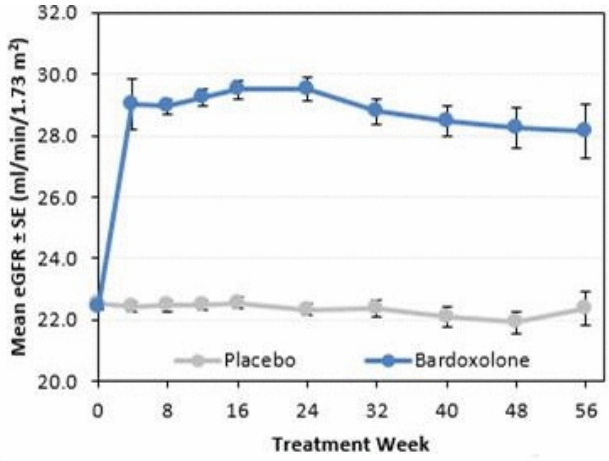
1 Unless noted, data are differences between mean eGFR changes from baseline for bardoxolone methyl versus placebo groups and p- values calculated comparing the difference in means between bardoxolone methyl and placebo groups.

2 Data are mean eGFR changes from baseline for bardoxolone methyl patients and p-values are calculated from two-sided paired t-tests comparing eGFR change to 0.

3 Study also demonstrated a significant increase in creatinine clearance.

In addition to the eGFR increase data, two separate trials, BEAM and BEACON, which included approximately 600 patients treated for one year or longer, showed that increases in eGFR in patients with CKD caused by diabetes treated with bardoxolone methyl were sustained for at least one year. In BEACON, bardoxolone methyl patients had mean increases in eGFR through Week 48 of 5.5 mL/min/1.73 m^2. In contrast, placebo-treated patients experienced a mean decline in eGFR of -0.9 mL/min/1.73 m^2, corresponding to a relative difference between groups of 6.4 mL/min/1.73 m^2 (p<0.001). The figure below shows the change in eGFR over time for both placebo and bardoxolone methyl patients in the BEACON trial demonstrating a durable response through at least one year.

One Year of Treatment with Bardoxolone Methyl in Stage 4 Patients with CKD caused by Diabetes (BEACON)



Number of Patients								
Placebo	1093	1023	885	726	547	402	281	125
Bardoxolone	1092	958	795	628	461	345	247	103

Furthermore, as shown in the table below, in BEACON, at 48 weeks, bardoxolone methyl significantly reduced the proportion of patients with an eGFR loss of 3, 5, or 7.5 mL/min/1.73 m^2, which represents losses of approximately 13%, 22%, and 33%, respectively, of baseline eGFR. The proportion of patients with a loss of eGFR of 30% from baseline at any visit was reduced by 67% (p<0.001).

Percentage of Patients with Large Losses of Kidney Function in BEACON

Decliner Category	BARD	PBO	p-value
D eGFR < -3.0 by WK48	20%	67%	p<0.001
D eGFR < -5.0 by WK48	14%	37%	p<0.001
D eGFR < -7.5 by WK48	8%	16%	p<0.01
D eGFR < -30% (any visit)	4%	12%	p<0.001

After one year of treatment, a residual eGFR increase from baseline was observed in bardoxolone methyl patients after cessation of drug for four weeks, while an eGFR decline from baseline was observed in placebo patients. These data suggest that the maladaptive structural deficits that contribute to declining kidney function may be improved over the course of longer-term treatment with bardoxolone methyl.

Retained eGFR Benefit After Withdrawal of Bardoxolone Methyl

	Baseline eGFR	Placebo-Corrected eGFR Change Post-Withdrawal	p-value
BEAM (n=172)			
Low Dose	33	0.6	p>0.05
Mid Dose	32	4.7	p<0.05
High Dose	32	5.0	p<0.05
BEACON (n=498)			
20mg	23	1.8	p<0.001

We believe that the improvements in renal function noted in many studies with bardoxolone methyl coupled with the BEACON data demonstrating reduced risk of loss of kidney function suggest that bardoxolone methyl may have the potential to prevent renal function decline, which may translate to a multi-year delay in disease progression to ESRD for patients with Alport syndrome.

Market Opportunity for Bardoxolone Methyl in Chronic Kidney Disease Caused by Alport Syndrome

There are no therapies currently approved for CKD caused by Alport syndrome. Alport syndrome is a rare and serious hereditary disease that we believe, based on literature, affects approximately 12,000 children and adults in the United States and 40,000 globally. Approximately 1,200 of the U.S. patients are identified in the Alport Syndrome Foundation's registry. Patients with Alport syndrome are often misdiagnosed with other congenital kidney diseases. In addition, family members of patients with Alport syndrome may not be formally diagnosed. We believe that, with the development of an effective treatment for Alport syndrome, identification of patients with CKD caused by Alport syndrome will increase.

Clinical Development for Bardoxolone Methyl in Chronic Kidney Disease Caused by Alport Syndrome

During a meeting with the FDA in October 2016, the FDA provided us with guidance on key elements of a single, pivotal clinical trial that would study the safety and efficacy of bardoxolone methyl in patients with CKD caused by Alport syndrome. We initially proposed a Phase 2 trial in Alport syndrome patients; however, the FDA provided guidance that a single pivotal trial with an eGFR endpoint could support both accelerated and full approval.

We have initiated the Phase 2 portion of CARDINAL, a single, pivotal Phase 2/3 clinical trial and dosed the first patient on March 2, 2017. With the aid of international key opinion leaders and the Alport Syndrome Foundation and based on the guidance from the FDA, we have designed the trial as an international, multi-center, double-blind, randomized, placebo-controlled trial that studies the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with Alport syndrome from age 12 to 60 at 50 to 60 sites. The Phase 2 portion of the trial will test bardoxolone methyl in 30 patients and is open-label and the primary endpoint will assess eGFR change at 12 weeks. These patients will be followed for two years, with eGFR measurements, including at weeks 48 and 100 on drug and 52 and 104 after withdrawal of drug for four weeks, and will not be included in the Phase 3 portion of the trial.

In designing the trial, we have leveraged data from our previous clinical experience in CKD patients, including the retained eGFR analysis for BEACON and BEAM discussed above. Our goal in designing the trial is to power the trial to replicate the BEAM mid-dose response of 4.7 mL/min/1.73m^2. We have designed the trial with substantially more patients than the BEAM mid-dose, which enrolled 90 patients, to ensure that the trial could potentially be successful with an effect that is approximately 50% less than the mid-dose of BEAM. The Phase 3 portion is designed to support registration and will enroll up to 180 patients. The patients in the Phase 3 portion of the trial are randomized 1:1 to either bardoxolone methyl or placebo. The eGFR change at one year will be measured after 48 weeks while the patient is on treatment, and after withdrawal of drug for four weeks (retained eGFR). After withdrawal, patients will be restarted on study drug with their

original treatment assignments and will continue on study drug for a second year. The change from baseline in eGFR in bardoxolone methyl-treated patients relative to placebo will be measured again after two years. The eGFR change at two years will also be measured after 100 weeks while the patient is on treatment and after withdrawal of drug for four weeks (retained eGFR). If the trial is successful, the year one retained eGFR data could support accelerated approval under subpart H of the Federal Food, Drug, and Cosmetic Act, or the FD&C Act, and the year two retained eGFR data could support full approval under the FD&C Act. We expect to have Phase 2 data by the end of 2017. We expect to have the one year withdrawal data that could support accelerated approval in the first half of 2019. In December 2016, we submitted a request to the FDA for orphan drug designation for bardoxolone methyl for the treatment of CKD caused by Alport syndrome.

Commercialization Rights for Bardoxolone Methyl

Under the terms of our collaboration agreements, we retain commercial rights to market and sell bardoxolone methyl in the United States. KHK has licensed from us the rights to develop and commercialize bardoxolone methyl in Asia, and AbbVie has licensed from us the right to market and sell bardoxolone methyl in all non-KHK territories outside of the United States. We plan, either alone, with our strategic collaborators AbbVie and KHK, or with new collaboration partners, to devise global commercialization strategies for bardoxolone methyl, if approved. We intend to market and sell bardoxolone methyl, if approved, in the United States.

Omaveloxolone for the Treatment of Friedreich's Ataxia, Mitochondrial Myopathies, and Other Indications

Omaveloxolone is a close structural analog of bardoxolone methyl that was developed to improve tissue distribution, including blood-brain barrier penetration. To date, omaveloxolone has been administered orally to patients with FA, MM, and solid tumors, and has been administered topically to patients receiving cataract surgery and to breast cancer patients receiving radiation therapy and suffering from radiation dermatitis. We believe that an omaveloxolone-induced increase in mitochondrial energy production could have beneficial effects on multiple organ systems, with the most profound effects being in skeletal muscle, the brain, and other tissues with a high energy demand.

Friedreich's Ataxia

Friedreich's ataxia is an inherited, debilitating, and degenerative neuromuscular disorder that is typically diagnosed during adolescence and can ultimately lead to early death. Patients with FA experience progressive loss of coordination, muscle weakness, and fatigue, which commonly progresses to motor incapacitation and wheelchair reliance. FA patients may also experience visual impairment, hearing loss, diabetes, and cardiomyopathy. Childhood-onset FA can occur as early as age five, is more common than later-onset FA, and typically involves more rapid disease progression. The majority of FA patients have disease onset by approximately 13 to 15 years of age, and thereafter have a mean duration until wheelchair use of 10 to 15 years. The median age of death is in the mid-30s.

A mutation in the frataxin gene leads to impaired transcription and reduced expression of the mitochondrial protein frataxin. Deficiency of frataxin in cells leads to a mitochondrial iron overload and poor cellular iron regulation, increased sensitivity to oxidative stress, and impaired mitochondrial ATP production. Impaired ATP production in FA patients likely accounts for the decreased coordination, progressive muscle weakness, exercise intolerance, and fatigue observed in these patients, as well as other disease manifestations.

No Approved Therapies for Friedreich's Ataxia

There are no currently approved therapies for the treatment of FA. Patients are usually given guidelines around certain lifestyle habits. They are recommended to follow a diet that is low in iron and encouraged to take vitamins and supplements.

Idebenone was previously approved as a treatment for FA in Canada, but it was withdrawn five years after it was launched because no evidence could be provided for its efficacy. Despite the lack of current marketing authorization and minimal evidence of effectiveness in FA, idebenone continues to be prescribed off-label by physicians we believe in part due to the lack of other therapeutic options for FA patients.

Omaveloxolone in Friedreich's Ataxia

Since patients suffering from FA experience increased sensitivity to oxidative stress and impaired mitochondrial ATP production, we believe that omaveloxolone may be effective in treating this indication. In FA patients, mitochondrial function (oxygen consumption) is inversely correlated with neurologic function. Further, data demonstrate that Nrf2 signaling is significantly impaired in FA patients, resulting in impairment of antioxidant defense mechanisms, while silencing of frataxin gene expression has been linked to decreases in expression of Nrf2. Additionally, omaveloxolone has been shown *in vitro* to restore mitochondrial transmembrane potential in fibroblasts isolated from FA patients. Accordingly, we believe that Nrf2 activation through omaveloxolone may result in a clinical benefit to FA patients.

Market Opportunity for Omaveloxolone in Friedreich's Ataxia

FA is an ultra-orphan disease with a prevalence ranging from 0.7 to 5 per 100,000 in Caucasians globally. Based on literature and proprietary research, we believe there are approximately 22,000 people globally with FA, including 6,000 in the United States. Approximately 2,700 worldwide patients are identified on the Friedreich's Ataxia Research Alliance's registry, including approximately 1,500 in the United States. Patients with FA are often undiagnosed or are misdiagnosed with a different cerebellar ataxia. However, we believe that if an effective treatment for FA is approved and marketed, more patients will be encouraged to be genetically tested for FA.

Clinical Development for Omaveloxolone in Friedreich's Ataxia

We are evaluating omaveloxolone in the MOXIe trial, a two-part randomized, placebo-controlled, double-blind, dose-escalation Phase 2 trial to evaluate the safety and efficacy of omaveloxolone. The protocol for the trial allows up to 108 patients with FA pursuant to an IND that we sponsored and filed in July 2014. MOXIe is being conducted at sites in the United States, Europe and Australia. In 2014, we met with the FDA to discuss our FA program. Based on discussions with the FDA, we designed a two-part trial with evaluation of a broad dose range in part one and a confirmatory evaluation of efficacy and safety in part two that could support registration. Part one focuses on the evaluation of safety and efficacy of omaveloxolone doses ranging from 2.5 mg to 300 mg. Data for multiple endpoints are being collected, with the primary efficacy endpoint being the change in peak work, as measured by exercise testing on a recumbent bicycle. The key secondary endpoint is a functional assessment based on the modified Friedreich's Ataxia Rating Scale, or mFARS. Part two is designed to provide additional efficacy and safety data and has the potential to be used for registration. We have observed no significant tolerability issues in MOXIe to date. The trial is being overseen by a data safety monitoring board, or DSMB, that reviews all data, including SAE and AE data, on an unblinded basis to assess safety. The DSMB has not reported any safety concerns to date. We completed enrollment of part one in February 2017. Data from the first part of MOXIe are expected in mid-year 2017, and if successful, we expect to initiate the second part of MOXIe after receiving these data.

In November 2014, we submitted a request to the FDA for orphan drug designation for omaveloxolone for the treatment of FA. The FDA has requested that we submit *in vivo* or human clinical data to support this application. In January 2017, we filed an amendment to the orphan application, which includes additional information.

Mitochondrial Myopathies

Mitochondrial myopathies are a multi-systemic group of myopathies associated with mitochondrial dysfunction that are caused by over 200 different genetic mutations. Patients with MM present a complex array of symptoms that can vary widely in terms of their severity, although the main symptoms that generally result from mitochondrial dysfunction include muscle weakness, exercise intolerance, and fatigue. Decreased muscle function can affect major muscle groups used for walking, climbing, lifting, and maintaining posture, and muscle weakness is also evident in smaller muscle groups that control, for example, movements of the eyes and eyelids. In addition to the skeletal muscular effects associated with mitochondrial dysfunction generally, patients with MM can also experience seizures, impaired gastrointestinal motility, impaired respiratory function, difficulty swallowing, impaired vision or hearing, and impaired balance and coordination. The prognosis for patients with MM varies widely depending on the degree of involvement of various organ systems in the disease, with disease progression leading to significant physical impairment and even to death in some individuals.

Despite the different array of symptoms of the diseases, a unifying feature of MM is dysfunctional mitochondrial respiration, which subsequently leads to a reduced ability to produce ATP.

No Approved Therapies for Mitochondrial Myopathies

There are currently no approved therapies for the treatment of MM. It is normally recommended that patients maintain a diet that is high in certain types of fat, low in sugar, and low in iron, take vitamins and supplements, and exercise regularly. Resistance training has been shown to increase functional muscle tissue; however, exercise is not known to reverse the effects of the disease, and cessation of resistance training results in loss of muscle strength. Patients with severe manifestations of certain MM may undergo surgery to address seizures, deafness, and cardiomyopathy.

Omaveloxolone in Mitochondrial Myopathies

Patients suffering from MM have a reduced ability to produce ATP, similar to those patients with FA, and we believe that omaveloxolone may be effective in treating this indication.

Market Opportunity for Omaveloxolone in Mitochondrial Myopathies

The prevalence of MM is estimated to range from 1 to 6 per 100,000 globally. Based on literature, we believe there are approximately 80,000 people globally with MM, including 20,000 in the United States. However, the true prevalence of MM is difficult to obtain as many MM patients remain undiagnosed due to similarity of their symptoms to those associated with other cellular metabolic diseases. We believe that, with the emergence of an effective therapy, testing for MM may increase.

Clinical Development for Omaveloxolone in Mitochondrial Myopathies

We are evaluating omaveloxolone in the MOTOR trial, a two-part randomized, placebo-controlled, double-blind, dose-escalation Phase 2 trial to evaluate the safety and efficacy of omaveloxolone. The protocol for the trial allows up to 100 patients with MM pursuant to an IND that we sponsored and filed in July 2014. MOTOR is being conducted at sites in the United States and Europe. In 2014, we met with the FDA to discuss our MM program. Based on discussions with the FDA, we designed a two-part trial with evaluation of a broad dose range in part one and confirmatory evaluation of safety and efficacy in part two that could support registration. Part one focuses on the evaluation of safety and efficacy of omaveloxolone doses ranging from 2.5 mg to 160 mg. Data for multiple endpoints are being collected, with the primary efficacy endpoint being the change in peak work, as measured by exercise testing on a recumbent bicycle. The key secondary endpoint is the change from baseline in patients' 6MWD. Part two is designed to provide additional efficacy and safety data and has the potential to be used for registration. We have observed no significant tolerability issues in MOTOR to date. The trial is being overseen by a DSMB that reviews all data, including SAE and AE data, on an unblinded basis to assess safety. The DSMB has not reported any safety concerns to date. Data from the first part of MOTOR are expected in the second half of 2017, and if successful, we expect to initiate the second part of MOTOR after receiving these data. We intend to submit a request to the FDA for orphan drug designation for omaveloxolone for the treatment of MM once we have *in vivo* or human clinical data to support this application.

Immuno-oncology

We believe that omaveloxolone may have utility in the treatment of certain types of advanced solid tumors. These tumors include melanoma, which accounts for approximately 75% of all skin cancer deaths, and more specifically metastatic melanoma, which generally results in lower survival rates in patients with signs of immuno-suppression. While new therapies, such as immune checkpoint inhibitors, have emerged to treat metastatic melanoma, patient response rates to treatment remain relatively low. Various mechanisms likely contribute to this poor response rate, one of which is believed to be the ability of tumors to "cloak" themselves from the immune system through the effects of myeloid derived suppressor cells, or MDSCs.

Treatment with bardoxolone methyl has been observed to abrogate the immune suppressive effect of MDSCs and elicit a corresponding improvement in immune response in tumor-bearing mice and cancer patients.

In addition, in preclinical studies, we observed that omaveloxolone and analogs may be effective in reducing ROS and reactive nitrogen species in the tumor microenvironment, which has been observed to have promise in restoring immune recognition of tumor-specific antigens, and in reducing tumor nitrotyrsine burden. Further, the effect of omaveloxolone in combination with a mouse specific anti-programmed-cell-death-protein-1, or anti-PD-1, antibody was evaluated in mice implanted subcutaneously with Lewis lung carcinoma cells, and it was observed that omaveloxolone enhanced the anti-tumor efficacy of anti-PD-1 immune therapy.

We are evaluating omaveloxolone in the REVEAL trial, an open-label, multi-center, dose-escalation Phase 1b/2 trial pursuant to an IND that we sponsored and filed in August 2013, to evaluate the safety, pharmacodynamics, and efficacy of omaveloxolone, in combination with existing immunotherapies, in up to 102 patients with metastatic melanoma. REVEAL is being conducted at sites in the United States. In REVEAL, patients receive omaveloxolone monotherapy for one week, followed by omaveloxolone in combination with the labeled treatment course of either Yervoy® or Opdivo®. We previously evaluated omaveloxolone in the DISCOVER trial, an open-label, multi-center, dose-escalation Phase 1 trial conducted at sites in the United States pursuant to an IND that we sponsored and filed in August 2013 to evaluate the safety, pharmacokinetics, and pharmacodynamics of omaveloxolone in patients with advanced solid tumors. We have observed no significant tolerability issues in DISCOVER or REVEAL to date. The REVEAL trial is being overseen by a PSRC that reviews all data, including SAE and AE data, to assess safety. The PSRC has not reported any safety concerns to date. Data from the 1b dose escalation portion of REVEAL are expected during the second half of 2017.

An orphan drug designation request was submitted in advanced malignant melanoma in November 2014. The FDA requested we submit *in vivo* or human clinical data to support the application. We anticipate submitting *in vivo* or human clinical data to support the orphan drug designation in 2017.

Commercialization Rights for Omaveloxolone

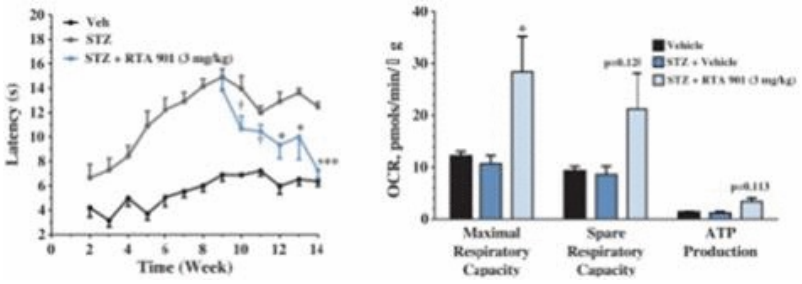
We retain all U.S. commercial rights to market and sell omaveloxolone and have licensed to AbbVie commercialization rights to the rest of the world for this product candidate. We plan, either alone, with our strategic collaborator AbbVie, or with new collaboration partners, to devise global commercialization strategies for omaveloxolone, if approved. We intend to market and sell omaveloxolone, if approved, in the United States. In September 2016, we and AbbVie mutually agreed that we would continue unilateral development of omaveloxolone. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the U.S. or we may be responsible for commercializing the product on a worldwide basis. We continue to evaluate the best indications for which to develop and commercialize omaveloxolone under the terms of our collaboration agreement.

RTA 901 for the Treatment of Orphan Neurological Indications

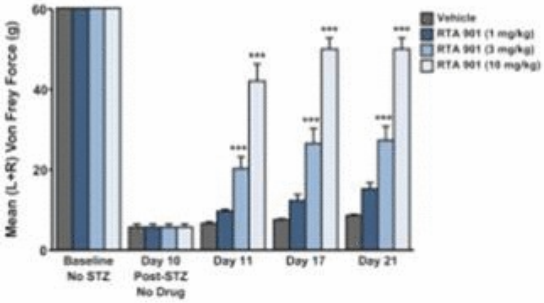
Our Hsp90 inhibitors, including RTA 901, are highly potent and selective C-terminal inhibitors of Hsp90. Inhibition of Hsp90 may result in activation of Hsp70, a molecular chaperone that plays a critical role in the process through which a protein assumes its functional shape and that serves as a central gatekeeper for mitochondrial protein import. Mitochondria rely on Hsp70-dependent protein import mechanisms for almost all of their activity, including the production of ATP. There are also indications that Hsp70 activation may play a profound role in neuroprotection since nerve cells are high consumers of ATP and rely on Hsp70-dependent protein import for proper mitochondrial function.

We have observed favorable activity of RTA 901 in a range of preclinical models of neurodegeneration and neuroprotection, including models of diabetic neuropathy and neural inflammation. RTA 901, administered orally once-daily, has been observed to rescue existing nerve function, restore thermal and mechanical sensitivity, and improve nerve conductance velocity and mitochondrial function in rodent disease models.

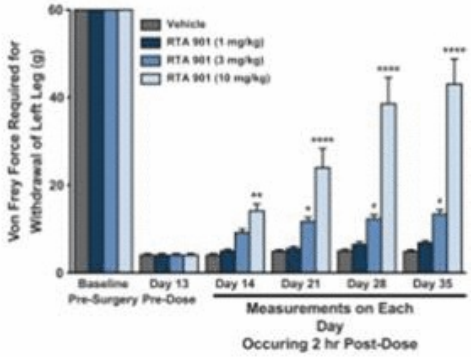
RTA 901 Effects on Thermal Sensitivity and Mitochondrial Function in Late Stage Streptozocin-Induced Diabetic Neuropathy in Mice



RTA 901 Rescues Neuropathic Pain in Early Streptozocin (STZ)-Induced Diabetic Neuropathy in Rats



RTA 901 Rescues Neuropathic Pain in Spinal Cord Injury in Rats



In January 2016, the FDA informed us that they were imposing a clinical hold on our IND for RTA 901 pending resolution of some outstanding questions related to our animal toxicology studies, in which no adverse effects were identified. We completed additional toxicology studies, and in November 2016, the FDA lifted our full clinical hold and allowed us to proceed with our planned Phase 1 clinical trial with

RTA 901 under a partial clinical hold. The single limitation imposed by the partial hold is that we may not exceed an upper limit on human exposure of 1840 hour x nanogram/milliliter or h*ng/mL. Based on initial pharmacokinetic data, the FDA's limit will not prevent us from adequately dose ranging in the Phase 1 trial.

We initiated a Phase 1 clinical trial in January 2017 to evaluate the safety, tolerability, and pharmacokinetic profile of RTA 901 in healthy adult volunteers. The trial is designed in two parts, part 1 with single ascending doses, or SAD, and part 2 with multiple ascending doses, or MAD. In part 1, approximately 56 healthy subjects in up to 7 groups of 8 subjects each are randomized in a 3:1 ratio to receive a single dose of RTA 901 or placebo, respectively. In part 2, approximately 30 healthy subjects in up to 3 groups of 10 subjects each will be randomized in a 4:1 ratio to receive 14 daily doses of RTA 901 or placebo, respectively. We plan to complete the trial and report data in the second half of 2017. If the Phase 1 clinical trial of RTA 901 supports further development, we plan to follow it with a Phase 2 clinical trial of RTA 901 for the treatment of an orphan neurological indication or diabetic neuropathy.

We retain all rights to our Hsp90 inhibitors, which are not subject to any existing commercial collaborations.

Preclinical Programs

Additional Nrf2 Activator Indications

If beneficial bioenergetic effects are demonstrated in our ongoing PAH, PH-ILD, FA and MM trials, this could indicate that our Nrf2 activator pharmacology may also provide therapeutic benefit for patients suffering from other diseases where mitochondrial dysfunction or chronic inflammation is implicated. In addition, if therapeutic benefits are demonstrated in CKD caused by Alport syndrome, the Nrf2 activator pharmacology may also provide therapeutic benefit in other renal diseases. Some of these diseases may be treated by our current lead product candidates, bardoxolone methyl and omaveloxolone.

Additional Hsp90 Inhibitor Indications

If beneficial neuroprotective and bioenergetic effects are demonstrated in our future Phase 2 trials, this could indicate that our Hsp90 inhibitor pharmacology may also provide therapeutic benefit for patients suffering from other diseases where neurodegenerative and mitochondrial dysfunction are implicated.

RORgT Inhibitors

We are pursuing preclinical development of novel, small-molecule, orally bioavailable RORgT inhibitors. RORgT is the master regulator of human T Helper 17, or Th17, cellular differentiation, function, and cytokine production, and represents a compelling target for a variety of autoimmune and inflammatory conditions. TH17 cells produce cytokines, including IL-17, that play a critical role in driving immune-mediated inflammation and are implicated in the pathogenesis of certain autoimmune diseases. The efficacy of suppressing IL-17 as a means of treating these conditions has been demonstrated both in animal models and in humans.

We have selected and are advancing a single RORgT development candidate into Good Laboratory Practices, or GLP, toxicology studies. We retain all rights to our RORgT inhibitors, which are not subject to any existing commercial collaborations.

Collaborations

Kyowa Hakko Kirin Co., Ltd.

In December 2009, we entered into an agreement with KHK, under which we provided KHK the right to develop and commercialize bardoxolone methyl for renal, cardiovascular, diabetes, and certain related metabolic indications in Japan, China (including Hong Kong and Macao), South Korea, Taiwan, Thailand, Singapore, Philippines, Malaysia, Indonesia, Brunei, Vietnam, Laos, Myanmar, and Cambodia. These indications include, among others, CKD and PH.

KHK is obligated to use commercially reasonable efforts to conduct all preclinical and clinical activities necessary for the commercialization of licensed products in each country in the licensed territory. KHK is not participating in the development program for bardoxolone methyl in PH at this time or CKD caused by Alport syndrome. Under this agreement, we are obligated to use commercially reasonable efforts to supply KHK with clinical supply of licensed product required for KHK's development in the licensed territory, and we are obligated to negotiate and execute a commercial supply agreement with KHK prior to KHK's initiation of a Phase 3 trial.

Consideration under this agreement includes an upfront payment of $35 million, up to $97 million in development and regulatory milestone payments, and up to $140 million in commercial milestone payments. Total consideration under this agreement could reach $272

million. The aggregate amount of such consideration received through December 31, 2016, totals $50 million. Additionally, KHK is required to pay us royalties on net sales of licensed product sold by KHK, its affiliates, and sublicensees in its territory ranging from the low teens to the low 20 percent range depending on the country of sale and the amount of annual net sales.

The KHK agreement will terminate automatically when the royalty term expires in all of KHK's territory. A royalty term expires in a country on the later of the expiration of all patents in such country and ten years after the first commercial sale in such country. Either party may terminate the agreement upon the other party's bankruptcy or insolvency or uncured material breach. Additionally, KHK may terminate the agreement at will upon advance written notice. In the event of any termination of the agreement by us for KHK's uncured breach, bankruptcy or insolvency or by KHK at will, KHK will transfer and assign to us the regulatory filings for bardoxolone methyl and will license to us the relevant trademarks used with the products in their respective territories.

AbbVie License Agreement

In September 2010, we entered into a license agreement with AbbVie, under which we provided AbbVie, formerly known as Abbott Pharmaceuticals PR Ltd., the exclusive right to conduct all regulatory activities, including obtaining regulatory approval, and commercialization of bardoxolone methyl or other molecules for renal, metabolic, and cardiovascular indications, including CKD and PH, in all other countries outside the United States not previously licensed to KHK under the KHK agreement. Under this agreement we retain the right to commercialize bardoxolone methyl in the United States. Also, both parties are obligated to use commercially reasonable efforts to develop bardoxolone methyl in accordance with agreed upon development plans.

Under this agreement, AbbVie is required to pay us consideration in the form of an upfront payment and development and commercial milestone payments. For each of the three licensed indications under this agreement, we are eligible to receive up to either $300 million or $350 million in development, regulatory and commercial milestone payments depending on the licensed indication and the number of compounds to achieve such milestones, however, these payments may only be made once per molecule developed. The aggregate amount of such consideration received through December 31, 2016 totaled $300 million, with a potential $50 million milestone related to commercial sales remaining. Additionally, AbbVie is required to pay us, under the AbbVie license agreement, tiered royalties on net sales of licensed product sold by AbbVie, its affiliates and sublicensees in its territory ranging from 15 percent to the high 20 percent range depending on the amount of annual net sales.

In addition, AbbVie invested $300 million in our preferred stock in September 2010 which was converted into common stock in January 2013.

At present, AbbVie has exercised their opt-out right with regard to PH and has not opted in to the development program in CKD caused by Alport syndrome, and therefore is not co-funding our development programs in either indication. AbbVie has the right to opt-in to either program at any time during development. Upon opting-in, AbbVie would be required to pay an agreed upon amount of all development costs accumulated up to the point of exercising their opt-in right. All development costs incurred after AbbVie's opt-in are split equally.

The AbbVie license agreement will terminate automatically when the royalty term expires in all countries in AbbVie's territory. The royalty term expires in a country on the later to occur of (i) the expiration of all patents and regulatory exclusivity, unless prior to such expirations generic sales have exceeded a certain percentage of all sales in a quarter, and (ii) ten years after the first commercial sale. Either party may terminate the agreement in its entirety for bankruptcy or insolvency of the other party and in its entirety or with respect to specific territories for an uncured material breach by the other party, and AbbVie may terminate the agreement in its entirety for specified reasons for cause and in its entirety or with respect to specified territories at will upon advance written notice. In the event of any termination of the agreement by us for AbbVie's breach or by AbbVie for cause or at will, AbbVie will license to us certain intellectual property rights to develop, manufacture and commercialize bardoxolone methyl, transfer and assign to us the regulatory filings for bardoxolone methyl and will assign or license us the relevant trademarks used with the products in their respective territories. Under certain terminations under the AbbVie license agreement, we are also obligated to pay reverse royalties on net sales of bardoxolone methyl in the terminated territory.

Payments to us under these agreements include $622 million in upfront and potential milestone payments, excluding development cost reimbursement.

AbbVie Collaboration Agreement

In December 2011, we entered into a collaboration agreement with AbbVie under which we provided AbbVie the right to jointly research, develop, and commercialize all second- and later-generation Nrf2 activators for all indications other than renal, cardiovascular, and metabolic indications. This is a multi-molecule, multi-product collaboration across all indications, other than renal, cardiovascular, and metabolic indications that are covered in our bardoxolone methyl license agreement with AbbVie and our agreement with KHK. Pursuant to

the AbbVie collaboration agreement, the parties have agreed to spend up to a certain amount in early development costs which include research, preclinical development and clinical development, with us paying 100% of a certain amount of such costs and the remaining costs being shared equally. For jointly developed products, all other worldwide costs are split equally and worldwide profits are also split equally except for any product designated for an indication for which Humira®, a drug marketed and sold by AbbVie, has received regulatory approval in the United States, the European Union, or Japan, in which case the costs and profits will be assumed 70% by AbbVie and 30% by us. Multiple indications can be developed for a single molecule subject to certain limitations. Upon conclusion of a Phase 2 trial for a given molecule in a given indication, either party may nominate the molecule as a product candidate, as defined in the agreement specifying the lead indication to advance for a given molecule. Once a product candidate has been named, both parties' agreement is required to advance any additional indications for this compound.

Jointly developed products are developed under agreed development plans and budgets and both parties are obligated to use commercially reasonable efforts to perform their respective obligations under such plans. With respect to omaveloxolone, we are the lead development party and the lead regulatory party globally. Manufacturing responsibilities during development are allocated between the parties pursuant to the agreed development plans. AbbVie will serve as the lead manufacturing party for commercial supply in all jointly developed omaveloxolone indications.

With respect to joint development, commercialization territory rights are divided on a molecule-by-molecule basis. We have the primary right to commercialize omaveloxolone in the United States, and AbbVie has the primary right to commercialize omaveloxolone in the rest of world, with exclusive commercialization rights in Japan. For subsequent product candidates, we retain the rights to at least one major market, although the first choice alternates between the collaboration parties as each new molecule is commercialized.

Products may be unilaterally developed by a party with the other party being entitled to opt-out of, and back into, development cost sharing and profit sharing at various stages of development. The developer would serve as the lead development, regulatory, and manufacturing party. The developer has the right to commercialize in all territories and must pay a royalty to the nonparticipating party ranging from the low single digits to 20%, depending principally on what stage of development, if any, was funded by the nonparticipating party. In September 2016, we and AbbVie mutually agreed that we would continue unilateral development of omaveloxolone. Therefore, AbbVie no longer co-funds the exploratory development costs of this program, but retains the right to opt back in at certain points in development. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the U.S. or we may be responsible for commercializing the product on a worldwide basis. Upon opting back in, AbbVie would be required to pay an agreed upon amount of all development costs accumulated up to the point of exercising their opt-in right, after which development costs incurred and product revenue worldwide would be split equally.

The AbbVie collaboration agreement will continue in effect until both parties mutually agree to terminate the agreement. Upon any uncured material breach under the AbbVie collaboration agreement with respect to a joint product, the non-breaching party will have the right to continue development of such product at its own cost and maintain all profits from such product unless the breaching party opts-in to continue development and pays a specified opt-in payment.

Payments to us under this agreement include a $400 million upfront payment that was received upon execution of the AbbVie collaboration agreement, and potential future payments including development cost reimbursement, profit share, and royalty payments.

Competition

Bardoxolone Methyl in PH and Chronic Kidney Disease Caused by Alport Syndrome

Pulmonary Arterial Hypertension

If bardoxolone methyl is approved for the treatment of patients with PAH for use in conjunction with currently approved therapies, such as ERAs, prostacyclins, and phosphodiesterase type 5, or PDE5 inhibitors, it will face competition with those current treatments such as macitentan, marketed by Actelion Pharmaceuticals US, Inc., or Actelion, as Opsumit®; riociguat, marketed by Bayer AG, or Bayer, as Adempas®; oral treprostinil, marketed by United Therapeutics Corporation as Orenitram™; ambrisentan, marketed by Gilead Sciences, Inc., or Gilead, as Letairis®; selexipag, marketed by Actelion as Uptravi®; and bosentan, marketed by Actelion as Tracleer®. Patients with PAH frequently use more than one therapy; however, we may face competition for patients' willingness and resources to add another clinical therapy.

We may also face competition from potential new therapies in development. For example, Arena Pharmaceuticals, Inc., Gilead, Bial-Portela & Ca., SA, Eiger Pharmaceuticals, Inc. and Karos Pharmaceuticals, Inc. are actively developing compounds that are attempting to address a problem outside of vasodilation and are to be used or allow use in combination with existing treatments. Their products appear to be in early clinical development. We consider these our most direct competitors.

Pulmonary Hypertension in Interstitial Lung Disease

If bardoxolone methyl is approved for the treatment of PH-ILD it will likely be the first treatment on the market for the indication. Currently, bardoxolone methyl faces pipeline competition for some subtypes of ILD such as idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, and sarcoidosis, from Adempas®, Letairis®, Tracleer®, Orenitram™, and inhaled treprostinil, marketed by United Therapeutics as Tyvaso®.

Chronic Kidney Disease Caused by Alport Syndrome

If bardoxolone methyl is approved for the treatment of patients with CKD caused by Alport syndrome, it will likely be the first treatment on the market for the indication. At least one therapy for the treatment of Alport syndrome is currently in development with a Phase 2 injectable product candidate, RG-012, from Regulus Therapeutics.

Omaveloxolone

Friedreich's Ataxia and Mitochondrial Myopathies

If omaveloxolone is approved for the treatment of FA or MM, it has the potential to be the first treatment on the market for each indication, but it currently faces pipeline competition in both of these disease spaces. Pipeline competition for such orphan diseases results in competition for patient recruitment as well as investigators' time and resources. Several competitor product candidates are in Phase 2 clinical development for FA, including SHP-622 from Shire plc. Several competitor product candidates are in Phase 2 and Phase 3 clinical development for MM, including cysteamine bitartrate from Horizon Pharmaceuticals, idebenone from Santhera Pharmaceuticals Holding AG, EPI 743 from Edison Pharmaceuticals Inc., and Elamipretide® from Stealth Biotherapeutics Inc. These have shown signs of potential in various preclinical models, but have yet to demonstrate substantial efficacy in advanced clinical trials.

Immuno-Oncology

If omaveloxolone is approved for the treatment of metastatic melanoma in combination with approved checkpoint inhibitors, it will likely be the first approved therapy for enhancing the effects of checkpoint inhibitors through suppression of MDSC activity. However, immuno-oncology is a highly competitive and rapidly changing landscape, and omaveloxolone will face competition from the patient's willingness and resources to add an additional therapy to their prescribed checkpoint inhibitor therapy.

Omaveloxolone also faces substantial pipeline competition from numerous therapies currently in Phase 2 clinical development for use in combination therapy in immuno-oncology, including Yervoy® and Opdivo® from Bristol Myers Squibb Co., Keytruda® from Merck & Company, MEDI-4736 from AstraZeneca plc, and MPDL3280A from Roche Holding AG, among others. Additionally, there are direct pipeline product candidate competitors in investigator-sponsored Phase 1 trials that address MDSC suppression, including phosphodiesterase-5 inhibitors, nitric oxide inhibitors, and MDSC migration inhibitors. All of these studies compete for the resources and patients that are needed for omaveloxolone studies.

Manufacture and Supply

We have historically relied on multiple third-party manufacturers and on our collaborators for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. Under unilateral development of our product candidates, we are responsible for manufacturing, and we expect to continue to rely on multiple third-party manufacturers. We believe there are multiple sources for all of the materials required for the manufacture of our product candidates. Our manufacturing strategy enables us to more efficiently direct financial resources to the research, development, and commercialization of product candidates rather than diverting resources to internally develop manufacturing facilities. As our product candidates advance through development, we expect to enter into longer-term commercial supply agreements with key suppliers and manufacturers to fulfill and secure the ongoing and planned preclinical, clinical, and, if our product candidates are approved for marketing, our commercial supply needs for ourselves and our collaborators.

Sales and Marketing

We currently intend to build the commercial infrastructure in the United States necessary to effectively support the commercialization of all of our product candidates if and when we believe regulatory approval of the first of such product candidates in the United States appears imminent. Commercial infrastructure for orphan products typically consists of a targeted, specialty sales force that calls on a limited and focused group of physicians supported by sales management, medical liaisons, internal sales support, an internal marketing group, and distribution support. One challenge unique to commercializing therapies for rare diseases is the difficulty in identifying eligible patients due to

the very small and sometimes heterogeneous disease populations. Our management team is experienced in maximizing patient identification for both clinical development and commercialization purposes in rare diseases.

Additional capabilities important to the orphan marketplace include the management of key accounts such as managed care organizations, group-purchasing organizations, specialty pharmacies, and government accounts. To develop the appropriate commercial infrastructure, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that any of our product candidates will be approved.

Outside of the United States, where appropriate and depending on the terms of our contractual arrangements, we plan, either alone, with our strategic collaborators AbbVie and KHK, or with new collaboration partners, to assist in the commercialization of our products. In certain instances, we may consider building our own commercial infrastructure.

Government Regulation

The clinical testing, manufacturing, labeling, storage, distribution, record keeping, advertising, promotion, import, export, and marketing, among other things, of our product candidates are subject to extensive regulation by governmental authorities in the United States and other countries. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable requirements at any time during the product development process, approval process, or after approval may subject an applicant and sponsor to a variety of administrative or judicial sanctions, including refusal by the applicable regulatory authority to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

United States Product Approval Process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act. Pharmaceutical products are also subject to regulation by other governmental agencies, such as the Federal Trade Commission, the Office of Inspector General of the U.S. Department of Health and Human Services, the Consumer Product Safety Commission, the Environmental Protection Agency, and the Department of Justice. The steps required before a drug may be approved for marketing in the United States generally include:

- Preclinical laboratory tests and animal tests conducted under GLPs;
- The submission to the FDA of an IND application for human clinical testing, which must become effective before any human clinical trial commences;
- Approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical trial may be initiated;
- Adequate and well-controlled human clinical trials to establish the safety and efficacy of the product and conducted in accordance with Good Clinical Practices, or GCPs;
- The submission to the FDA of a New Drug Application, or NDA, for the applicable small molecule drug product;
- FDA acceptance, review, and approval of the NDA (including the product labeling and package insert); and
- Satisfactory completion of an FDA inspection of the manufacturing facilities at which the product is made to assess compliance with current Good Manufacturing Practices, or CGMPs.

The testing and approval process requires substantial time, effort, and financial resources, and the receipt and timing of any approval is uncertain.

Preclinical studies include laboratory evaluations and animal studies to assess the potential safety and efficacy of the product candidate. Preclinical studies must be conducted in compliance with FDA regulations regarding GLPs. The results of the preclinical studies, together with manufacturing information and analytical data, are submitted to the FDA as part of the IND, which includes a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated if the clinical trial lends itself to an efficacy determination. The IND will become effective automatically 30 days after receipt by the FDA, unless the FDA raises concerns or questions about the conduct of the studies as outlined in the IND prior to that time. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed. The IND must become effective before clinical trials may be commenced.

Clinical trials involve the administration of the product candidates to healthy human volunteers or patients with the disease to be treated under the supervision of a qualified principal investigator. Clinical trials must be conducted under the supervision of one or more qualified principal investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial, and in accordance with protocols detailing the objectives of the applicable phase of the trial, dosing procedures, research subject selection and exclusion criteria, and the safety and effectiveness criteria to be evaluated. Progress reports detailing the status of clinical trials must be submitted to the FDA annually. Sponsors must also report in a timely manner to the FDA serious and unexpected adverse events, any clinically important increase in the rate of serious suspected adverse events over that listed in the protocol or investigator's brochure, or any findings from other studies or tests that suggest a significant risk in humans exposed to the product candidate. Further, the protocol for each clinical trial must be reviewed and approved by an IRB, either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, ethical factors, and the safety of human subjects and the possible liability of the institution.

Clinical trials are typically conducted in three sequential phases prior to approval, but the phases may overlap or be combined and different studies may be initiated with the same drug candidate within the same phase of development in similar or different patient populations. These phases generally include the following:

Phase 1. Phase 1 clinical trials represent the initial introduction of a product candidate into human subjects, frequently healthy volunteers. In Phase 1, the product candidate is usually tested for pharmacodynamic and pharmacokinetic properties such as safety (including adverse effects), dosage tolerability, absorption, distribution, metabolism, and excretion.

Phase 2. Phase 2 clinical trials usually involve a limited patient population to (1) preliminarily evaluate the efficacy of the product candidate for specific indications, (2) determine dosage tolerability and optimal dosage, and (3) identify possible adverse effects and safety risks.

Phase 3. If a product candidate is found to be potentially effective and to have an acceptable safety profile in Phase 2 trials, the clinical trial program may be expanded to Phase 3 clinical trials to further evaluate clinical efficacy, optimal dosage, and safety within an expanded patient population at geographically dispersed clinical trial sites.

Phase 4. Phase 4 clinical trials may be conducted after approval to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of drugs approved under accelerated approval regulations, or when otherwise requested by the FDA in the form of post-market requirements or commitments. Failure to promptly conduct any required Phase 4 clinical trials could result in withdrawal of approval.

Pursuant to the 21st Century Cures Act, which was enacted on December 13, 2016, the manufacturer of an investigational drug for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access. This requirement applies on the later of 60 days after the date of enactment or the first initiation of a Phase 2 or Phase 3 trial of the investigational drug.

A pivotal trial is an adequate and well-controlled clinical trial that permits FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for labeling of the drug. In most cases FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances where the trial is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. The FDA may accept results from Phase 2 trials as pivotal if the trial design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need and the results are sufficiently robust.

The FDA, the IRB, or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group determines whether or not a trial may move forward at designated check points based on access to certain data from the trial. A clinical trial sponsor may also suspend or terminate a clinical trial based on evolving business objectives or competitive climate.

The clinical trial process can take three to ten years or more to complete, and there can be no assurance that the data collected will support FDA approval or licensure of the product.

The results of preclinical studies and clinical trials, together with detailed information on the manufacture, composition, and quality of the product candidate, are submitted to the FDA in the form of an NDA requesting approval to market the product. The application must be accompanied by a significant user fee payment, currently $2.0 million for fiscal year 2017. The FDA has substantial discretion in the approval process and may refuse to accept any application or decide that the data are insufficient for approval and require additional preclinical, clinical, or other studies.

Review of Application

Once the NDA submission has been accepted for filing, which occurs, if at all, 60 days after submission, the FDA informs the applicant of the specific date by which the FDA intends to complete its review. This is typically 12 months from the date of submission. The review process is often extended by the FDA as a result of submission of additional information, sometimes at the FDA's request, during the review. The FDA reviews NDAs to determine, among other things, whether the proposed product is safe and effective for its intended use and whether the product is being manufactured in accordance with CGMP to assure and preserve the product's identity, strength, quality, and purity. Before approving an NDA, the FDA may inspect the facilities at which the product is manufactured and will not approve the product unless the manufacturing facility complies with CGMPs. The FDA will also inspect clinical trial sites for integrity of data supporting safety and efficacy. During the approval process, the FDA also will determine whether a REMS is necessary to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the application must submit a proposed REMS; the FDA will not approve the application without an approved REMS, if required. A REMS can substantially increase the costs of obtaining approval. The FDA may also convene an advisory committee of external experts to provide input on certain review issues relating to risk, benefit, and interpretation of clinical trial data. The FDA may delay approval of an NDA if applicable regulatory criteria are not satisfied or the FDA requires additional testing or information. The FDA may require post-marketing testing and surveillance to monitor safety or efficacy of a product. The FDA will issue either an approval of the NDA or a Complete Response Letter detailing the deficiencies and information required for reconsideration of the application.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA regulated products are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

The Orphan Drug Act

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications 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. 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. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee.

Pediatric Exclusivity and Pediatric Use

Under the Best Pharmaceuticals for Children Act, or BPCA, certain drugs may obtain an additional six months of exclusivity in an indication, if the sponsor submits information requested in writing by the FDA in what is known as a Written Request, relating to the use of the active moiety of the drug in children. The FDA may not issue a Written Request for studies on unapproved or approved indications where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

To receive the six-month pediatric market exclusivity, a sponsor would have to receive a Written Request from the FDA and conduct the requested studies in accordance with a written agreement with the FDA. If there is no written agreement, studies would be conducted in accordance with commonly accepted scientific principles, and reports submitted of those studies. A Written Request may include studies for indications that are not currently in the labeling if the FDA determines that such information will benefit the public health. The FDA will accept the reports upon its determination that the studies were conducted in accordance with and are responsive to the original Written Request, agreement, or commonly accepted scientific principles, as appropriate, and that the reports comply with the FDA's filing requirements.

In addition, the Pediatric Research Equity Act, or PREA, requires a sponsor to conduct pediatric studies for most drugs, for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Under PREA, original NDAs and supplements thereto must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must include the evaluation of the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA, on its own initiative or at the request of the sponsor, may defer pediatric trial requirements for some or all of the pediatric subpopulations. A deferral may be granted by the FDA if it believes that additional safety or effectiveness data in the adult population need to be collected before the pediatric studies begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current, or fails to submit a request for approval of a pediatric formulation.

Breakthrough Therapy Designation

The FDA is required to expedite the development and review of the application for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate the FDA's review and approval of NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval or approval on the basis of a surrogate endpoint, if relevant criteria are met.

Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit.

Based on results of the Phase 3 clinical trial(s) submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA a priority review designation, which sets the target date for FDA action on the application at eight months after the NDA submission. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of twelve months after NDA submission. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Post-Approval Requirements

Even after approval, drugs manufactured or distributed pursuant to FDA approvals are subject to continuous regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product distribution, advertising and promotion, and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with CGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented.

FDA regulations also require investigation and correction of any deviations from CGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain CGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may also result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- Restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market, or voluntary product recalls;
- Fines, untitled and warning letters, or holds on post-approval clinical trials;
- Refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- Product seizure or detention, or refusal to permit the import or export of products; and
- Injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising, and promotion of drug products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Prescription Drug Marketing Act and Drug Supply Chain Security Act

The distribution of pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level and sets minimum standards for the registration and regulation of drug distributors at the state level. Under the PDMA and state law, states require the registration of manufacturers and distributors who provide pharmaceuticals in that state, including in certain states manufacturers and distributors that ship pharmaceuticals into the state even if such manufacturers or distributors have no place of business within the state. The PDMA and state laws impose requirements and limitations upon drug sampling to ensure accountability in the distribution of samples. The PDMA sets forth civil and criminal penalties for violations of these and other provisions.

The federal Drug Supply Chain Security Act, signed in to law on November 27, 2013, imposes new obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing, identification, verification, and other elements. Among the requirements of this federal legislation, manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product. Further, under this legislation, manufacturers will have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

Federal and State Fraud and Abuse and Data Privacy and Security and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict certain business practices in the biopharmaceutical industry. These laws include, but are not limited to, anti-kickback, false claims, data privacy and security, and transparency statutes and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration, directly or indirectly, to induce, or in return for, purchasing, leasing, ordering, or arranging for the purchase, lease, or order of any good, facility, item, or service reimbursable under Medicare, Medicaid, or other federal healthcare programs. The term “remuneration” has been broadly interpreted to include anything of value, including, for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests, and providing anything at less than its fair market value. The federal Anti-Kickback Statute has been interpreted to apply to certain arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and our practices may not in all

cases meet all of the criteria for a statutory exception or safe harbor protection. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. The intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, PPACA, to a lower intent standard such that a person or entity no longer needs to have actual knowledge of this statute or the specific intent to violate it to have committed a violation. In addition, PPACA codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below). Further, civil monetary penalties statutes impose penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal false claims laws, including the federal civil False Claims Act, prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment or approval to the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes "any request or demand" for money or property presented to the U.S. government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal healthcare programs for the product. Other pharmaceutical companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payers and knowingly and willfully falsifying, concealing, or covering up a material fact, or making any materially false, fictitious, or fraudulent statement in connection with the delivery of, or payment for, healthcare benefits, items, or services. Like the federal Anti-Kickback Statute, PPACA amended the intent standard for certain healthcare fraud statutes under HIPAA such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes certain requirements on certain types of entities relating to the privacy, security, and transmission of individually identifiable health information. Among other things, HITECH made HIPAA's security standards directly applicable to business associates—independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act within the PPACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biologicals, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program (with certain exceptions) annually report information to the Centers for Medicare and Medicaid Services, or CMS, related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and certain ownership and investment interests held by physicians and their immediate family members.

Also, many states have similar healthcare statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Some states require the posting of information relating to clinical trials. In addition, California requires pharmaceutical companies to implement a comprehensive compliance program that includes a limit on expenditures for, or payments to, individual medical or health professionals. If our operations are found to be in violation of any of the health regulatory laws described above or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal, civil, and administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion of products from reimbursement under government programs, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products will be sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Pharmaceutical Coverage, Pricing, and Reimbursement

In both domestic and foreign markets, our sales of any approved products will depend in part on the availability of coverage and adequate reimbursement from third-party payers. Third-party payers include government health administrative authorities, managed care providers, private health insurers, and other organizations. Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payers to reimburse all or part of the associated healthcare costs.

Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Sales of our products will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by third-party payers. These third-party payers are increasingly focused on containing healthcare costs by challenging the price and examining the cost-effectiveness of medical products and services. In addition, significant uncertainty exists as to the coverage and reimbursement status of newly approved healthcare product candidates. The market for our products and product candidates for which we may receive regulatory approval will depend significantly on access to third-party payers' drug formularies, or lists of medications for which third-party payers provide coverage and reimbursement. The industry competition to be included in such formularies often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available.

Because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming, costly, and sometimes unpredictable process. We may be required to provide scientific and clinical support for the use of any product to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct expensive pharmacoeconomic studies to demonstrate the cost-effectiveness of our products. This process could delay the market acceptance of any product and could have a negative effect on our future revenue and operating results. We cannot be certain that our products and our product candidates will be considered cost-effective. Because coverage and reimbursement determinations are made on a payer-by-payer basis, obtaining acceptable coverage and reimbursement from one payer does not guarantee that we will obtain similar acceptable coverage or reimbursement from another payer. If we are unable to obtain coverage of, and adequate reimbursement and payment levels for, our product candidates from third-party payers, physicians may limit how much or under what circumstances they will prescribe or administer them and patients may decline to purchase them. This in turn could affect our ability to successfully commercialize our products and adversely affect our profitability, results of operations, financial condition, and future success.

In addition, in many foreign countries, particularly the countries of the European Union and China, the pricing of prescription drugs is subject to government control. In some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of a company placing the medicinal product on the market. We may face competition for our product candidates from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, there may be importation of foreign products that compete with our own products, which could adversely affect our profitability.

Healthcare Reform

In the United States and foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations as we begin to commercialize our products. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state level that seek to reduce healthcare costs.

Furthermore, political, economic, and regulatory influences are subjecting the healthcare industry in the United States to fundamental change. Initiatives to reduce the federal budget and debt and to reform healthcare coverage are increasing cost-containment efforts. We anticipate that Congress, state legislatures, and the private sector will continue to review and assess alternative healthcare benefits, controls on healthcare spending through limitations on the growth of private health insurance premiums and Medicare and Medicaid spending, the creation of large insurance purchasing groups, price controls on pharmaceuticals, and other fundamental changes to the healthcare delivery system. Any proposed or actual changes could limit or eliminate our spending on development projects and affect our ultimate profitability. For example, in March 2010, PPACA was signed into law. PPACA has the potential to substantially change the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, PPACA established: an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents; revised the methodology by which rebates owed by manufacturers to the state and federal government for covered outpatient drugs under the Medicaid Drug Rebate Program are calculated; increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; and extended the Medicaid

Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations. PPACA also expanded eligibility criteria for Medicaid programs, created a new Medicare Part D discount program, expanded the entities eligible for discounts under the Public Health Services Pharmaceutical pricing program, and created a new Patient-Centered Outcomes Research Insitute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit the prices we are able to charge or the amounts of reimbursement available for our products, or which could otherwise affect our commercial operations and ability to be profitable. If future legislation were to impose direct governmental price controls and access restrictions, it could have a significant adverse effect on our business. Managed care organizations, as well as Medicaid and other government agencies, continue to seek price discounts. Some states have implemented, and other states are considering, price controls or patient access constraints under the Medicaid program, and some states are considering price-control regimes that would apply to broader segments of their populations that are not Medicaid-eligible. In addition, recently, President Donald Trump has made statements that he plans to seek repeal of all or portions of PPACA, and has stated that he will ask Congress to replace PPACA with new legislation. There is uncertainty with respect to the impact these changes, if any, may have, and any changes likely will take time to unfold.

In addition, on August 2, 2011, the Budget Control Act of 2011 was enacted and created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the fiscal years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These reductions included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013. These reductions have been extended through 2025 unless additional Congressional action is taken. Also, in January 2013, the American Taxpayer Relief Act of 2012 was signed in to law, which, among other things, reduced Medicare payments to several types of health care providers.

Due to the volatility in the current economic and market dynamics, we are unable to predict the effect of any unforeseen or unknown legislative, regulatory, payer, or policy actions, which may include cost containment and healthcare reform measures. Such policy actions could have a material adverse effect on our profitability.

New Legislation and Regulations

From time to time, legislation is drafted, introduced, and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing, and marketing of products regulated by the FDA. For example, the 21st Century Cures Act, which was enacted on December 13, 2016, contains a number of provisions related to the development of drug and biological products, including provisions intended to encourage the modernization of clinical trial design and support broader use of tools like biomarkers and methods to collect patient experience data. While the 21st Century Cures Act is intended to make drug and biological product development less time-consuming and less costly, it does not change the scientific/medical standard for approval or the quality or quantity of evidence necessary to support approval. In addition to new legislation, FDA regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether further legislative changes will be enacted or whether FDA regulations, guidance, policies, or interpretations changed or what the effect of such changes, if any, may be.

Foreign Regulation

We are planning on seeking approval for our product candidates in Europe, Japan, and other countries. To market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety, and efficacy that govern, among other things, clinical trials, manufacturing, marketing authorization, commercial sales, and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable foreign regulatory authorities before we can commence clinical trials or marketing of the product in foreign countries and jurisdictions. Although many of the issues discussed above with respect to the United States apply similarly in the context of other countries in which we may seek approval, the approval process varies among countries and jurisdictions and can involve different amounts of product testing and additional administrative review periods. For example, in Europe, a sponsor must submit a clinical trial application, or CTA, much like an IND prior to the commencement of human clinical trials. A CTA must be submitted to each national health authority and an independent ethics committee.

For other countries outside of the European Union, such as the countries in Eastern Europe, Latin America, or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary from country to country. The time required to obtain approval in other countries and jurisdictions might differ from or be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively affect the regulatory approval process in other countries.

United States Patent Term Restoration and Regulatory Exclusivity for Approved Products

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act, permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. The patent term restoration period is generally one-half the time between the effective date of an initial IND and the submission date of an NDA, plus the time between the submission date of the NDA and the approval of that product candidate application. Patent term restoration cannot, however, extend the remaining term of a patent beyond a total of 14 years from the product's approval date. In addition, only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves applications for any patent term extension or restoration. In the future, we expect to apply for restoration of patent term for patents relating to each of our product candidates to add patent life beyond the current expiration date of such patents, depending on the length of the clinical trials and other factors involved in the filing of the relevant NDA.

Market exclusivity provisions under the Federal Food, Drug, and Cosmetic Act can also delay the submission or the approval of certain applications of companies seeking to reference another company's NDA. For example, the Hatch-Waxman Act provides a five-year period of exclusivity to any approved NDA for a product containing a new chemical entity, or NCE, never previously approved by FDA either alone or in combination with another active moiety. No application or abbreviated new drug application, or ANDA, that references the NDA for the NCE may be submitted during the five-year exclusivity period, except that such applications may be submitted after four years if they contain a certification of patent invalidity or non-infringement of the patents listed with the FDA for the innovator NDA.

Foreign Country Data Exclusivity

The European Union also provides opportunities for additional market exclusivity. For example, in the European Union, upon receiving marketing authorization, an NCE generally receives eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic product can be marketed until the expiration of the market exclusivity.

Intellectual Property

Our success depends in part upon our ability to obtain and maintain patent and other intellectual property protection for our product candidates including patents claiming compositions of matter, therapeutic uses, distinct forms of specific compounds, formulations, manufacturing methods, and uses in specific indications and patient populations. We are actively engaged in research to further develop and maintain our competitive position, and may rely in part on trade secrets, proprietary know-how, and continuous technological innovation to support and enhance our competitive position.

We seek to protect and strengthen our proprietary position by, among other methods, filing United States and foreign patent applications related to our proprietary technologies, inventions, and any improvements that we consider important to the development and implementation of our business and strategy. Our ability to maintain and solidify our proprietary position for our products and technologies will depend, in part, on our success in obtaining and enforcing valid patent claims. Additionally, we may benefit from a variety of regulatory frameworks in the United States, Europe, Japan, China, and other territories that provide periods of non-patent-based exclusivity for qualifying drug products. See "Business—Government Regulation—United States Patent Term Restoration and Regulatory Exclusivity for Approved Products."

We cannot ensure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications that may be filed by us in the future, nor can we ensure that any of our existing or subsequently granted patents will be useful in protecting our drug candidates, technological innovations, or processes. Additionally, any existing or subsequently granted patents may be challenged, invalidated, circumvented, or infringed. We cannot guarantee that our intellectual property rights or proprietary position will be sufficient to permit us to take advantage of current market trends or otherwise to provide or protect competitive advantages. Furthermore, our competitors may be able to independently develop and commercialize similar products, or may be able to duplicate our technologies, business model, or strategy, without infringing our patents or otherwise using our intellectual property.

Our patent estate (patents and patent applications owned by or exclusively licensed to Reata and one family of patent applications owned by AbbVie and contractually available for Reata's use), on a worldwide basis, encompasses more than 240 granted patents and more than 280 pending patent applications, including more than 140 granted patents and more than 150 pending patent applications related to bardoxolone methyl, omaveloxolone, and RTA 901. More than 60 granted patents and more than 100 pending applications claim additional structural classes of Nrf2 activators, providing further protection for the franchise and a potential source of additional development candidates. One issued United States patent, one issued foreign patent, a pending United States patent application, and eleven pending foreign patent applications contain composition of matter claims to RTA 901 and related compounds.

Our later-expiring granted patents with claims to compositions of matter for bardoxolone methyl, including patents claiming the commercial form, have an expiration date of 2029 in the United States and 2028 elsewhere. Other patents and patent applications relating to specific uses of bardoxolone methyl, including the treatment of PH, PAH, and CKD, will, if granted, have expiration dates ranging from 2029 to 2034. Fundamental composition of matter patents and applications claiming omaveloxolone have a statutory expiration date in 2033. These patents and applications also contain claims to therapeutic uses of omaveloxolone. The fundamental United States composition of matter patent claiming RTA 901, and its foreign equivalents, have a statutory expiration date in 2033.

The protection afforded by any particular patent depends upon many factors, including the type of patent, scope of coverage encompassed by the granted claims, availability of extensions of patent term, availability of legal remedies in the particular territory in which the patent is granted, and success of any challenges to the patent, if asserted. Changes in either patent laws or in the interpretation of patent laws in the United States and other countries could diminish our ability to protect our inventions and to enforce our intellectual property rights. Accordingly, we cannot predict with certainty the enforceability of any granted patent claims or of any claims that may be granted from our patent applications.

The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Our ability to maintain and solidify our proprietary position for our products and core technologies will depend on our success in obtaining effective claims and enforcing those claims once granted. We have in the past been involved in various administrative proceedings with respect to our patents and patent applications and may, as a result of our extensive portfolio, be involved in such proceedings in the future. Additionally, in the future, we may claim that a third party infringes our intellectual property or a third party may claim that we infringe its intellectual property or that our intellectual property is invalid or unenforceable. In any of the administrative proceedings or in litigation, we may incur significant expenses, damages, attorneys' fees, costs of proceedings and experts' fees, and management and employees may be required to spend significant time in connection with these actions.

Because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that any patent related to our product candidates may expire before any of our product candidates can be commercialized, or may remain in force for only a short period of time following commercialization, thereby reducing the advantage afforded by any such patent.

The patent positions for our most advanced programs are summarized below.

Bardoxolone Methyl Patent Portfolio

Our bardoxolone methyl patent portfolio includes five families of granted United States patents, some with related applications pending, and two additional families of pending United States patent applications. Granted and pending claims offer various forms of protection for bardoxolone methyl including claims to compositions of matter, pharmaceutical compositions, specific forms (such as crystalline or non-crystalline forms), specific formulations, and methods for treating a variety of diseases, including PAH and chronic kidney disease, using bardoxolone methyl or its analogs. These United States patents and applications, and their foreign equivalents, are described in more detail below.

The original patent family containing claims to bardoxolone methyl and related compounds was filed in 1998 and exclusively licensed to Reata in 2004 (see "Business—Intellectual Property—Licenses"). Exclusive of any patent term extension, one granted United States patent from this family containing claims covering bardoxolone methyl has an expiration date in 2022. Corresponding patents granted in Canada, Europe (validated in multiple European Patent Convention member states), and Japan have expiration dates in 2019. Exclusive of any patent term extension, the granted United States patents containing claims covering specific forms of bardoxolone methyl, including the commercial form, are due to expire in 2028 or 2029. Two corresponding regional patents have been granted in Europe and the first has been validated in multiple European Patent Convention member states, with validation in multiple states scheduled for the second. Additional corresponding patents have been granted in Japan, China, Canada, and several other countries, and related applications provide broad international protection in additional territories worldwide. Exclusive of any patent term extension, these granted foreign patents and pending patent applications, if granted, are due to expire in 2028.

In some cases, granted United States patents claiming bardoxolone methyl have a longer statutory term than the corresponding foreign patents. This results from the USPTO's practice of granting patent term adjustments for prosecution delays originating at the USPTO. Such adjustments are generally not available under foreign patent laws. If bardoxolone methyl is approved for marketing in the United States, under the Hatch-Waxman Act we may be eligible for up to five years patent term extension for a granted United States patent containing claims covering bardoxolone methyl. Similar term extensions may be available in Europe, Japan, Australia, and certain other foreign jurisdictions. The amount of any such term extension, and the identity of the patent to which it would apply, are dependent upon several factors including the duration of the development program and the date of marketing approval. See "Business—Government Regulation—United States Patent Term Restoration and Regulatory Exclusivity for Approved Products."

We also own or exclusively license various United States and foreign granted patents and pending patent applications containing claims covering formulations of bardoxolone methyl including the planned commercial formulation, and methods of using bardoxolone methyl for the treatment of multiple diseases including PH, PAH, endothelial dysfunction (an essential component of many cardiovascular disorders including PAH), cardiovascular disease, chronic kidney disease, metabolic disorders, and obesity.

The most relevant granted United States patents with composition of matter or method of use claims covering bardoxolone methyl are listed below, along with their projected expiration dates exclusive of any patent term extension.

Patent Number	Title	Projected Expiration
7,863,327	Therapeutic Compounds and Methods of Use	April 15, 2022
8,034,955	Therapeutic Compounds and Methods of Use	June 17, 2019
8,088,824	Forms of CDDO Methyl Ester	October 19, 2029
8,309,601	Forms of CDDO Methyl Ester	August 13, 2028
8,129,429	Synthetic triterpenoids and methods of use in treatment of disease	February 22, 2030
8,747,901	Delayed Release, Oral Dosage Compositions that Contain Amorphous CDDO-Me	November 6, 2030

Omaveloxolone Patent Portfolio

Omaveloxolone is protected by three families of patents. The first, filed in April 2009, contains composition of matter claims that encompass omaveloxolone and many related compounds. This family includes two issued United States patents and a number of granted patents in foreign jurisdictions including China, Mexico, and Japan. Additional United States and foreign applications from this family are pending. The second family, filed in April 2013, is specifically focused on omaveloxolone and includes composition of matter claims and method of use claims. The initial United States patent from this family was issued on March 31, 2015. The issued claims include composition of matter claims to omaveloxolone without regard to morphic form, to several distinct morphic forms of omaveloxolone including the form used in oral dosing formulations, and to various methods of therapeutic use. Foreign equivalents of this application have been filed in Europe, Canada, Mexico, Japan, China, and more than 20 other territories. The European application was recently allowed, and a United States continuation application has been filed. A third patent family, filed by AbbVie in April 2014 and subject to the terms of the AbbVie collaboration agreement, claims additional morphic forms of omaveloxolone.

The most relevant granted United States patents with claims covering omaveloxolone are listed below, along with their projected expiration dates. As discussed above for bardoxolone methyl, if omaveloxolone is approved for marketing in the United States, we may be eligible for term extension under the Hatch-Waxman Act for a granted United States patent containing claims covering omaveloxolone. Similar term extensions may be available in Europe, Japan, and certain other foreign jurisdictions. The amount of any such term extension, and the identity of the patent to which it would apply, are dependent upon several factors including the duration of the development program and the date of marketing approval. See "Government Regulation—United States Patent Term Restoration and Regulatory Exclusivity for Approved Products."

Patent Number	Title	Projected Expiration
8,124,799	Antioxidant Inflammation Modulators: Oleanolic Acid Derivatives with Amino and Other Modifications at C-17	December 3, 2029
8,440,854	Antioxidant Inflammation Modulators: Oleanolic Acid Derivatives with Amino and Other Modifications at C-17	April 20, 2029
8,993,640	2,2-Difluoropropionamide Derivatives of Bardoxolone Methyl, Polymorphic Forms and Methods of Use Thereof	April 24, 2033

RTA 901 Patent Portfolio

RTA 901 is protected by a family of patents and applications based on a PCT application filed in 2013. Patents from this family have been granted in the United States and New Zealand. Applications are pending in Europe, Japan, Canada, Australia, China, Mexico, Eurasia, and several other countries. In addition, a divisional application has been filed in the United States. Both issued and pending claims in this family include composition of matter claims that specifically cover RTA 901 regardless of form, and other claims that cover related compounds. Patents from this family will expire in 2033 unless extended. Details of the issued United States patent are shown below.

Patent Number	Title	Projected Expiration
9,422,320	C-Terminal Hsp90 Inhibitors	February 8, 2033

Trade Secrets and Know-How

Certain aspects of our activities, such as our research and manufacturing efforts, rely in part on proprietary know-how or trade secrets. Because we may employ third-party contractors to conduct certain aspects of those activities and because we collaborate with various organizations and academic institutions on the advancement of our technology platform, we must at times share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements, or other similar agreements with our collaborators, advisors, employees, and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite these contractual provisions, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business. We also seek to preserve the integrity and confidentiality of our proprietary technology and processes by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Licenses

2004 Dartmouth and MD Anderson License

In 2004, we entered into an agreement with the Board of Regents of The University of Texas System in which we obtained from The Trustees of Dartmouth College, or Dartmouth, and The University of Texas MD Anderson Cancer Center, or MD Anderson, an exclusive, sublicenseable, worldwide license to compounds, including bardoxolone methyl, and claims in certain patents and patent applications, along with associated know-how, to manufacture, have manufactured, use and sell defined licensed products for use within the field of human therapeutic and diagnostic uses, research reagents and veterinary uses. Dartmouth and MD Anderson retain certain limited rights related to academic research and educational use of these compounds, and the U.S. government retains certain limited rights.

Under the terms of this license, we paid an initial licensing fee and sunk-in patent costs and are required to pay annual license maintenance fees. In addition, the license requires us to make certain development milestone payments depending on the licensed indication, a portion of sublicensing revenue received by us from sublicenses that we grant under the licensed technology at percentages between mid-teen digits and low-single digits, and royalties in the low single digits on net sales of licensed products by us, our affiliates, and our sublicensees subject to specified annual minimums. To date, we have made $25.2 million in development and sublicense payments under the license.

We have a continuing obligation to use best efforts to commercialize the licensed technology. The license is effective until the last expiration of a claim in a licensed patent that covers the licensed product or 20 years if no licensed patent covers the licensed product. The license can be terminated by the licensors for our material breach subject to a specified notice and cure period based on the nature of the breach, if we become insolvent or enter bankruptcy or receivership proceedings, if we fail to provide satisfactory evidence that we are exercising best efforts to commercialize a licensed invention, or if two payments are late or unpaid within a twelve-month period. Upon any termination of the license, we grant licensors a non-exclusive, sublicenseable license to any improvements that we make to the licensed technology, including those that we license from third parties, subject to a mutually agreed royalty.

2012 Amendment to the 2004 Dartmouth and MD Anderson License

In July 2012, the parties executed an amendment to the 2004 license. This amendment provides, among other terms, that we will pay to the licensors a certain amount from the next one or more milestone payments received by us under the AbbVie license agreement and a low single-digit royalty on net sales of certain Nrf2 activator compounds under the AbbVie collaboration agreement, including omaveloxolone, that are claimed in certain patents and patent applications that are wholly owned by or assigned to us as identified in the AbbVie collaboration agreement.

2009 Dartmouth License

In 2009, we entered into an agreement with Dartmouth, pursuant to which Dartmouth granted us an exclusive, worldwide, sublicenseable license to Dartmouth's rights in patents and patent applications jointly owned by us and Dartmouth claiming the use of bardoxolone methyl and related compounds in the treatment of renal, cardiovascular, and certain metabolic diseases, along with associated know-how, to make, have made, use and sell defined licensed products in the licensed field. Dartmouth retains certain limited rights related to academic research and educational use of these compounds.

Under the terms of this license, we paid to Dartmouth an initial licensing fee and we are required to pay annual maintenance fees and payments associated with the achievement of certain development and aggregate sales milestones. In addition, Dartmouth is entitled to receive from us a portion of our sublicensing revenue from sublicenses that we grant under the licensed technology at a percentage in the low single digits, and royalties in the low single digits on net sales of licensed products by us, our affiliates and our sublicensees. In July 2012, the parties executed an amendment to the license, which provides, among other terms, that we pay to Dartmouth a sublicensing fee in connection with a specified milestone under the AbbVie license agreement. To date, we have made $10.2 million in development and sublicense payments under the license.

We are obligated to exert commercially reasonable efforts to develop and commercialize and effectively manufacture and market licensed products, including, targeting certain development milestones specified in the agreement.

The license is effective until the last valid claim of the licensed patents in the territory expires. Each party has the right to terminate the license for the other party's material breach, subject to a specified notice and cure period. The license terminates automatically in the event that we become insolvent, make an assignment for the benefit of creditors, or file for bankruptcy.

2014 University of Kansas Licenses

In September 2014, we entered into two exclusive, worldwide license agreements with KU Center for Technology Commercialization, Inc., the manager of intellectual property owned by University of Kansas and the University of Kansas Medical Center, or the University of Kansas, to compounds claimed in certain patents and patent applications either owned exclusively by the University of Kansas or owned jointly by the University of Kansas and the National Institutes of Health, or the NIH, that act as small molecule modulators of heat shock protein activity and responses in all human and veterinary therapeutic and diagnostic uses.

Under the terms of these licenses, we paid the University of Kansas initial licensing fees and reimbursed University of Kansas for past patent expenses incurred. Under each agreement, we are required to pay annual license maintenance fees, are obligated to spend a specified threshold for sponsored research to be performed by the University of Kansas, and are obligated to pay University of Kansas development and regulatory milestone payments for each of the first two products, and sales milestone payments only on the first product developed. Under each agreement the University of Kansas is entitled to receive from us a portion of any sublicensing revenue we receive from sublicenses that we grant under the licensed technology at a percentage ranging from the low single digits to the low thirties depending on the stage of development at the time the sublicense is granted. Under each agreement, the University of Kansas is entitled to receive royalties on net sales of licensed products sold by us, our affiliates, and our sublicensees at a percentage ranging in the low single digits depending on the type of licensed product, subject to minimum annual royalties. To date, we have made $0.7 million in development and sublicense payments under these licenses. Under each license agreement we are obligated to use commercially reasonable efforts to develop, manufacture, and market at least one licensed compound. Additionally, under each license agreement, the University of Kansas retains limited rights related to research and educational use of these compounds, and the U.S. government also retains certain limited rights related to these compounds arising from federal funding of the research that led to their discovery. Under one agreement, the NIH retains limited rights related to research and educational use of compounds claimed in patents that name NIH as an assignee.

Each license agreement is effective on a per-country basis until the later of: (i) the last expiration of a claim in a licensed patent that covers the licensed product in such country; (ii) ten years from first commercial sale of a licensed product in such country; or (iii) the expiration of any period of regulatory exclusivity for a licensed product that bars the entry of generic competitors in such country.

Each license agreement can be terminated by the University of Kansas if we fail to make required payments or reports, fail to use commercially reasonable efforts to commercialize a licensed product, file for bankruptcy or become insolvent, enter into receivership or a composition with creditors, or fail to perform certain other obligations including the achievement of certain developmental milestones within specified time limits, and we fail to cure any such breach within 30 days of receiving a notice of default from the licensors.

Third-Party Filings

A number of United States and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing products. Because patent applications can take many years to issue, there may be currently pending applications unknown to us that, if granted, could pose an infringement risk with respect to our use of our product candidates or proprietary technologies.

If a third party claims that we infringe its intellectual property rights, we may face a number of issues, including but not limited to litigation expenses, substantial damages, attorney fees, injunction, royalty payments, cross-licensing of our patents, redesign of our products, or processes and related fees and costs.

We may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our products, product candidates, and proprietary technologies infringe their intellectual property rights. If one of these patents were to be found to cover our products, product candidates, proprietary technologies, or their uses, we could be required to pay damages and could be restricted from commercializing our products, product candidates, or using our proprietary technologies unless we obtain a license to the patent. A license may not be available to us on acceptable terms, if at all. In addition, during litigation, the patent holder might obtain a preliminary injunction or other equitable right, which could prohibit us from making, using or selling our products, technologies, or methods.

Employees

As of December 31, 2016, we had 75 full-time employees, 21 of whom held Ph.D. or M.D. degrees, 49 of whom were engaged in research and development, and 26 of whom were engaged in business development, finance, information systems, facilities, human resources, legal functions, or administrative support. None of our employees is represented by a labor union, and none of our employees has entered into a collective agreement with us. We consider our employee relations to be good.

Research and Development

In each of the last three fiscal years ended December 31, 2016, 2015, and 2014, we have spent $39.5 million, $35.1 million, and $34.3 million, respectively, on research and development.

Facilities

Our principal executive offices are located in Irving, Texas, where we lease approximately 34,890 square feet of office and laboratory space. Our lease expires in October 2018. We believe that our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

Legal Proceedings

We are not currently a party to any legal proceedings, and we are not aware of any claims or actions pending or threatened against us; however, from time to time we may become involved in legal proceedings or be subject to claims arising in the ordinary course of business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources, and other factors.

Directors and Executive Officers

The following table sets forth certain information with respect to our executive officers and directors:

Name	Position
Dawn C. Bir	Vice President, Chief Commercial Officer
J. Warren Huff	Chief Executive Officer, President, and Chairman of the Board of Directors
Colin Meyer, M.D.	Chief Medical Officer and Vice President, Product Development
Keith W. Ward, Ph.D	Vice President, Chief Development Officer
Jason D. Wilson	Chief Financial Officer and Vice President, Strategy
Michael D. Wortley	Vice President, Chief Legal Officer
James E. Bass (1)(2)(3)	Director
William D. McClellan, Jr. (1)(2)(3)	Director
R. Kent McGaughy, Jr. (1)(2)(3)	Director
Jack B. Nielsen (1)(2)(3)	Director
William E. Rose (1)(2)	Director

(1) Member of the audit committee.
(2) Member of the compensation committee.
(3) Member of the nominating and corporate governance committee.

Executive Officers

Dawn C. Bir joined Reata as Chief Commercial Officer in September 2016 to develop and oversee marketing, market access, sales, training, and commercial operations. Prior to joining Reata, Ms. Bir most recently served as Vice President of Sales with Pharmacyclics, LLC. From February 2013 to September 2016, she built and led their first hematology national sales organization of sales representatives, division managers, and regional sales directors, responsible for the launch of IMBRUVICA in the US and Puerto Rico. From October 2011 to February 2013, Ms. Bir served as Vice President Sales & Marketing with McKesson US Pharmaceutical, SKY Pharmaceuticals, and RxPak. Prior thereto, she held positions of increasing responsibility within McKesson Corporation, Genentech, Inc., and Bristol-Myers Squibb Company. Ms. Bir holds a B.S. in Biology from Binghamton University.

J. Warren Huff is the Chairman, Chief Executive Officer and President of Reata. He has served as our sole CEO, President, and as Chairman of the board of directors since our founding in 2002. Prior to founding Reata, Mr. Huff served as CEO in a number of health care and information technology start-up enterprises. Mr. Huff started his career as an attorney with Johnson & Gibbs, P.C., where he was a partner and Chairman of the Corporate Securities Practice. Mr. Huff received a B.B.A. magna cum laude from the University of Texas at Austin and a J.D. from Southern Methodist University. Our board of directors believes that Mr. Huff is qualified to serve on our board of directors due to his extensive experience investing and working in the pharmaceuticals industry.

Colin Meyer, M.D. joined Reata as one of our first employees in 2003 and is Reata's Chief Medical Officer. Dr. Meyer received a B.S. in chemistry with specialization in biochemistry and a B.A. in biology from the University of Virginia. He received an M.D. from the University of Texas Southwestern Medical School and an M.B.A. from Southern Methodist University Cox School of Business.

Keith W. Ward, Ph.D. is Reata's Chief Development Officer and oversees research and development, clinical operations, regulatory affairs, manufacturing, and project management. Dr. Ward joined Reata in July 2011. Prior to joining Reata, he developed ophthalmic pharmaceuticals and medical devices in positions of increasing responsibility for Bausch & Lomb Incorporated, including as Global Vice President of Pharmaceutical R&D, from May 2005 to June 2011. Before that, Dr. Ward held positions of increasing responsibility within GlaxoSmithKline PLC and SmithKline Beecham Pharmaceuticals. Dr. Ward earned a B.S. in Toxicology with a minor in Chemistry from Northeast Louisiana University and a Ph.D. in Toxicology from The University of North Carolina at Chapel Hill.

Jason D. Wilson is Reata's Chief Financial Officer and oversees corporate strategy, finance, accounting and treasury, human resources, business development, investor relations, and information technology. He joined Reata in 2006. Prior to joining Reata he held positions as Vice President, Finance & Corporate Controller at Caris Diagnostics and as a Senior Manager in the health-sciences group at Ernst & Young LLP. Mr. Wilson holds a B.B.A. in Accounting from Henderson University and an M.B.A. from University of Central Arkansas.

Michael D. Wortley joined Reata as Chief Legal Officer and Vice President in April 2015. Prior to joining Reata, Mr. Wortley was an attorney at Vinson & Elkins LLP from 1995 to March 2015, serving in various capacities, including Chief Operating Partner of the firm and Managing Partner of the Dallas office, and at Johnson & Wortley, P.C., serving as Chairman of the Board and President. He currently serves on the board of directors of Pioneer Natural Resources Company. Mr. Wortley earned a B.A. in Political Science from Southern Methodist University, a Master's degree in Regional Planning from the University of North Carolina at Chapel Hill, and a J.D. from Southern Methodist University Dedman School of Law.

Non-Employee Directors

James E. Bass has served as a member of the Board of Directors since July 2004. Mr. Bass is a member of the Board of Snowbird Holdings, LLC and Trinity Summits, LLC. For the past five years, Mr. Bass has been managing family assets and investments as his primary business activity. He previously served as an executive director of FB Gemini Limited, an Asian regional investment bank based in Hong Kong, prior to which he was an associate attorney and later partner at Gibson, Dunn & Crutcher LLP. Mr. Bass graduated with a B.A. from Yale University and obtained his J.D. from Stanford University. Our board of directors believes that Mr. Bass is qualified to serve on our board of directors due to his extensive experience investing and extensive service on the boards of directors and boards of managers of other enterprises.

Willam D. McClellan, Jr. is a financial management consultant to healthcare and life sciences companies. From June 2004 until June 2016, Mr. McClellan, Jr. was the Chief Financial Officer and Executive Vice President, Finance at On-X Life Technologies Holdings, Inc. Prior to June 2004, Mr. McClellan, Jr. held financial and accounting positions at various healthcare and other companies and was a certified public accountant serving as an auditor with Price Waterhouse Coopers for nine years. He currently serves on the board of directors of Apollo Endosurgery, Inc., a publicly-traded company, and chairs its audit committee. Mr. McClellan, Jr. received a B.B.A. in accounting from Abilene Christian University and is a Certified Public Accountant. Our Board believes that Mr. McClellan, Jr. is qualified to serve on our Board due to his extensive experience in finance and accounting roles in the healthcare and life sciences industry and in serving as a certified public accountant at a large public accounting firm.

R. Kent McGaughy, Jr. has served as a member of the Board of Directors since December 2004. Mr. McGaughy, Jr. is a partner in CPMG, Inc. Prior to joining CPMG's predecessor, Cardinal Investment Company, Inc. in 1997, he worked in mergers and acquisitions at Simmons & Company International. He currently serves on the boards of Apollo Endosurgery, Inc., a publicly-traded company, and several private companies. Mr. McGaughy, Jr. received his B.A. from The University of Texas (summa cum laude and member of Phi Beta Kappa) and his M.B.A. from Harvard Business School. Our board of directors believes that Mr. McGaughy, Jr. is qualified to serve on our board of directors due to his extensive experience investing and extensive service on the boards of directors of other companies.

Jack B. Nielsen has served as a member of the Board of Directors since June 2006. Mr. Nielsen is a consultant to Vivo Capital, LLC, a healthcare focused investment firm. Prior to March 1, 2017, Mr. Nielsen worked within the Novo A/S organization and its venture activities since 2001 in several roles, most recently being employed as a Senior Partner based in Copenhagen, Denmark. From 2006 to 2012, Mr. Nielsen was employed as a Partner at Novo Ventures (US) Inc. in San Francisco, where he established the office which provides certain consultancy services to Novo A/S. Mr. Nielsen served on the board of directors of publicly-traded company Akebia Therapeutics, Inc. from 2013 to June 2015 and currently serves on the board of directors of publicly-traded companies Merus, B.V and Apollo Endosurgery, Inc. He is also currently a member of the board of directors of a number of private companies. Mr. Nielsen received a M.Sc. in Chemical Engineering from the Technical University in Denmark, and a Masters in Management of Technology from Center for Technology, Economics and Management; Technical University of Denmark. Our board of directors believes that Mr. Nielsen is qualified to serve on our board due to his extensive industry experience, his experience with venture capital investments, and his board service for several companies in the biotechnology sector.

William E. Rose has served as a member of the Board of Directors since February 2016. Mr. Rose is the President of Montrose Capital, Inc. Prior to Montrose, Mr. Rose was associated with HBK Capital Management from 1991 until 2012, serving in various capacities, including Co-Chief Investment Officer. He currently serves as the Chairman of the Board of Trustees for Greenhill School and is also a member of the Investment Committee for the Dallas Museum of Art. Mr. Rose received a B.A. in Political Science from Duke University in 1989. Our board of directors believes that Mr. Rose is qualified to serve on our board due to his extensive experience investing, his experience with venture capital investments, and his board service for other enterprises.

Corporate Information

We were formed in Delaware in 2002 and maintain our principal corporate offices at 2801 Gateway Dr., Suite 150, Irving, Texas 75063. Our Class A common stock is listed on The NASDAQ Global Market and is traded under the symbol "RETA." Our telephone number is 972-865-2219 and our internet website address is www.reatapharma.com. We make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and, if applicable, amendments to those reports filed or furnished pursuant to Section 13(a) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. In addition to the reports filed or furnished with the SEC, we publicly disclose information from time to time in our press

releases, at annual meetings of stockholders, in publicly accessible conferences and investor presentations, and through our website (principally in our "Investors & News" page). References to our website in this Annual Report on Form 10-K are provided as a convenience and do not constitute, and should not be deemed, an incorporation by reference of the information contained on, or available through, the website, and such information should not be considered part of this Annual Report on Form 10-K.

Item 1A. Risk Factors.

Investing in our Class A common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and Part II, Item 7 entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations," and in any documents incorporated in this Annual Report on Form 10-K by reference, before deciding whether to invest in our Class A common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations, and growth prospects. In such an event, the market price of our Class A common stock could decline, and you may lose all or part of your investment. Although we have discussed all known material risks, the risks described below are not the only ones that we may face. Additional risks and uncertainties not currently known to us or that we currently deem immaterial may also impair our business operations. Certain statements below are forward-looking statements. See also "Special Note Regarding Forward-Looking Statements" in this Annual Report on Form 10-K.

Risks Related to Our Financial Condition

We have incurred significant losses since our inception. We anticipate that we will continue to incur losses for the foreseeable future and may never achieve or sustain profitability. We may require additional financings to fund our operations.

We are a biopharmaceutical company with two lead product candidates in clinical development, bardoxolone methyl in pulmonary hypertension, or PH, and Alport syndrome, and omaveloxolone in Friedreich's ataxia, or FA, mitochondrial myopathies, or MM, metastatic melanoma and other indications. Pharmaceutical product development is a highly risky undertaking. To date, we have focused our efforts and most of our resources on developing our lead product candidates and on our earlier pipeline assets. We are not profitable and have only had net income in the year ended December 31, 2014, due to recognition of deferred collaboration revenue. Furthermore, other than in the years ended December 31, 2009, 2010, and 2012, due to cash received from our collaborations with AbbVie Ltd., or AbbVie, and Kyowa Hakko Kirin Co., Ltd., or KHK, we have had negative cash flows from operations in each year since our inception. We have not generated any revenue based on product sales to date. We continue to incur significant research and development and other expenses related to our ongoing operations. For the years ended December 31, 2016, 2015, and 2014, our net loss was $6.2 million and $1.5 million and net income, which continues to be due to recognition of deferred collaboration revenue, was $0.7 million, respectively. As of December 31, 2016, we had an accumulated deficit of $289.4 million and capital resources consisting of cash and cash equivalents of $84.7 million. Despite cost coverage commitments from KHK and the potential to receive development cost sharing, milestone, and other payments from our collaborators, we anticipate that, without taking into account deferred revenue, we will continue to incur losses for the foreseeable future, and we anticipate these losses will increase as we continue our development of, and seek regulatory approval for, our product candidates. If we do not successfully develop and obtain regulatory approval for our existing or any future product candidates and effectively manufacture, market, and sell any products that are approved, we may never generate product sales, and even if we do generate product sales, we may never achieve or sustain profitability. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our failure to become and remain profitable would depress the market price of our Class A common stock and could impair our ability to raise capital, expand our business, diversify our product offerings, or continue our operations.

We believe that we will continue to expend substantial resources for the foreseeable future as we continue clinical development of bardoxolone methyl, omaveloxolone, and RTA 901, expand our clinical development efforts for bardoxolone methyl, omaveloxolone, and RTA 901, seek regulatory approval and prepare for the commercialization of our product candidates, and pursue the development of additional molecules and treatment of additional indications. These expenditures will include costs associated with research and development, conducting preclinical studies and clinical trials, seeking regulatory approvals in various jurisdictions, and manufacturing and supplying products and product candidates for ourselves and our collaborators. The outcome of any clinical trial or regulatory approval process is highly uncertain, and we are unable to fully estimate the actual costs necessary to successfully complete the development and regulatory approval process, or the likelihood of success, for our product candidates in development and any future product candidates. Our operating plans or third-party collaborations may change as a result of many factors, which are discussed in more detail below, and other factors that may not currently be known to us, and we therefore may need to seek additional funds sooner than planned through public or private offerings of securities, debt financings, or other sources, such as royalty monetization or other structured financings. Such financings may result in dilution to stockholders, imposition of debt covenants and repayment obligations, or other restrictions that may adversely affect our business. We may seek additional capital due to favorable market conditions or strategic considerations even if we currently believe that we have sufficient funds for our current or future operating plans.

Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress in the development of and the conduct of clinical trials with respect to our lead product candidates, bardoxolone methyl and omaveloxolone;
- the costs of development efforts, including the conduct of our current and contemplated Phase 3 trials, for our product candidates, including the degree of participation by our collaborators;
- the costs to initiate and continue research, preclinical, and clinical development efforts for any future product candidates;
- the costs associated with identifying additional product candidates;
- the costs necessary to obtain regulatory approvals, if any, for our product candidates in the United States and other jurisdictions, and the costs of post-marketing studies that could be required by regulatory authorities in jurisdictions where approval is obtained;
- the continuation of our existing third-party collaborations and entry into new third-party collaborations;
- the time and unreimbursed costs necessary to commercialize products in territories where our product candidates may be approved for sale;
- the revenue, if any, from any future sales of our products, if approved, as well as revenue earned from profit share, royalties, and milestones;
- the level of reimbursement or third-party payor pricing available to our products, if approved;
- the costs of obtaining third-party suppliers of our product candidates and products, if any, manufactured in accordance with regulatory requirements;
- the costs associated with being a public company; and
- the costs we incur in the filing, prosecution, maintenance, and defense of our patent portfolio and other intellectual property rights.

Additional funds may not be available when we require them or on terms that are acceptable to us. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce, or terminate our research and development efforts or other operations or activities that may be necessary to commercialize our product candidates.

Substantially all of our recent revenue has been from collaboration arrangements for our product candidates under development.

During the past three completed fiscal years, substantially all of our revenue was from our collaborators, including $48.2 million, $48.1 million, and $48.1 million under the AbbVie collaboration agreement and $1.5 million, $1.5 million, and $2.6 million under the KHK agreement, constituting 100%, 99%, and 99% of our revenue, for each of the years ended December 31, 2016, 2015, and 2014, respectively. Furthermore, this revenue consists of the recognition of deferred revenue from upfront, nonrefundable payments that we received from AbbVie and KHK in prior years and not from new collaboration payments.

AbbVie is currently not participating in the development efforts for bardoxolone methyl or omaveloxolone. If AbbVie continues not to jointly develop and commercialize bardoxolone methyl or omaveloxolone, we could require significant additional capital to proceed with the commercialization of our product candidates. If adequate funds are not available to us on a timely basis or on favorable terms, we may be required to delay, limit, reduce, or terminate our efforts or other operations.

If we are unable to continue to advance our development efforts and achieve development milestones under our collaboration agreements due to disagreements, or, if our collaborations are reprioritized by our collaborators or renegotiated, our revenue may decrease and our activities may fail to lead to commercial products.

Revenue from research and development collaborations depends upon continuation of the collaborations, reimbursement of development costs from KHK, the achievement of milestones, and royalties and profits from our product sales, if any, derived from future products developed from our research. Collaboration agreements are often complex relationships intended to last for a long term; as a result, we may have disagreements or our collaborations may be reprioritized by our collaborators or renegotiated from time to time to change economic and other terms. If we are unable to successfully advance the development of our product candidates or achieve milestones, or, if our collaboration agreements are renegotiated, we may not receive some or all of the revenue currently contemplated under our collaboration agreements. A significant portion of the milestone payments that could occur under our existing contractual arrangements arise from our KHK agreement.

Risks Related to the Development and Commercialization of Our Product Candidates

We are substantially dependent on the success of our lead product candidates, bardoxolone methyl and omaveloxolone.

To date, we have invested a substantial portion of our efforts and financial resources in the research and development of bardoxolone methyl and omaveloxolone, which are currently our lead product candidates. Other than our Phase 1 clinical trial in RTA 901, these are our only current product candidates that have advanced into clinical development, and it may be years before the trials required for their approval are completed, if ever. Our preclinical programs are less advanced in development and may never enter into clinical trials. Although we believe that Nrf2 activators have many potential clinical applications, we may fail to pursue successful indications and may miss opportunities for development in other indications as a result of limited resources. We also may fail to focus our efforts by attempting to develop single product candidates in multiple indications and formulations without success.

At this time, our only development programs for bardoxolone methyl are in PH and chronic kidney disease, or CKD, caused by Alport syndrome. Our near-term prospects are dependent upon successful interactions with global regulatory authorities and on successful Phase 3 development and commercialization of bardoxolone methyl.

Omaveloxolone is in clinical development for FA, MM, and metastatic melanoma. We will need to complete larger and more extensive controlled clinical trials to validate the results observed in clinical trials to date to continue further development of this product candidate. In addition, although there may be many potentially promising indications beyond those listed above, we are still exploring indications for which further development of, and investment for, omaveloxolone may be appropriate. Accordingly, the costs and time to complete development and the related risks are currently unknown.

The clinical and commercial success of bardoxolone methyl and omaveloxolone will depend on a number of factors, many of which are beyond our control.

The clinical and commercial success of bardoxolone methyl and omaveloxolone will depend on a number of factors, including the following, many of which are beyond our control:

- the timely initiation, continuation, and completion of our Phase 2 and Phase 3 clinical trials for bardoxolone methyl and omaveloxolone, which will depend substantially upon requirements for such trials imposed by the U.S. Food and Drug Administration, or FDA, and other regulatory agencies and bodies;
- our ability to demonstrate the safety and efficacy of our product candidates to the satisfaction of the relevant regulatory authorities;
- whether we are required by the FDA or other regulatory authorities to conduct additional clinical trials, and the scope and nature of such clinical trials, prior to approval to market our products;
- the timely receipt of necessary marketing approvals from the FDA and foreign regulatory authorities, including pricing and reimbursement determinations;
- the ability to successfully commercialize our product candidates for marketing and sale, if approved by the FDA or foreign regulatory authorities, whether alone or in collaboration with others;
- our ability and the ability of third-party manufacturers to manufacture the quantities of our product candidates with quality attributes necessary to meet regulatory requirements and at a scale and yield sufficient to meet anticipated demand at a cost that allows us to achieve profitability;
- our success in educating health care providers and patients about the benefits, risks, administration, and use of our product candidates, if approved;
- acceptance of our product candidates, if approved, as safe and effective by patients and the healthcare community;
- the achievement and maintenance of compliance with all regulatory requirements applicable to our product candidates, our third-party manufacturers, and our internal operations;
- the maintenance of an acceptable safety profile of our products, if any, following any approval;
- the availability, perceived advantages, relative cost, relative safety, and relative efficacy of alternative and competitive treatments;
- our ability to successfully enforce our intellectual property rights for our product candidates and against the products of potential competitors; and
- our ability to avoid or succeed in third-party patent interference or patent infringement claims.

We cannot assure you that we will ever be able to achieve profitability through the sale of, or royalties from, our product candidates. If we or our collaborators are not successful in obtaining approval for and commercializing our product candidates, or are delayed in completing those efforts, our business and operations would be adversely affected.

If our product candidates receive regulatory approval, we will be subject to ongoing regulatory requirements and we may face future development, manufacturing, and regulatory difficulties.

Our product candidates, if approved, will also be subject to ongoing regulatory requirements for labeling, packaging, storage, advertising, promotion, sampling, record-keeping, submission of safety and other post-market approval information, importation, and exportation. In addition, approved products, manufacturers, and manufacturers' facilities are required to comply with extensive FDA and European Medicines Agency, or EMA, requirements and the requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practices, or CGMP, requirements. As such, we and our potential future contract manufacturers will be subject to continual review and periodic inspections to assess compliance with CGMPs. Accordingly, we and others with whom we work will be required to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control. We will also be required to report certain adverse reactions and production problems, if any, to the FDA, EMA, and other similar agencies and to comply with certain requirements concerning advertising and promotion for our product candidates. Promotional communications with respect to prescription drugs also are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Accordingly, once approved, we may not promote our products, if any, for indications or uses for which they are not approved.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing, or labeling of a product, it may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters;
- request voluntary product recalls;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us or our potential future collaborators to enter into a consent decree or obtain a permanent injunction against us or our potential future collaborators, which can include shutdown of manufacturing facilities, imposition of fines, reimbursements for inspection costs, taking of specific actions by required due dates, and penalties for noncompliance;
- impose other administrative or judicial civil or criminal penalties or pursue criminal prosecution;
- withdraw regulatory approval;
- refuse to approve pending applications or supplements to approved applications filed by us or by our collaborators or potential collaborators;
- impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products.

Success in earlier Phase 1 and 2 clinical trials for our product candidates, bardoxolone methyl and omaveloxolone, may not be indicative of the results that may be obtained in larger registrational clinical trials, which may delay or prevent obtaining regulatory approval.

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Success in preclinical studies and early clinical trials may not be predictive of results in larger clinical trials, and successful results from early or small clinical trials may not be replicated or show as favorable an outcome in larger clinical trials, even if successful. For example, we have previously endeavored to develop bardoxolone methyl for the treatment of CKD caused by diabetes. While bardoxolone methyl appeared to be safe and effective throughout Phase 2 clinical development for kidney disease, we encountered heart failure related to fluid overload during the pivotal Phase 3 trial that resulted in the termination of the CKD caused by diabetes program. Heart failure appeared to occur at a very low rate in only a particular type of patient studied during the Phase 3 program, which was not observed during Phase 2. Our other clinical programs with bardoxolone methyl and omaveloxolone have involved a relatively small number of patients exposed for a relatively short period of time compared to the Phase 3 clinical trials that we will need to conduct. Accordingly, the Phase 2 clinical trials that we have conducted may not have uncovered safety issues, even if they exist. The biochemical pathways that we believe are affected by bardoxolone methyl and omaveloxolone are implicated in a variety of biological processes and disease conditions, and it is possible that the use of our product candidates to treat larger numbers of patients will demonstrate unanticipated adverse effects, including possible drug-drug interactions, which may negatively affect their safety profile.

In addition, we cannot assure you that any potential advantages that we believe bardoxolone methyl may have for treatment of patients with pulmonary arterial hypertension, or PAH, and pulmonary hypertension due to interstitial lung disease, or PH-ILD, will be substantiated by our Phase 3 clinical trials or that we will be able to include a discussion of any advantages in our labeling should we obtain approval. Based on the data from our ongoing Phase 2 clinical trial, we believe that bardoxolone methyl, combined with current standard of care, may have benefits compared to treatment with current standard of care. However, our belief that bardoxolone methyl may offer those benefits is based on a limited amount of data from our Phase 2 trial and our understanding of the likely mechanisms of action for bardoxolone methyl, and such data may not be replicated in a larger Phase 3 trial. In addition, we cannot assure you that our previous data in CKD caused by diabetes may predict effects in Alport syndrome. Additionally, while we have discussed the PAH trial data with the FDA and the Japanese Pharmaceuticals and Medical Devices Agency, or PMDA, and the CKD caused by diabetes data with the FDA, we have not yet discussed these trial data with any other global health authority, and these regulatory bodies may not concur that these benefits would translate to approvable trial endpoints or be reflected on our product label.

In addition, we cannot assure you that the potential advantages that we believe omaveloxolone may have will be substantiated by our Phase 3 clinical trials or that we will be able to include a discussion of such advantages in our labeling should we obtain approval. Additionally, we have not yet discussed any trial with global regulatory health authorities, and these regulatory bodies may not concur that these benefits would translate to approvable trial endpoints or be reflected on our product label.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early stage development, and we have had, and may face, similar setbacks. In addition, the patient populations under investigation with bardoxolone methyl and omaveloxolone have many co-morbidities that may cause severe illness or death, which may be attributed to bardoxolone methyl and omaveloxolone in a manner that negatively affects the safety profile of our product candidate. If the results of our ongoing or future clinical trials for bardoxolone methyl and omaveloxolone are inconclusive with respect to efficacy, if we do not meet our clinical endpoints with statistical significance, or if there are unanticipated safety concerns or adverse events that emerge during clinical trials, we may be prevented from or delayed in obtaining marketing approval, and even if we obtain marketing approval, any sales may suffer.

We may face delays in completing our ongoing or planned clinical trials with bardoxolone methyl and omaveloxolone due to a number of factors, or these studies may not be completed at all.

Clinical trials can be delayed, suspended, or terminated for a variety of reasons, including delay or failure to:

- reach timely agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- manufacture sufficient quantities of product candidate with acceptable quality attributes for use in clinical trials;
- obtain required regulatory or institutional review board, or IRB, approval, or guidance;
- maintain clinical sites in compliance with clinical trial protocols and good clinical practices, or GCP;
- initiate or add a sufficient number of clinical trial sites;
- recruit, enroll, and retain patients through the completion of the trial; and
- address any physician or patient safety concerns that arise during the course of the trial.

In addition, we could encounter delays if a clinical trial is suspended or terminated by us, by the relevant IRBs at the sites at which such studies are being conducted, or by the FDA or other regulatory authorities. A suspension or termination of clinical trials, including imposition of a clinical hold, may result from any number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities, unforeseen safety issues or adverse side effects, changes in laws or regulations, or a principal investigator's determination that a serious adverse event could be related to our product candidates. Any delays in completing our clinical trials will increase the costs of the trial, delay or prevent the product candidate's development and approval, and jeopardize our ability to commence marketing and generate revenue. Any of these occurrences may materially and adversely harm our business and operations and prospects.

Our product candidates may cause or have attributed to them undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our product candidates or that may be identified as related to our product candidates by investigators conducting our clinical trials or even related to competing products in development that utilize a similar mechanism of action or act through a similar biological disease pathway could cause us or regulatory authorities to interrupt, delay, or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. Adverse events and serious

adverse events, or SAEs, that emerge during treatment with our product candidates or other compounds acting through similar biological pathways may be deemed to be related to our product candidate. This may require longer and more extensive Phase 3 clinical development, or regulatory authorities may increase the amount of data and information required to approve, market, or maintain our product candidates and could result in negative labeling or a restrictive Risk Evaluation and Mitigation Strategy, or REMS. This may also result in an inability to obtain approval of our product candidates.

The occurrence of any or all of these events may cause the development of our product candidates to be delayed or terminated, which could materially and adversely affect our business and prospects. Our product candidates have in the past and may in the future be deemed to cause adverse effects and SAEs.

Clinical trials of our product candidates may not uncover all possible adverse effects that patients may experience.

Clinical trials are conducted in representative samples of the potential patient population, which may have significant variability. By design, clinical trials are based on a limited number of subjects, and are of limited duration of exposure to the product, to determine whether the product candidate demonstrates the substantial evidence of efficacy and safety necessary to obtain regulatory approval. As with the results of any statistical sampling, we cannot be sure that all side effects of our product candidates may be uncovered. It may be the case that only with a significantly larger number of patients exposed to the product candidate for a longer duration may a more complete safety profile be identified. Further, even larger clinical trials may not identify rare SAEs, and the duration of such studies may not be sufficient to identify when those events may occur. Other products have been approved by the regulatory authorities for which safety concerns have been uncovered following approval. Such safety concerns have led to labeling changes, restrictions on distribution through use of a REMS, or withdrawal of products from the market, and any of our product candidates may be subject to similar risks.

Although to date we have not seen evidence of significant safety concerns with our product candidates in the patient populations currently undergoing clinical trials with bardoxolone methyl or omaveloxolone beyond those seen in our Phase 3 BEACON trial of bardoxolone methyl for the treatment of CKD caused by diabetes, patients treated with our products, if approved, may experience adverse reactions, and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. If safety problems occur or are identified after our products, if any, reach the market, we may make the decision or be required by regulatory authorities to amend the labeling of our products, recall our products, or even withdraw approval for our products.

We may fail to enroll a sufficient number of patients in our clinical trials in a timely manner, which could delay or prevent clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on the rate at which we can recruit and enroll patients in testing our product candidates. Patients may be unwilling to participate in clinical trials of our product candidates for a variety of reasons, some of which may be beyond our control, including:

- severity of the disease under investigation;
- real or perceived availability of alternative treatments;
- size and nature of the patient population;
- eligibility criteria for and design of the trial in question;
- perceived risks and benefits of the product candidate under study;
- ongoing clinical trials of potentially competitive agents;
- physicians' and patients' perceptions as to the potential advantages of our product candidates being studied in relation to available therapies or other products under development;
- our CRO's and our trial sites' efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- the need to monitor patients and collect patient data adequately during and after treatment.

Patients may be unwilling to participate in our clinical trials for bardoxolone methyl due to the adverse events we previously detected in a subset of patients with advanced CKD caused by diabetes, and patients currently controlling their disease with standard of care may be reluctant to participate in a clinical trial with an investigational drug. Likewise, patients may be unwilling to participate in our clinical trials for bardoxolone methyl and omaveloxolone due to unforeseen factors beyond our control. Some of the conditions that we are studying, including PH, Alport syndrome, FA, and MM, are rare diseases and enrollment in clinical trials may be limited by the lack of suitable patients with these

diseases. We may not be able to successfully initiate or continue clinical trials if we cannot rapidly enroll a sufficient number of eligible patients to participate in the clinical trials required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit, or terminate on-going or planned clinical trials, any of which could have a material adverse effect on our business and prospects.

If we, our collaborators, or our third-party manufacturers cannot manufacture our product candidates or products at sufficient yields, we may experience delays in development, regulatory approval, and commercialization.

Completion of our clinical trials and commercialization of our product candidates require access to, or development of, facilities to manufacture our product candidates at sufficient yields and at commercial scale. We have limited direct experience in manufacturing, or managing third parties in manufacturing, certain types of our product candidates in the volumes that are expected to be necessary to support commercialization. Our efforts to establish these capabilities may not meet our requirements as to scale-up, timeliness, yield, cost, or quality in compliance with CGMP. Our clinical trials must be conducted with product candidates produced under applicable CGMP regulations. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Our collaborators or experienced third-party manufacturers may encounter difficulties in production, which may include:

- costs and challenges associated with scale-up and attaining sufficient manufacturing yields;
- supply chain issues, including the timely availability and shelf life requirements of raw materials and supplies;
- quality control and assurance;
- shortages of qualified personnel and capital required to manufacture large quantities of product;
- compliance with regulatory requirements that vary in each country where a product might be sold;
- capacity limitations and scheduling availability in contracted facilities; and
- natural disasters or other *force majeure* events that affect facilities and possibly limit production or loss of product inventory maintained in third party storage facilities.

Even if we are able to obtain regulatory approval of our product candidates, we cannot predict the labeling we will obtain and it may be more narrow than originally sought.

Our clinical trials for bardoxolone methyl and omaveloxolone are still at a relatively early stage of clinical development and, while we have initiated our Phase 3 CATALYST trial in CTD-PAH patients and our Phase 2/3 CARDINAL trial in patients with CKD caused by Alport syndrome, specific labeling language has not yet been discussed with health regulatory authorities. For both bardoxolone methyl and omaveloxolone, regulatory approvals, if obtained at all, may include very narrowly-defined indications for which these products may be marketed, since this limitation is a common outcome of health authority review and approval processes. Alternatively, the specific labeling language could highlight real or potential perceived risks that could limit the use of the product candidates in the marketplace, or require a REMS. These labeling limitations may be driven by either preclinical or clinical outcomes, some of which may not yet have been observed in our early studies. Such limitations or warnings may affect our ability to successfully commercialize our products. Due to the rarity of the diseases for which our product candidates are targeted, a narrower than expected indication or other restrictions in labeling could significantly affect our ability to generate revenue.

We have never completed a Phase 3 clinical trial or submitted a New Drug Application, or NDA, and may be unable to do so efficiently or at all for bardoxolone methyl, omaveloxolone, or any product candidate we are developing or may in the future develop.

We have conducted, or are currently conducting, Phase 2 trials for bardoxolone methyl and omaveloxolone and are conducting a Phase 3 trial with bardoxolone methyl, and we may need to conduct additional Phase 2 trials before initiating our Phase 3 clinical trials with omaveloxolone. The conduct of Phase 3 trials and the submission of an NDA is a complicated process. We have not previously completed a Phase 3 trial, have limited experience in preparing, submitting, and prosecuting regulatory filings, and have not previously submitted an NDA. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials and other requirements in a way that leads to NDA submission and approval of any product candidate we are developing. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop.

If we are unable to establish sales, marketing, and distribution capabilities or enter into or maintain agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sales, marketing, or distribution of pharmaceutical products in any country. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish sales and marketing capabilities or make and maintain our existing arrangements with third parties to perform these services at a level sufficient to support our commercialization efforts.

To the extent that we would undertake sales and marketing of any of our products directly, there are risks involved with establishing our own sales, marketing, and distribution capabilities. Factors that may inhibit our efforts to commercialize our products, if any, include:

- our inability to recruit, train, and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- our inability to effectively manage geographically dispersed sales and marketing teams;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

With respect to bardoxolone methyl and omaveloxolone, we are currently dependent in part in certain territories on the commercialization capabilities of our collaborators, AbbVie and KHK. If our collaborators were to fail to devote the necessary resources and attention to sell and market our products, or in any way be unsuccessful in commercializing our products, if any, in their respective appropriate territories, our business and financial condition would suffer.

If the market opportunities for our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. Because the target patient populations of our product candidates are small, we must be able to successfully identify patients and acquire a significant market share to achieve profitability and growth.

We focus our research and product development on treatments for rare and ultra-rare diseases. Given the small number of patients who have the diseases that we are targeting, our profitability and growth depend on successfully identifying patients with these rare and ultra-rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and internal estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, and market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases, and, as a result, the number of patients with these diseases may turn out to be lower than expected. Our effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Finally, even if we obtain significant market share for our product candidates, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

We face substantial competition. There is a possibility that our competitors may discover and develop drugs and obtain regulatory approval before we do.

The development and commercialization of new pharmaceutical products is highly competitive. Our future success depends on our ability to achieve and maintain a competitive advantage with respect to the development and commercialization of our product candidates. Our objective is to discover, develop, and commercialize new products with superior efficacy, convenience, tolerability, and safety in areas with unmet medical need. Our current development programs are intended to either significantly complement existing therapies or serve disease states for which there are no satisfactory existing products. However, we expect that in some cases, the products that we commercialize, if any, may compete with existing or future products of companies that have large, established commercial organizations.

If bardoxolone methyl is approved and launched commercially for patients with PAH, it would launch into a product landscape of numerous approved therapeutics, including Opsumit® (macitentan), Adempas® (riociguat), Orenitram™ (treprostinil), Letairis® (ambrisentan), Tracleer® (bosentan), Uptravi® (selexipag), and others. These agents, used alone or in combination, currently comprise the standard of care in the treatment of patients with PAH. While we expect our anticipated product profile would be complementary to these therapies, and would add to, rather than attempt to displace, these products, it may be difficult to encourage treatment providers and patients to add our product to

their treatment paradigm. We may also face competition from potential new therapies currently in clinical development. For example ralinepag, GS-4997, BIA-5-1058, ubenimex, and KAR5585 are purported to be in development by such companies as Arena Pharmaceuticals, Inc., Gilead Sciences, Inc., Bial-Portela & Ca., SA, Eiger BioPharmaceuticals, Inc., and Karos Pharmaceuticals, Inc., respectively. These product candidates may be in competition with bardoxolone methyl for patient recruitment and enrollment for clinical trials and may be in competition with bardoxolone methyl if it is approved and launched commercially. Some of these product candidates may enter the market prior to bardoxolone methyl, and some of these product candidates could limit the market or level of reimbursement available for bardoxolone methyl if it is commercialized.

If bardoxolone methyl is approved and launched commercially for patients with PH-ILD, it could be the first therapy to serve this subset population. We may face competition from potential new therapies currently in clinical development or additional approvals of existing therapies. For example, Adempas®, Tracleer®, and Orenitram™ are purported to be in development by such companies as Bayer AG, Actelion Pharmaceuticals US Inc., and United Therapeutics Corporation, respectively. These product candidates may be in competition with bardoxolone methyl for patient recruitment and enrollment for clinical trials and may be in competition with bardoxolone methyl if it is approved and launched commercially. Some of these product candidates may enter the market prior to bardoxolone methyl, and could limit the market or level of reimbursement available for bardoxolone methyl if it is commercialized.

If bardoxolone methyl is approved for the treatment of patients with CKD caused by Alport syndrome, it will likely be the first treatment on the market for the indication. At least one therapy for the treatment of Alport syndrome is currently in development with a Phase 2 injectable product candidate, RG-012, from Regulus Therapeutics.

Omaveloxolone may face similar competitive risks as bardoxolone methyl. For our development program in mitochondrial disorders such as FA and MM, if omaveloxolone is approved and launched commercially it may face market competition. Although there are no currently approved therapies for these conditions, there are several competitors who purport to be developing products in this space, including SHP-622, Elamipretide®, cysteamine bitartrate, idebenone, and EPI-743. These candidates are being developed by such companies as Shire plc, Stealth Biotherapeutics Inc., Horizon Pharma plc, Santhera Pharmaceuticals Holding AG, and Edison Pharmaceuticals Inc., respectively.

Omaveloxolone may face market competition if it is approved and launched commercially as part of our development program in immuno-oncology. Numerous therapies are in development for combination treatments in immuno-oncology, including Yervoy®, Opdivo®, Keytruda®, MEDI-4735, MPDL-3280A, and others. These candidates are being developed by such companies as Bristol-Myers Squibb Company, Merck & Co., Inc., AstraZeneca plc, and Roche Holding AG, respectively.

The success of any of these potential competitive products may negatively affect the development and potential for success of our product candidates. In addition, any competitive products that are on the market or in development may compete with our product candidates for patient recruitment and enrollment for clinical trials or may force us to add or change our clinical trial comparators, whether placebo or active, to compare our product candidates against another drug, which may be the new standard of care.

Moreover, many of our competitors have significantly greater resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients, manufacturing pharmaceutical products, and commercialization. Such large and established companies compete aggressively to maintain their market shares. In particular, these companies have greater experience and expertise in securing reimbursement, government contracts, and relationships with key opinion leaders; conducting testing and clinical trials; obtaining and maintaining regulatory approvals and distribution relationships to market products; and marketing approved products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in later stages of development. If we and our collaborators are not able to compete effectively against existing and potential competitors, our business and financial condition may be materially and adversely affected.

Our future commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, third-party payors, and others in the health care community.

Even if we obtain marketing approval for our product candidates, these product candidates may not gain market acceptance among physicians, third-party payors, patients, and others in the health care community. Market acceptance of any approved product depends on a number of other factors, including:

- the clinical indications for which the product is approved and the labeling required by regulatory authorities for use with the product, including any warnings that may be required in the labeling;
- acceptance by physicians and patients of the product as a safe and effective treatment and the willingness of physicians to prescribe new therapies and of the target patient population to try new therapies;
- the cost, safety, efficacy, and convenience of treatment in relation to alternative treatments;

- the restrictions on the use of our products together with other medications, if any;
- the availability of adequate coverage and adequate reimbursement or pricing by third-party payors and government authorities; and
- the effectiveness of our sales and marketing efforts.

We may not be successful in our efforts to identify, license, discover, develop, or commercialize additional product candidates.

Although a substantial amount of our effort will focus on the continued clinical testing, potential approval, and commercialization of our existing product candidates, the success of our business also depends upon our ability to identify, license, discover, develop, or commercialize additional product candidates. Research programs to identify new product candidates require substantial technical, financial, and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. Our research programs or licensing efforts may fail to yield additional product candidates for clinical development and commercialization for a number of reasons, including but not limited to the following:

- our research or business development methodology or search criteria and process may be unsuccessful in identifying potential product candidates;
- we may not be able or willing to assemble sufficient resources to acquire or discover additional product candidates;
- our product candidates may not succeed in preclinical or clinical testing;
- our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may be covered by third parties' patents or other exclusive rights;
- the market for a product candidate may change during our program so that such a product may become unreasonable to continue to develop;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by patients, the medical community, or third-party payors.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, or we may not be able to identify, license, discover, develop, or commercialize additional product candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations.

It is difficult to predict the reimbursement or insurance coverage of our products, if approved. Failure to obtain adequate coverage and reimbursement, or obtaining limited reimbursement, from third-party payors may render our products less attractive to patients and healthcare providers.

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. Market acceptance and sales of any approved products will depend significantly on obtaining adequate coverage and sufficient reimbursement of our products by third-party payors and may be affected by existing and future healthcare reform measures or the prices of related products for which third-party reimbursement applies. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective, and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide supporting scientific, clinical, and cost-effectiveness data for the use of our products to the third-party payor, which we may not be able to provide. Furthermore, the reimbursement policies of third-party payors may significantly change in a manner that renders our clinical data insufficient for adequate reimbursement or otherwise limits the successful marketing of our products. Moreover, the process for determining whether a third-party payor will provide coverage for a drug product may be separate from the process

for setting the price of a drug product or for establishing the reimbursement rate that such payor will pay for the drug product. Even if we obtain coverage for our product candidates, third-party payors may not establish adequate reimbursement amounts, which may reduce the demand for, or the price of, our products, if any. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. If coverage and reimbursement are not available or are available only to limited levels, we may not be able to commercialize certain of our products, if any.

In countries outside of the United States, price controls may limit the price at which products, if approved, are sold. For example, reference pricing is often used by various European Union member states. Parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available products to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products, if any, is unavailable or limited in scope or amount, or if pricing is set at unacceptable levels, we or our collaborators may elect not to commercialize our products, if any, in such countries, and our business and financial condition could be adversely affected.

The continuing efforts of the government, insurance companies, managed care organizations, and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any products that may be approved for sale;
- the price and profitability of our products;
- coverage and reimbursement applicable to our products;
- the ability to successfully position and market any approved product; and
- the taxes applicable to our pharmaceutical product revenue.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing, manufacturing, and commercialization of our product candidates. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in a product, negligence, strict liability, or breach of warranty. Claims could also be asserted under state consumer protection acts. If we are unable to obtain insurance coverage at levels that are appropriate to maintain our business and operations, or if we are unable to successfully defend ourselves against product liability claims, we may incur substantial liabilities or otherwise cease operations. Product liability claims may result in:

- termination of further development of unapproved product candidates or significantly reduced demand for any approved products;
- material costs and expenses to defend the related litigation;
- a diversion of time and resources across the entire organization, including our executive management;
- voluntary product recalls, withdrawals, or labeling restrictions;
- termination of our collaboration relationships or disputes with our collaborators; and
- reputational damage negatively affecting our other product candidates in development.

We maintain product liability insurance in a customary amount for the stage of development of our product candidates. We currently carry $15 million of clinical trial insurance. The amount of such insurance coverage may not be adequate, we may be unable to maintain such insurance, or we may not be able to obtain additional or replacement insurance at a reasonable cost, if at all. Although we believe that we have sufficient coverage based on the advice of our third-party advisors, there can be no assurance that such levels will be sufficient for our needs. Moreover, our insurance policies have various exclusions, and we may be in a dispute with our carrier as to the extent and nature of our coverage, including whether we are covered under the applicable product liability policy. If we are not able to ensure coverage or are required to pay substantial amounts to settle or otherwise contest the claims for product liability, our business and operations would be negatively affected.

Risks Related to Our Reliance on Third Parties

If our collaborators do not participate in the development and commercialization of our product candidates or prioritize other initiatives over their collaborations with us, our ability to successfully develop and commercialize our product candidates could suffer.

We have entered into an agreement with KHK with respect to the development and commercialization of bardoxolone methyl for renal, cardiovascular, diabetes, and certain related metabolic indications in certain territories in Asia. We have also entered into a license agreement with respect to the development and commercialization of bardoxolone methyl for renal, metabolic, and cardiovascular indications with AbbVie in certain territories outside the United States that are not covered by the KHK agreement. However, neither AbbVie nor KHK is currently participating in the development of bardoxolone methyl in PH or CKD caused by Alport syndrome. Additionally, we have entered into a collaboration agreement with AbbVie with respect to the development and commercialization of omaveloxolone and other Nrf2 activator product candidates globally, and currently AbbVie is not participating in the development of omaveloxolone. These agreements contain various provisions related to cost-sharing of product development in certain instances and also provide for commercialization and revenue recognition terms for certain products throughout the major territories of the world.

Our agreements with AbbVie and KHK provide them with certain rights and responsibilities related to participation in product development and commercial product supply of given products in specific territories. If AbbVie or KHK were to continue to elect not to participate in the development and commercialization of our product candidates or to determine that their collaborations with us are no longer a strategic priority, were unable to perform their obligations under the collaboration agreements, or if a successor were to reduce their level of commitment to their collaborations with us, our ability to develop and commercialize our product candidates could suffer. In addition, some of our collaborations are exclusive and preclude us from entering into additional collaboration agreements with other parties in the area or field of exclusivity.

If we fail to establish and maintain strategic collaborations related to our product candidates, we could bear all of the risk and costs related to the development and commercialization of any such product candidate, and we may need to seek additional financing, hire additional employees, and otherwise develop expertise at our cost. This in turn may negatively affect the development of our other product candidates as we direct resources to our most advanced product candidates.

Conflicts with our collaborators could jeopardize our collaboration agreements and our ability to develop and commercialize our product candidates.

Our collaborator AbbVie has certain rights to control decisions and activity regarding the development or commercialization of various product candidates with respect to certain territories. If we have any disagreements with AbbVie with respect to those matters, our plans for obtaining approval may be revised and negatively affect the anticipated timing and potential for success of our product candidates. We have the right under our collaboration agreement with AbbVie to designate omaveloxolone as a product candidate for one indication and two related indications, and pursue further development of omaveloxolone in such indications, without AbbVie's consent. However, we are required to obtain AbbVie's consent to pursue the development of additional indications for omaveloxolone, once it is designated as a product candidate, which may not be obtainable. Even if omaveloxolone or another product candidate is approved, we may remain substantially dependent outside the United States on the commercialization strategy and efforts of our collaborator outside the United States, and our collaborator may not have experience in the areas we elect to pursue.

With respect to the AbbVie collaboration agreement, additional complexities exist. For example, if AbbVie were to opt back in to development of omaveloxolone, we and AbbVie must reach a consensus on our Phase 3 development program with respect to jointly developed product candidates. Alternately, depending upon what point, if any, AbbVie opts back in, we could be responsible for commercializing omaveloxolone globally. Similarly, our collaboration with KHK for bardoxolone methyl requires cooperation between the parties, and failure to do so can negatively affect the development and commercialization of certain of our product candidates or result in termination of the KHK agreement. Multi-party decision-making is complex and involves significant time and effort. There can be no assurance that the parties will cooperate or reach consensus, or that one or both of our collaborators will not ask to proceed independently in some or all of their respective territories or functional areas of responsibility in which the applicable collaborator would otherwise be obligated to cooperate with us. Any disputes or lack of cooperation with AbbVie or KHK may negatively affect the timing or success of our planned clinical trials or commercialization plans.

Certain of our collaborators could also become our competitors in the future. If our collaborators develop competing products, or if we fail to obtain necessary regulatory approvals, or fail to devote sufficient resources to the development and commercialization of our product candidates, the development and commercialization of our product candidates and products could be delayed.

We are also conducting proprietary research programs with molecules and programs that are not covered by our collaboration agreements. Our pursuit of such opportunities could result in conflicts with our collaborators in the event that they take the position that our internal activities overlap with those areas that are exclusive to our collaboration agreements, and we should be precluded from such internal

activities. Moreover, disagreements with our collaborators could develop over rights to our intellectual property. In addition, our collaboration agreements may have provisions that give rise to disputes regarding the rights and obligations of the parties. Any conflict with our collaborators could delay collaborative activities, reduce our ability to renew agreements or obtain future collaboration agreements, result in termination of agreements, or result in litigation or arbitration and would negatively affect our relationship with existing collaborators.

We rely on third parties for the conduct of most of our preclinical studies and clinical trials for our product candidates, and if our third-party contractors do not properly and successfully perform their obligations under our agreements with them, we may not be able to obtain or may be delayed in receiving regulatory approvals for our product candidates.

We rely heavily on universities, hospitals, and other institutions and third parties, including the principal investigators and their staff, to carry out our preclinical studies and clinical trials in accordance with our protocols and designs. We also rely on a number of third-party CROs to assist in undertaking, managing, monitoring, and executing our ongoing clinical trials. We expect to continue to rely on CROs, clinical data management organizations, medical institutions, and clinical investigators to conduct our development efforts in the future, including our Phase 3 development programs. We compete with many other companies for the resources of these third parties, and large pharmaceutical companies often have significantly more extensive agreements and relationships with such third-party providers, and such providers may prioritize the requirements of such large pharmaceutical companies over ours. The third parties upon whom we rely may terminate their engagements with us at any time, which may cause delay in the development and commercialization of our product candidates. If any such third party terminates its engagement with us or fails to perform as agreed, we may be required to enter into alternative arrangements, which would result in significant cost and delay to our product development program. Moreover, our agreements with such third parties generally do not provide assurances regarding employee turnover and availability, which may cause interruptions in the research on our product candidates by such third parties.

While our reliance on these third parties for certain development and management activities will reduce our control over these activities, it will not relieve us of our responsibilities. For example, the FDA and foreign regulatory authorities require compliance with regulations and standards, including GCP requirements, for designing, conducting, monitoring, recording, analyzing, and reporting the results of clinical trials to ensure that the data and results from studies are credible and accurate and that the rights, integrity, and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we are responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators, and trial sites. If we or any of our CROs fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other regulatory authorities may require us to perform additional clinical trials prior to any marketing approval, if granted.

We cannot assure you that, upon inspection by a regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP requirements. Similarly, we rely on certain CROs that conduct nonclinical studies, some of which must be conducted in compliance with good laboratory practice, or GLP, requirements for designing, conducting, monitoring, recording, analyzing, and reporting the results of such studies. If we or any of the CROs that perform nonclinical studies for us fail to comply with applicable GLP requirements, the data generated in those studies may be deemed unreliable and the FDA or other regulatory authorities may require us to repeat or to perform additional studies before an investigational new drug, or IND, application becomes effective or prior to any marketing approval, if granted.

If CROs and other third parties do not successfully carry out their duties under their agreements with us, if the quality or accuracy of the data they obtain is compromised due to their failure to adhere to trial protocols or to regulatory requirements, or if they otherwise fail to comply with regulations and trial protocols or meet expected standards or deadlines, the studies of our product candidates may not meet regulatory requirements. If studies do not meet regulatory requirements or if these third parties need to be replaced, the development of our product candidates may be delayed, suspended, or terminated, or the results may not be acceptable. If any of these events occur, we may not be able to obtain regulatory approval of our product candidates on a timely basis, at a reasonable cost, or at all.

We currently rely, and expect to continue to rely, on third parties to conduct many aspects of our product candidate manufacturing activities and we intend to rely on third parties for potential commercial product manufacturing. Our business could be harmed if those third parties fail to provide us with sufficient quantities of product or fail to do so at acceptable quality levels or prices.

We do not own any facility that may be used to conduct clinical-scale manufacturing and processing, and we must rely on collaborators and outside vendors to manufacture supplies and process our product candidates. We have not yet caused our product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates. In addition, our anticipated reliance on a limited number of third-party manufacturers exposes us to certain risks.

If a replacement contractor is needed, we may be unable to identify manufacturers, especially with acceptable terms, because the number of potential manufacturers is limited. Additionally, the FDA or an equivalent foreign regulatory agency must evaluate any replacement contractor added after initial approval and we must demonstrate comparability of product produced at any new manufacturer added after completion of Phase 3 clinical trials or initial product approval. This process would require additional development work, testing, and compliance inspections. A new manufacturer would also have to be educated in, or develop substantially equivalent processes for, production of our product candidates and products, if any.

Our third-party manufacturers might be unable to timely formulate and manufacture our product candidates or produce the quantity and quality required to meet our clinical and commercial needs, if any. Contract manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately. Our contract manufacturers may not perform as agreed, may not devote sufficient resources to our product candidates, or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store, and distribute our products.

Manufacturers are subject to ongoing periodic unannounced inspection by the FDA or corresponding agencies in other geographic locations, to ensure strict compliance with CGMP and other government regulations and corresponding foreign standards. Although we do not have control over third-party manufacturers' compliance with these regulations and standards, we are ultimately responsible for ensuring that our product candidates are manufactured in accordance with CGMP.

Failure of any third-party manufacturer to maintain compliance with applicable laws and regulations could result in sanctions by the FDA, including request for a voluntary recall, warning letter, seizure of products, injunctions prohibiting some or all further sales and/or recalling product on the market, possible consent decree imposing substantial fines, preclusion of government contracts, import alerts, and criminal liability. In addition, failure of a third-party manufacturer for a product undergoing review by the FDA to maintain an acceptable CGMP compliance status could result in a decision by the FDA not to approve a pending NDA.

We may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our product candidates and products, if any. Our third-party manufacturers could misappropriate our proprietary technology, including our trade secrets and know-how.

Our third-party manufacturers could breach or terminate their agreements with us in a manner or at a time that may negatively affect our planned development and commercialization activities or the timelines for the achievement of development and commercialization activities.

Raw materials and components used in the manufacturing process, particularly those for which we have no other source or supplier, may not be available or may not be suitable or acceptable for use due to material or component defects. Our contract manufacturers and critical reagent suppliers may be subject to inclement weather, as well as natural or man-made disasters. Disruptions to the operations of our third-party manufacturers or suppliers unrelated to our product candidates could occur, including the bankruptcy of a manufacturer or supplier or a catastrophic event or another type of *force majeure* event affecting a manufacturer or supplier.

Each of the risks discussed could delay our clinical trials, the approval of any of our product candidates by the FDA, or the commercialization of our product candidates, and could result in higher costs or deprive us of potential product revenue. In addition, we will rely on third parties to perform release tests on our product candidates prior to delivery to patients. If these tests are not appropriately done and test data are not reliable, patients could be put at risk of serious harm and the FDA could place significant restrictions on our company until deficiencies are remedied to the FDA's satisfaction.

Our product candidates and certain of the components of our product candidates are currently acquired from single-source suppliers and have been purchased without long-term supply agreements. The loss of any of these suppliers, or their failure to supply us with supplies of sufficient quantity and quality to obtain and complete manufacture of drug substance or finished drug product of acceptable quality at an acceptable price, would materially and adversely affect our business.

We do not have agreements with alternative or secondary suppliers of drug substance, a drug product intermediate, or final drug product candidates. Additionally, we do not have agreements with alternative suppliers of certain components of our product candidates. To date, we have used purchase orders for the supply of key materials that we use in our product candidates. We may be unable to enter into long-term commercial supply arrangements with our vendors or to do so on commercially reasonable terms, which could have a material adverse effect upon our business. In addition, we rely on our contract manufacturers to purchase from third-party suppliers some of the materials necessary to produce our product candidates. In certain instances, we do not have direct control over the acquisition of those materials by our contract manufacturers. Moreover, we do not have any agreements for the commercial production of those materials. If a key supplier became unable to supply a key intermediate, the drug substance, or a key component, the lead time required to reinitiate supply source from the alternative suppliers presents risk of delay and potential shortages of supply of our product candidates. The logistics of our product candidate supply chains, which includes shipment of non-FDA regulated materials and intermediates from countries such as China, Japan, and Spain, adds additional time and risk to the manufacture of our product candidates.

Risks Related to Our Intellectual Property

We rely on adequate protection of our proprietary technologies to compete effectively in our market.

We rely upon a combination of intellectual property rights, patents, trademarks, and trade secrets, and contractual arrangements to protect the intellectual property related to our technologies. We will only be able to protect our products and proprietary information and technology by preventing unauthorized use by third parties to the extent that our patents, trademarks, trade secrets, and contractual position allow us to do so. Any disclosure to or misappropriation by third parties of our trade secrets or confidential information could compromise our competitive position. Moreover, we may in the future be involved in legal or administrative proceedings involving our intellectual property that are initiated by us or by third parties. As our product candidates continue in development, third parties may infringe or misappropriate, or attempt to challenge the validity and enforceability of, our patents, trademarks, trade secrets, and proprietary information and technologies. In addition, third parties may accuse our product candidates of infringement of third party intellectual property. Any of these proceedings can result in significant costs and commitment of management time and attention.

We also may in the future be involved in initiating legal or administrative proceedings involving our intellectual property and the product candidates of our competitors. These proceedings can result in significant costs and commitment of management time and attention, and there can be no assurance that our efforts would be successful in preventing or limiting the ability of our competitors to market competing products.

Composition-of-matter patents relating to the active pharmaceutical ingredient are generally considered to be the strongest form of patent protection for pharmaceutical products, as such patents provide protection not limited to a particular method of use or formulation. Method-of-use patents protect the use of a product for the specified method(s), and do not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Bardoxolone methyl, omaveloxolone, and RTA 901 are protected by issued United States and foreign patents containing composition-of-matter claims, with additional applications still pending in the United States and a number of foreign jurisdictions. In addition, all three candidates are protected by issued United States and foreign patents claiming methods of use, with additional applications still pending in the United States and a number of foreign jurisdictions. We rely on a combination of these and other types of patents to protect our product candidates, and there can be no assurance that our intellectual property will create and sustain the competitive position of our product candidates. We may choose not to file patent applications to protect certain technologies, and may also choose to allow certain patents or patent applications to lapse or expire based on cost-benefit considerations.

Pharmaceutical product patents involve highly complex legal and scientific questions and can be uncertain. Patent laws vary from country to country, and may change over time. In addition, the interpretation of patent law by the court systems in a country may change over time. This variability adds uncertainty with respect to the validity and enforceability of our patents and the likelihood that our patent applications will result in granted patents. Pending patent applications that we own or license, and new applications filed by us or our licensors, may fail to result in issued patents. Third parties may challenge the validity or enforceability of our issued patents or patents resulting from our pending or future applications, which may result in such patents being narrowed, invalidated, or held unenforceable. Even if our patents and patent applications are not challenged by third parties, those patents and patent applications may not prevent others from designing around our claims and may not otherwise adequately protect our product candidates. If the breadth or strength of protection provided by the patents and patent applications we hold with respect to our product candidates is threatened, competitors with significantly greater resources could threaten our ability to commercialize our product candidates. Discoveries are generally published in the scientific literature well after their actual development. Patent applications in the United States and other countries are typically not published until 18 months after filing and in some cases are never published. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned

and licensed patents or patent applications, or that we or our licensors were the first to file for patent protection covering such inventions. Subject to meeting other requirements for patentability, for U.S. patent applications filed prior to March 16, 2013, the first to invent the claimed invention is entitled to receive patent protection for that invention while, outside the United States, the first to file a patent application encompassing the invention is entitled to patent protection for the invention. The United States moved to a "first to file" system under the Leahy-Smith America Invents Act, or AIA, effective March 16, 2013. The effects of this change and other elements of the AIA are currently unclear, as the U.S. Patent and Trademark Office, or USPTO, is still implementing associated regulations, and the applicability of the AIA and associated regulations to our patents and patent applications have not been fully determined. This new system also includes new procedures for challenging issued patents and pending patent applications, which creates additional uncertainty. We may become involved in opposition or interference proceedings challenging our patents and patent applications or the patents and patent applications of others, and the outcome of any such proceedings are highly uncertain. An unfavorable outcome in any such proceedings could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology and compete directly with us, or result in our inability to manufacture, develop, or commercialize our product candidates without infringing the patent rights of others.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how, information, or technology that is not covered by our patents. Although our agreements require all of our employees to assign their inventions to us, and we require all of our employees, consultants, advisors, and any third parties who have access to our trade secrets, proprietary know-how, and other confidential information and technology to enter into appropriate confidentiality agreements, we cannot be certain that our trade secrets, proprietary know-how, and other confidential information and technology will not be subject to unauthorized disclosure or that our competitors will not otherwise gain access to or independently develop substantially equivalent trade secrets, proprietary know-how, and other information and technology. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property globally. If we are unable to prevent unauthorized disclosure of our intellectual property related to our product candidates and technology to third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business and operations.

We may be involved in intellectual property disputes with third parties and competitors that could be costly and time consuming and negatively affect our competitive position.

Our commercial success may depend on our avoiding infringement of the patents and other proprietary rights of third parties as well as on enforcing our patents and other proprietary rights against third parties. Pharmaceutical and biotechnology intellectual property disputes are characterized by complex, lengthy, and expensive litigation over patents and other intellectual property rights. We may initiate, become a party to, or be threatened with, future litigation or other proceedings regarding intellectual property rights with respect to our product candidates and competing products.

As our product candidates advance toward commercialization, we or our collaborators may be subject to intellectual property infringement or misappropriation claims from third parties. We attempt to ensure that our product candidates do not infringe third-party patents and other proprietary rights. However, the patent landscape in competitive product areas is highly complex, and there may be patents of third parties of which we are unaware that may result in claims of infringement. Accordingly, there can be no assurance that our product candidates do not infringe proprietary rights of third parties, and parties making claims against us may seek and obtain injunctive or other equitable relief, which could potentially block further efforts to develop and commercialize our product candidates including bardoxolone methyl or omaveloxolone. Any litigation involving defense against claims of infringement, regardless of the merit of such claims, would involve substantial litigation expense and would be a substantial diversion of management time.

If we succeed in commercializing one or more of our product candidates, including bardoxolone methyl or omaveloxolone, under U.S. law, the approved product would likely be considered a new chemical entity and, if so, would benefit from a period of data exclusivity in which no competitor could receive marketing approval for a product containing the same active pharmaceutical ingredient. Similar laws provide various periods of data exclusivity for new chemical entities in Europe and certain other foreign jurisdictions. Once the applicable period of regulatory exclusivity has expired, competitors may seek to market generic versions of our products even though issued patents protecting those products are still in force. In the event that a generic competitor seeks such approval, it may be necessary for us to take legal action to enforce our patents. In addition, the generic competitor may seek to invalidate our patents or to obtain a ruling of non-infringement in a court proceeding or by challenging our patents through interference, reexamination, *inter partes* review, and post-grant review proceedings before the USPTO or through other comparable proceedings, such as oppositions or invalidation proceedings, before foreign patent offices. Any such resulting litigation or administrative proceedings would involve substantial expense, would be a substantial diversion of management time, and could create uncertainty regarding future sales of our products. Findings of invalidity or non-infringement with respect to our patents could have a material adverse effect on our business. Moreover, third parties, including generic competitors or others, may initiate judicial or administrative proceedings in the United States and foreign jurisdictions to challenge our patents from time to time, which could have a material adverse effect on our business.

We may consider administrative proceedings and other means for challenging third-party patents and patent applications. Third parties may also challenge our patents and patent applications, through interference, reexamination, *inter partes* review, and post-grant review proceedings before the USPTO, or through other comparable proceedings, such as oppositions or invalidation proceedings, before foreign patent offices. An unfavorable outcome in any such challenge could result in loss of patent protection for our technology or require us to cease using the related technology and to attempt to license rights to it from the prevailing third party, which may not be available on commercially reasonable terms, if at all, in which case our business could be harmed. Even if we are successful, participation in administrative proceedings before the USPTO or a foreign patent office may result in substantial costs and time on the part of our management and other employees.

Furthermore, there is a risk that any public announcements concerning the existence, status, or outcomes of intellectual property litigation or administrative proceedings may adversely affect the price of our stock. If securities analysts or our investors interpret such existence, status, or outcomes as negative or otherwise creating uncertainty, our Class A common stock price may be adversely affected.

Our reliance on third parties and our agreements with collaborators require us to share our trade secrets. Confidentiality agreements may not prevent a competitor from discovering, misappropriating, or disclosing them.

Our reliance on third-party contractors to develop and manufacture our product candidates is based upon agreements that limit the rights of the third parties to use or disclose our confidential information, including our trade secrets and know-how. Despite the contractual provisions, the need to share trade secrets and other confidential information increases the risk that such trade secrets and information are disclosed or used, even if unintentionally, in violation of these agreements. In the highly competitive markets in which our product candidates are expected to compete, protecting our trade secrets, including our strategies for addressing competing products, is imperative, and any unauthorized use or disclosure could impair our competitive position and may have a material adverse effect on our business and operations.

In addition, our collaborators are larger, more complex organizations than ours, and the risk of inadvertent disclosure of our proprietary information may be increased despite their internal procedures and the contractual obligations in place with our collaborators. Despite our efforts to protect our trade secrets and other confidential information, a competitor's discovery of such trade secrets and information could impair our competitive position and have an adverse effect on our business.

We may be subject to claims asserting that our employees, consultants, or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our business.

In addition, while we require our employees or contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

We have an extensive worldwide patent portfolio. The cost of maintaining our patent protection is high and requires continuous review and compliance. We may not be able to effectively maintain our intellectual property position throughout the major markets of the world.

The USPTO and foreign patent authorities require maintenance fees and payments as well as continued compliance with a number of procedural and documentary requirements. Noncompliance may result in abandonment or lapse of the subject patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance may result in reduced royalty payments for lack of patent coverage in a particular jurisdiction from our collaborators or may result in increased competition, either of which could have a material adverse effect on our business.

We have made, and will continue to make, certain strategic decisions in balancing costs and the potential protection afforded by the patent laws of certain countries. As a result, we may not be able to prevent third parties from practicing our inventions in all countries throughout the world, or from selling or importing products made using our inventions in and into the United States or other countries. Third parties may use our technologies in territories in which we have not obtained patent protection to develop their own products and, further, may infringe our patents in territories which provide ineffective or inadequate enforcement mechanisms, even if we have patent protection. Such third-party products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

The laws of some foreign countries do not protect proprietary rights to the same extent as do the laws of the United States, and we may encounter significant problems in securing and defending our intellectual property rights outside the United States.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries, particularly certain developing countries, do not always favor the enforcement of patents, trade secrets, and other intellectual property rights, particularly those relating to pharmaceutical products, which could make it difficult for us to stop infringement of our patents, misappropriation of our trade secrets, or marketing of competing products in violation of our proprietary rights. Proceedings to enforce our intellectual property rights in foreign countries could result in substantial costs, divert our efforts and attention from other aspects of our business, and put our patents in these territories at risk of being invalidated or interpreted narrowly, or our patent applications at risk of not being granted, and could provoke third parties to assert claims against us. We may not prevail in all legal or other proceedings that we may initiate and, if we were to prevail, the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Intellectual property rights do not prevent all potential threats to competitive advantages we may have.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and intellectual property rights may not adequately protect our business or permit us to maintain our competitive advantage.

The following examples are illustrative:

- Others may be able to make compounds that are the same as or similar to our current or future product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed;
- We or any of our licensors or collaborators might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- We or any of our licensors or collaborators might not have been the first to file patent applications covering certain of our inventions;
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- The prosecution of our pending patent applications may not result in granted patents;
- Granted patents that we own or have licensed may not cover our products or may be held not infringed, invalid, or unenforceable, as a result of legal challenges by our competitors;
- With respect to granted patents that we own or have licensed, especially patents that we either acquire or in-license, if certain information was withheld from or misrepresented to the patent examiner, such patents might be held to be unenforceable;
- Patent protection on our product candidates may expire before we are able to develop and commercialize the product, or before we are able to recover our investment in the product;
- Our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for such activities, as well as in countries in which we do not have patent rights, and may then use the information learned from such activities to develop competitive products for sale in markets where we intend to market our product candidates;
- We may not develop additional proprietary technologies that are patentable;
- The patents of others may have an adverse effect on our business; and
- We may choose not to file a patent application for certain technologies, trade secrets, or know-how, and a third party may subsequently file a patent covering such intellectual property.

Additionally, competitors could enter the market with generic versions of our product candidates, which may adversely affect sales of our product candidates, if approved. Under the Drug Price Competition and Patent Term Restoration Action of 1984, also referred to as the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or ANDA, seeking approval of a generic copy of an approved innovator product. A manufacturer may also submit an NDA under Section 505(b)(2) of the U.S. Federal Food, Drug, and Cosmetic Act that references the FDA's finding of safety and effectiveness of a previously approved drug. An NDA product submitted under Section 505(b)(2) (a 505(b)(2) NDA) may be a new or improved version of the original innovator product. Innovative small molecule drugs may be eligible for certain periods of regulatory exclusivity (e.g., five years for new chemical entities, three years for changes to an approved drug requiring a new clinical trial, and seven years for orphan drugs), which precludes FDA approval of, or in some circumstances, the FDA filing and review of, an ANDA or 505(b)(2) NDA relying on the FDA's finding of safety and effectiveness for the innovative drug. In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation, or an approved use of the drug, which would be listed with the product in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the Orange Book. If there are patents listed in the Orange Book, a generic applicant that seeks to market its product before expiration of the patents listed in the Orange Book must include in the ANDA or 505(b)(2) NDA what is known as a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents. Notice of the certification must also be given to the innovator and, if within 45 days of receiving notice the innovator sues to protect its patents, approval of the ANDA will be stayed for 30 months or a longer or shorter period determined by the court.

Accordingly, if our product candidates are approved, competitors could file ANDAs for generic versions of our product candidates that reference our product candidates. If there are patents listed for our product candidates in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA applicant does or does not intend to challenge the patent. We cannot predict whether any patents issuing from our pending patent applications will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any patents that are granted and listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could more immediately face generic competition and its sales would likely decline materially. Should sales decline, we may have to write off a portion or all of the intangible assets associated with the affected product and our results of operations and cash flows could be materially and adversely affected.

We will need to obtain FDA approval of any proposed product names, and any failure or delay associated with such approval may adversely affect our business.

Any proprietary name or trademark we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the USPTO. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies certain medical claims or contributes to an overstatement of efficacy. If the FDA objects to any product names we propose, we may be required to adopt an alternative name for our product candidates. If we adopt an alternative name, we would lose the benefit of our existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

If we do not obtain additional protection under the Hatch-Waxman Act and similar foreign legislation extending the terms of our patents and obtaining data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration, and specifics of FDA regulatory approval for our product candidates, one or more of our U.S. patents may be eligible for limited patent term restoration under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. Patent term restorations, however, are limited to a maximum of five years and cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval by the FDA.

The application for patent term extension is subject to approval by the USPTO, in conjunction with the FDA. It takes at least six months to obtain approval of the application for patent term extension. We may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened, our competitors may obtain earlier approval of competing products, and our ability to generate revenue could be materially adversely affected.

If we fail to comply with our obligations in the agreements under which we license intellectual property and other rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, we may be required to make certain payments to the licensor, we may lose the exclusivity of our license, or the licensor may have the right to terminate the license, in which event we would not be able to develop or market products covered by the license. Additionally, the milestone and other payments associated with these licenses will make it less profitable for us to develop our drug candidates. See "Business—Intellectual Property- Licenses" for a description of our license agreements with Dartmouth College, M.D. Anderson Cancer Center, and the University of Kansas, which include descriptions of the termination provisions of these agreements.

Disputes may arise regarding intellectual property subject to a licensing agreement, including but not limited to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our collaborators; and
- the priority of invention of patented technology.

If disputes over intellectual property and other rights that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

Risks Related to Government Regulation

The regulatory approval process is highly uncertain, and we may not obtain regulatory approval for the commercialization of our product candidates.

The time required to obtain approval, if any, by the FDA and comparable foreign regulatory authorities is unpredictable, but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate, and it is possible that none of bardoxolone methyl, omaveloxolone, or any future product candidates we may discover, in-license, or acquire and seek to develop in the future will ever obtain regulatory approval.

Our product candidates could fail to receive regulatory approval from the FDA or other regulatory authorities for many reasons, including:

- inadequate design or implementation of our clinical trials;
- failure to demonstrate to the satisfaction of regulatory authorities that a product candidate is safe and effective for its proposed indication;
- failure of clinical trials to meet the level of statistical or clinical significance required for approval;
- failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- FDA refusal to accept efficacy results from clinical trial sites outside the United States where the standard of care is potentially different from that in the United States;
- the insufficiency of data collected from preclinical studies and clinical trials of our present or future product candidates to support the submission and filing of an NDA or other submission or to obtain regulatory approval;
- inadequate manufacturing processes or facilities of third-party manufacturers with whom we contract for clinical and commercial supplies;
- changes in the approval policies or regulations that render our preclinical and clinical data insufficient for approval;

- the CROs that conduct clinical trials on our behalf may take actions outside of our control that materially adversely affect our clinical trials;
- collaborators may not perform or complete their activities contributing to our development programs in a timely manner or at all; or
- one or more SAEs may be related or possibly related to one of our product candidates, and any such determination may adversely affect our ability to obtain regulatory approval, whether or not the determination is correct.

The FDA or other regulatory authorities may require more information, including additional preclinical or clinical data to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program altogether. Even if we do obtain regulatory approval, our product candidates may be approved for fewer or more limited indications than we request, approval may be contingent on the performance of costly post-marketing clinical trials, or approval may require labeling that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. In addition, if our product candidates produce undesirable side effects or safety issues, the FDA may require the establishment of a REMS, or other regulatory authorities may require the establishment of a similar strategy, that may restrict distribution of our approved products, if any, and impose burdensome implementation requirements on us. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Even if we believe our current or planned clinical trials are successful, regulatory authorities may not agree that our completed clinical trials provide adequate data on safety or efficacy. Approval by one regulatory authority does not ensure approval by any other regulatory authority. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. We may not be able to file for regulatory approvals, and even if we file we may not receive the necessary approvals to commercialize our product candidates in any market.

We may be unable to obtain orphan drug designations for some of our product candidates or to maintain the benefits associated with orphan drug designation status, including market exclusivity, which may cause our revenue, if any, to be reduced.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug in the United States will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including an NDA, to market the same drug for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority to the product with orphan product exclusivity or if the FDA finds that the holder of the orphan product exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. A product may obtain orphan drug exclusivity for each indication that has been designated upon approval of the indication, subject to the qualifications above. Any orphan drug exclusivity granted for second or subsequent indications applies only to those subsequent indications and does not block approval of a product for the first indication once the intial period of exclusivity has expired. Moreover, even if one of our drug candidates receives orphan product exclusivity, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication or disease.

We have received orphan drug designation for bardoxolone methyl for the treatment of PAH. We have requested orphan drug designation for omaveloxolone for the treatment of FA and malignant melanoma, and for bardoxolone methyl for the treatment of CKD caused by Alport syndrome, and plan to seek orphan drug designation for some of our other product candidates in specific orphan indications in which there is a medically plausible basis for the use of these products, including MM. The FDA has requested additional information on our request for the orphan drug designation of omaveloxolone for the treatment of FA and malignant melanoma. We have filed an amendment to our application for the treatment of FA and included additional information. In the future, exclusive marketing rights in the United States, if granted, may be limited if we seek approval for an indication broader than the orphan drug designated indication and may be lost if the FDA later determines that the request for the orphan drug designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. In addition, although we have sought or intend to seek orphan drug designation, we may never receive approval for such designations.

We may fail to obtain breakthrough therapy designation for some or all of our product candidates.

In 2012, the U.S. Congress established a breakthrough therapy designation which is intended to expedite the development and review of products that treat serious or life-threatening diseases when "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." The designation of a product candidate as a breakthrough therapy provides potential benefits that include more frequent meetings with the FDA to discuss the development plan for the product candidate and help to ensure collection of appropriate data needed to support approval, more frequent written correspondence from the FDA about such things as the design of the proposed clinical trials and use of biomarkers, intensive guidance on an efficient drug development program, beginning as early as Phase 1, organizational commitment involving senior managers, and eligibility for rolling review and priority review.

Breakthrough therapy designation does not change the standards for product approval. Once we have obtained the requisite preliminary clinical evidence, we intend to seek breakthrough therapy designation for those of our product candidates being tested in serious or life-threatening disease areas, including CTD-PAH, PH-ILD, FA, MM, malignant melanoma, and CKD caused by Alport syndrome, but there can be no assurance that we will receive breakthrough therapy designation.

If our product candidates obtain marketing approval, we will be subject to more extensive healthcare laws, regulation, and enforcement, and our failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.

If we obtain approval for any of our product candidates, the regulatory requirements applicable to our operations, in particular our sales and marketing efforts, will increase significantly with respect to our operations. Also, the potential for civil and criminal enforcement by the federal government and the states and foreign governments will increase with respect to the conduct of our business. The laws that may affect our operations in the United States, currently and in the future, include, without limitation:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering, or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the civil False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims that are false or fraudulent to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements, including mandatory contractual terms, on certain types of entities, relating to the privacy, security, and transmission of individually identifiable health information;
- the federal legislation commonly referred to as the Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics, and medical supplies to report annually to the Centers for Medicare and Medicaid Services, or CMS, information related to payments and other transfers of value to physicians, teaching hospitals, and ownership and investment interests held by physicians and their immediate family members;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- state law equivalents of each of the above federal laws, such as the federal Anti-Kickback Statute and false claims laws, that may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or which otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other and from HIPAA in significant ways, thus complicating compliance efforts.

The scope of these laws and our lack of experience in establishing the compliance programs necessary to comply with this complex and evolving regulatory environment increase the risks that we may violate the applicable laws and regulations. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state

healthcare programs, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, and imprisonment, any of which could materially adversely affect our ability to operate our business and our financial results.

The full effect of recent U.S. healthcare reform and other changes in the healthcare industry and in healthcare spending is currently unknown, and the reform and other changes may adversely affect our business model.

The commercial potential for our approved products, if any, could be affected by changes in healthcare spending and policy in the United States and abroad. We operate in a highly regulated industry. New laws, regulations, or judicial decisions or new interpretations of existing laws, regulations, or decisions, related to healthcare availability, the method of delivery, or payment for healthcare products and services could adversely affect our business, operations, and financial condition.

For example, the Patient Protection and Affordable Care Act, or PPACA, was enacted in 2010 with a goal, among others, of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The PPACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program 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, and creates a new Medicare Part D coverage gap discount program in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. PPACA also expanded eligibility criteria for Medicaid programs and created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. In addition, other legislative changes have been proposed and adopted in the United States since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the fiscal years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013. These reductions have been extended through 2025 unless additional Congressional action is taken. Additionally, in January 2013, the American Taxpayer Relief Act of 2012 was signed in to law, which, among other things, reduced Medicare payments to several types of health care providers.

It is likely that federal and state legislatures within the United States and foreign governments will continue to consider changes to existing healthcare legislation. For example, PPACA has faced ongoing legal challenges, including litigation seeking to invalidate some of or all of the law or the manner in which it has been implemented. In addition, recently, President Donald Trump has made statements that he plans to seek repeal of all or portions of PPACA, and has stated that he will ask Congress to replace PPACA with new legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations, and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any products that may be approved for sale;
- the price and profitability of our products;
- coverage and reimbursement applicable to our products;
- the ability to successfully position and market any approved product; and
- the taxes applicable to our pharmaceutical product revenue.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties for clinical trials outside of the United States, to sell our products abroad once we enter a commercialization phase, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations

described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could result in significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, comply with the FCPA and other anti-bribery laws, report financial information or data accurately, or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions, delays in clinical trials, or serious harm to our reputation. We have adopted a code of conduct for our directors, officers and employees, or the Code of Ethics and Business Conduct, but it is not always possible to identify and deter employee misconduct. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could harm our business, results of operations, financial condition, and cash flows, including through the imposition of significant fines or other sanctions.

If we fail to comply with laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health, and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment, and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials, and also produce hazardous waste products. We contract with third parties for the disposal of these materials and wastes but we cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous, or radioactive materials.

In addition, we may incur substantial costs to comply with current or future environmental, health, and safety laws and regulations applicable to our operations in the United States and foreign countries. These current or future laws and regulations may impair our research, development or manufacturing efforts.

We are also subject to regulation by various federal, state, and local laws, including employment and labor laws, tax laws and other regulations. Our failure to comply with these laws and regulations also may result in substantial fines, penalties, or other sanctions.

Risks Related to Our International Operations

A variety of risks associated with operating our business internationally could materially adversely affect our business.

We plan to seek regulatory approval of our product candidates outside of the United States and, accordingly, we expect that we and any potential collaborators in those jurisdictions will be subject to additional risks related to operating in foreign countries, including:

- different regulatory requirements for drug approvals in foreign countries;
- different standards of care in various countries that could complicate the evaluation of our product candidates;
- different United States and foreign drug import and export rules;
- reduced protection for intellectual property rights in certain countries;
- unexpected changes in tariffs, trade barriers, and regulatory requirements;
- different reimbursement systems and different competitive drugs indicated to treat the indications for which our product candidates are being developed;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration, and labor laws for employees living or traveling abroad;
- compliance with the FCPA, and other anti-corruption and anti-bribery laws;
- foreign taxes, including withholding of payroll taxes;

- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- potential liability resulting from development work conducted by foreign distributors; and
- business interruptions resulting from natural disasters or geopolitical actions, including war and terrorism.

Risks Related to the Operation of Our Business

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials and, if approved, through commercialization, we will likely need to expand our development, regulatory, quality assurance, manufacturing, commercialization, and administration capabilities or contract with third parties to provide these capabilities for us. As our operations expand and we undertake the efforts and expense to operate as a public reporting company, we expect that we will need to increase the responsibilities on members of management and manage any future growth effectively. Our failure to effectively manage our growth in this regard could prevent us from successfully implementing our strategy and maintaining the confidence of investors in our company.

If we fail to attract and keep senior management and key personnel, in particular our Chief Executive Officer, Chief Medical Officer, and Chief Development Officer, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our product candidates.

We are highly dependent on our Chief Executive Officer, Warren Huff, our Chief Medical Officer, Colin Meyer, and our Chief Development Officer, Keith Ward. The loss of the services of Mr. Huff, Dr. Meyer, or Dr. Ward, could significantly negatively affect the development and commercialization of our product candidates, our existing collaborative relationships, and our ability to successfully implement our business strategy.

Recruiting and retaining qualified commercial, development, scientific, clinical, and manufacturing personnel is and will continue to be critical to our success. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of, and commercialize product candidates. We may be unable to hire, train, retain, or motivate these key personnel on acceptable terms given the intense competition among numerous companies for similar personnel. This may be particularly the case in the Dallas area, which does not possess as large a talent base of pharmaceutical professionals as that found in some other areas of the country.

If we are unable to continue to attract and retain personnel with the quality and experience applicable to our product candidates, our ability to pursue our strategy will be limited and our business and operations would be adversely affected.

Our business and operations may be materially adversely affected in the event of computer system failures or security breaches.

Despite the implementation of security measures, our internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, cyber-attacks, natural disasters, fire, terrorism, war, and telecommunication and electrical failures. If such an event were to occur and interrupt our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical trial data from ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, loss of trade secrets or inappropriate disclosure of confidential or proprietary information, including protected health information or personal data of employees or former employees, access to our clinical data, or disruption of the manufacturing process, we could incur liability and the further development of our drug candidates could be delayed. We may also be vulnerable to cyber-attacks by hackers or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and adversely affect our business or result in legal proceedings.

The occurrence of natural disasters, including a tornado, an earthquake, fire, or any other catastrophic event, could disrupt our operations or the operations of third parties who provide vital support functions to us, which could have a material adverse effect on our business, results of operations and financial condition.

We and the third-party service providers on which we depend for various support functions, such as data storage, are vulnerable to damage from catastrophic events, such as power loss, natural disasters, terrorism, and similar unforeseen events beyond our control. Our

corporate headquarters and other facilities are located in the Dallas area, which in the past has experienced damaging storms including tornadoes. Natural disasters could severely disrupt our operations and have a material adverse effect on our business, results of operations, financial condition, and prospects.

If a natural disaster, power outage, or other event occurred that prevented us from using all or a significant portion of our headquarters, damaged critical infrastructure such as our data storage facilities, financial systems or manufacturing resource planning and quality systems, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business.

Furthermore, parties in our supply chain may be operating from single sites, increasing their vulnerability to natural disasters or other sudden, unforeseen, and severe adverse events. If such an event were to affect our supply chain, it could have a material adverse effect on our business.

Risks Related to Our Class A Common Stock

The market price of our Class A common stock may be highly volatile, which may affect the value of your investment in our Class A common stock.

Our initial public offering occurred in May 2016. Therefore, there has only been a public market for our Class A common stock for a short period of time. Although our Class A common stock is listed on The NASDAQ Global Market, an active trading market for our Class A common stock may not develop or be sustained, and you may not be able to sell your shares quickly. Since shares of our Class A common stock were sold in our initial public offering in May 2016 at $11.00 per share, our closing stock price has reached a high of $41.60 and a low of $11.03 through February 28, 2017.

In general, pharmaceutical, biotechnology, and other life sciences company stocks have been highly volatile in the current market. The volatility of pharmaceutical, biotechnology, and other life sciences company stocks is sometimes unrelated to the operating performance of particular companies, and stocks often respond to trends and perceptions rather than financial performance. In particular, the market price of shares of our Class A common stock could be subject to wide fluctuations in response to the following factors:

- results of clinical trials of our product candidates, including bardoxolone methyl and omaveloxolone;
- the timing of the release of results of and regulatory updates regarding our clinical trials;
- the level of expenses related to any of our product candidates or clinical development programs;
- results of clinical trials of our competitors' products;
- safety issues with respect to our product candidates or our competitors' products;
- regulatory actions with respect to our product candidates and any approved products or our competitors' products;
- fluctuations in our financial condition and operating results;
- adverse developments concerning our third-party collaborations and our manufacturers;
- the termination of a third-party collaboration, significant difficulties with an established collaboration, or the inability to establish additional collaborations;
- the publication of research reports by securities analysts about us or our competitors or our industry or negative recommendations or withdrawal of research coverage by securities analysts;
- the inability to obtain adequate product supply for any approved drug product or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- the ineffectiveness of our internal controls;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- additions and departures of key personnel;
- announced strategic decisions by us or our competitors;

- changes in legislation or other regulatory developments affecting our product candidates or our industry;
- fluctuations in the valuation of the pharmaceutical industry and particular companies perceived by investors to be comparable to us;
- sales of our Class A common stock or Class B common stock by us, our insiders, or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- changes in accounting principles;
- terrorist acts, acts of war, or periods of widespread civil unrest;
- natural disasters such as earthquakes and other calamities;
- changes in market conditions for pharmaceutical stocks;
- changes in general market and economic conditions; and
- the other factors described in this "Risk Factors" section.

As a result of fluctuations caused by these and other factors, comparisons of our operating results across different periods may not be accurate indicators of our future performance. Any variances that we report in the future may differ from the expectations of market analysts and investors, which could cause the price of our Class A common stock to fluctuate significantly. Moreover, securities class action litigation has often been initiated against companies following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation.

If securities or industry analysts do not publish research or reports about our business, or if they change their recommendations regarding our stock adversely, our stock price and trading volume could decline.

The trading market for our Class A common stock is influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us downgrade our stock, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

The dual class structure of our common stock and the existing ownership of capital stock by our executive officers, directors, and principal stockholders have the effect of concentrating the voting power of our common stock and will limit your control over matters subject to stockholder approval.

Each share of Class A common stock is entitled to one vote per share, and each share of Class B common stock is entitled to three votes per share. As of February 28, 2017, our executive officers, directors and principal stockholders, together with their respective affiliates, collectively owned shares representing approximately 87.5% of our total Class B common stock, including shares subject to outstanding options that are exercisable within 60 days of such date, and approximately 43.4% of our total Class A common stock. Because of the greater number of votes per share attributed to our Class B common stock, our executive officers, directors, and principal stockholders collectively own shares representing approximately 72.2% of the voting power of our outstanding capital stock. The holders of Class B common stock collectively will continue to be able to control a majority of the voting power even if their stock holdings represent as few as approximately 25.1% of the outstanding number of shares of our common stock.

Accordingly, these stockholders will be able to exert control over our management and affairs and over matters requiring stockholder approval, including the election of our board of directors and approval of significant corporate transactions. The interests of those stockholders may differ from those of other stockholders, and they may vote their shares in a way that is contrary to the way other stockholders vote their shares. This concentration of ownership could have the effect of entrenching our management or the board of directors, delaying or preventing a change in our control, or otherwise discouraging a potential acquirer from attempting to obtain control of us, which in turn could have a material and adverse effect on the market value of our Class A common stock. Future transfers by holders of Class B common stock will generally result in those shares converting on a 1 for 1 basis to Class A common stock, which will have the effect, over time, of increasing the relative voting power of those holders of Class B common stock who retain their shares in the long-term, which may include our executive officers, directors, and affiliates.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, and the reduced disclosure requirements applicable to emerging growth companies may make our Class A common stock less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and for so long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. Specifically, the JOBS Act:

- eliminates the requirement to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- removes the requirement to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board;
- reduces disclosure obligations regarding executive compensation; and
- exempts us from the requirements of holding a non-binding stockholder advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

This Annual Report on Form 10-K is based upon the reduced reporting burdens under the JOBS Act, and we expect to continue reporting at these reduced levels for so long as we are permitted under the JOBS Act. Specifically, we could be an emerging growth company until December 31, 2021, although circumstances could cause us to lose that status earlier, including any of the following: if the market value of our Class A common stock held by non-affiliates exceeds $700 million as of June 30 in any calendar year before that time or if we have total annual gross revenue of $1 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the end of such year or, if we issue more than $1 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company immediately. If any investors find our Class A common stock less attractive as a result, there may be a less active market for our Class A common stock and our stock price may be more volatile.

A significant portion of our total outstanding shares may be sold, which could cause the market price of our Class A common stock to drop significantly and impede our ability to raise future capital, even if our business is doing well.

As of February 28, 2017, we have 8,456,249 shares of Class B common stock outstanding representing 37.8% of our outstanding shares of common stock, all of which are currently restricted as a result of securities laws, but may be converted into shares of Class A common stock and sold, subject to any applicable volume limitations under federal securities laws with respect to affiliate sales, in the near future.

Additionally, our Seventh Amended and Restated Registration Rights Agreement dated as of November 10, 2010, or the Registration Rights Agreement, entered into with certain of our investors in connection with our Series A through H preferred stock financings, provides certain registration rights for 6,792,605 shares of Class B common stock and 2,173,965 shares of Class A common stock as of February 28, 2017. Once we register these shares, they can be freely sold in the public market.

In addition, as of February 28, 2017, there are approximately 2,313,046 shares subject to outstanding options to purchase Class B common stock that will become eligible for sale in the public market to the extent permitted by any applicable vesting requirements and Rule 144 under the Securities Act. We have registered all shares of Class A common stock or Class B common stock that we issue under our employee benefit plans, including our Amended and Restated 2007 Long Term Incentive Plan, or 2007 LTIP. Once they are issued in accordance with the terms of the plans, they can be freely sold in the public market upon issuance, subject to the restrictions imposed on our affiliates under Rule 144 and, in the case of Class B common stock, conversion to Class A common stock.

Sales of a substantial number of shares of our Class A common stock in the public market, or the market perception that the holders of a large number of shares intend to sell shares, could reduce the market price of our Class A common stock. If the market price of our Class A common stock is low, we may not be able to raise additional equity in amounts sufficient to fund our business plans or we may issue significant additional shares to raise funds, resulting in significant dilution to our stockholders.

We incur significant costs as a result of operating as a public company, and we devote substantial resources to public company compliance programs.

As a public company, we incur significant legal, insurance, accounting, and other expenses. The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, the listing requirements of The NASDAQ Global Market, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We have invested, and will continue to invest, in resources to comply with laws, regulations, and standards, and this investment will result in increased general and administrative expenses and may divert management's time and attention from product development activities. If our efforts to comply with new laws, regulations, and standards differ from the activities intended by regulatory or governing bodies, regulatory authorities may initiate legal

proceedings against us and our business may be harmed. As a public company, it is more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These factors could also make it more difficult for us to attract and retain qualified members of our board of directors, particularly to serve on our audit committee and compensation committee, and qualified executive officers. We are currently evaluating and monitoring developments with respect to these rules, and we cannot predict or estimate the amount of additional costs we may incur or the timing of such costs.

Specifically, to comply with the requirements of being a public company, we are undertaking various actions, including implementing new internal controls and procedures and hiring new accounting or internal audit staff. The Sarbanes-Oxley Act requires that we maintain effective disclosure controls and procedures and internal control over financial reporting. We are continuing to develop and refine our disclosure controls and other procedures that are designed to ensure that information required to be disclosed by us in the reports that we file with the Securities and Exchange Commission, or the SEC, is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms, and that information required to be disclosed in reports under the Securities Exchange Act of 1934, or the Exchange Act, is accumulated and communicated to our principal executive and financial officers. Any failure to develop or maintain effective controls could adversely affect the results of periodic management evaluations. In the event that we are not able to demonstrate compliance with the Sarbanes-Oxley Act, that our internal control over financial reporting is perceived as inadequate, or that we are unable to produce timely or accurate financial statements, investors may lose confidence in our operating results and the price of our Class A common stock could decline. In addition, if we are unable to continue to meet these requirements, we may not be able to remain listed on The NASDAQ Global Market and could be subject to fines, sanctions, and other regulatory action, and potentially civil litigation.

We are not currently required to comply with the SEC's rules that implement Section 404 of the Sarbanes-Oxley Act, or Section 404, and are therefore not yet required to make a formal assessment of the effectiveness of our internal control over financial reporting for that purpose. We are required to comply with certain of these rules, which require management to certify financial and other information in our quarterly and annual reports and provide an annual management report on the effectiveness of our internal control over financial reporting commencing with our second annual report. This assessment includes the disclosure of any material weaknesses in our internal control over financial reporting identified by our management or our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we continue to dedicate internal resources and utilize outside consultants and continue to execute a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. We cannot assure you that there will not be material weaknesses or significant deficiencies in our disclosure controls or our internal controls over financial reporting in the future.

We may engage in future acquisitions that could disrupt our business, cause dilution to our stockholders, and harm our business, results of operations, financial condition, and cash flows and future prospects.

While we have no specific plans to acquire any other businesses, we may, in the future, make acquisitions of, or investments in, companies that we believe have products or capabilities that are a strategic or commercial fit with our present or future product candidates and business or otherwise offer opportunities for our company. In connection with these acquisitions or investments, we may:

- issue stock that would dilute our existing stockholders' percentage of ownership;
- incur debt and assume liabilities; and
- incur amortization expenses related to intangible assets or incur large and immediate write-offs.

We may not be able to complete acquisitions on favorable terms, if at all. If we do complete an acquisition, we cannot assure you that it will ultimately strengthen our competitive position or that it will be viewed positively by customers, financial markets, or investors. Furthermore, future acquisitions could pose numerous additional risks to our operations, including:

- problems integrating the purchased business, products or technologies, or employees or other assets of the acquisition target;
- increases to our expenses;
- disclosed or undisclosed liabilities of the acquired asset or company;
- diversion of management's attention from their day-to-day responsibilities;
- reprioritization of our development programs and even cessation of development and commercialization of our current product candidates;
- harm to our operating results or financial condition;

- entrance into markets in which we have limited or no prior experience; and
- potential loss of key employees, particularly those of the acquired entity.

We may not be able to complete any acquisitions or effectively integrate the operations, products, or personnel gained through any such acquisition.

Provisions in our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current directors or management.

Provisions in our amended and restated certificate of incorporation and second amended and restated bylaws contain provisions that may have the effect of discouraging, delaying, or preventing a change in control or changes in our management. These provisions could also limit the price that investors might be willing to pay in the future for shares of our Class A common stock, thereby depressing its market price. In addition, because our board of directors is responsible for appointing the members of our executive management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- provide for a dual class common stock structure, as a result of which our current Class B common stock holders will have control over matters requiring stockholder approval, including significant corporate transactions such as a merger;
- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend, and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors pursuant to a resolution adopted by a majority of the total number of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed prior to the end of their term only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- require a supermajority vote of the holders of our common stock or the majority vote of our board of directors to amend our bylaws; and
- require a supermajority vote of the holders of our common stock to amend the classification of our board of directors into three classes and to amend certain other provisions of our amended and restated certificate of incorporation.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

Moreover, because we are incorporated in Delaware, we are governed by certain anti-takeover provisions under Delaware law which may discourage, delay, or prevent someone from acquiring us or merging with us whether or not it is desired by or beneficial to our stockholders. We are subject to the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who acquires in excess of 15% of our outstanding voting power without the prior approval of our board of directors from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting power, unless the merger or combination is approved in a prescribed manner.

Any provision of our amended and restated certificate of incorporation, our second amended and restated bylaws, or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our Class A common stock, and could also affect the price that some investors are willing to pay for our Class A common stock.

Because we do not intend to declare cash dividends on our shares of common stock in the foreseeable future, stockholders must rely on appreciation of the value of our common stock for any return on their investment.

We currently anticipate that we will retain future earnings for the development, operation, and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, we expect that only appreciation of the price of our Class A common stock, if any, will provide a return to holders of our Class A common stock for the foreseeable future.

Our ability to use net operating losses and research and development credits to offset future taxable income may be subject to certain limitations.

In general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses or tax credits, or NOLs or credits, to offset future taxable income or taxes. For these purposes, an ownership change generally occurs where the aggregate stock ownership of one or more stockholders or groups of stockholders who owns at least 5% of a corporation's stock increases its ownership by more than 50 percentage points over its lowest ownership percentage within a specified testing period. Our existing NOLs or credits may be subject to substantial limitations arising from previous ownership changes, and if we undergo an ownership change, our ability to utilize NOLs or credits could be further limited by Sections 382 and 383 of the Code. In addition, future changes in our stock ownership, many of which are outside of our control, could result in an ownership change under Sections 382 and 383 of the Code. Our NOLs or credits may also be impaired under state law. Accordingly, we may not be able to utilize a material portion of our NOLs or credits. Furthermore, our ability to utilize our NOLs or credits is conditioned upon our attaining profitability and generating U. S. federal and state taxable income. As described above under "Risk Factors—Risks Related to our Financial Condition," we have incurred significant net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future; and therefore, we do not know whether or when we will generate the U.S. federal or state taxable income necessary to utilize our NOL or credit carryforwards that are subject to limitation by Sections 382 and 383 of the Code.

Our amended and restated certificate of incorporation designates the state or federal courts located in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, subject to limited exceptions, the state and federal courts located in the State of Delaware will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law or as to which the Delaware General Corporation Law confers jurisdiction on the Court of Chancery of the State of Delaware, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine including any action to interpret, apply, or enforce our amended and restated certificate of incorporation or our amended and restated bylaws. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage such lawsuits against us and our directors, officers, and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our corporate headquarters are located in Irving, Texas, where we lease approximately 34,890 square feet of office and laboratory space. Our lease expires in October 2018. We believe that our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

Item 3. Legal Proceedings.

We are not currently a party to any legal proceedings, and we are not aware of any claims or actions pending or threatened against us; however, from time to time we may become involved in legal proceedings or be subject to claims arising in the ordinary course of business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources, and other factors.

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 Class A common stock has been traded on The NASDAQ Global Market since May 26, 2016 under the symbol "RETA". Prior to such time, there was no public market for our common stock. As a result, we have not set forth quarterly information with respect to the high and low prices for our Class A common stock for the two most recent fiscal years. The following tables set forth the intraday high and low prices of our Class A common stock as reported by NASDAQ from May 26, 2016, our first day of trading on NASDAQ, to December 31, 2016. On February 28, 2017, the closing price of our Class A common stock on the NASDAQ Global Market was $25.35 per share.

	For the Year Ended December 31, 2016	
	High	Low
Second Quarter (May 26, 2016 through June 30, 2016)	$ 26.90	$ 11.03
Third Quarter	$ 32.22	$ 15.17
Fourth Quarter	$ 41.60	$ 18.51

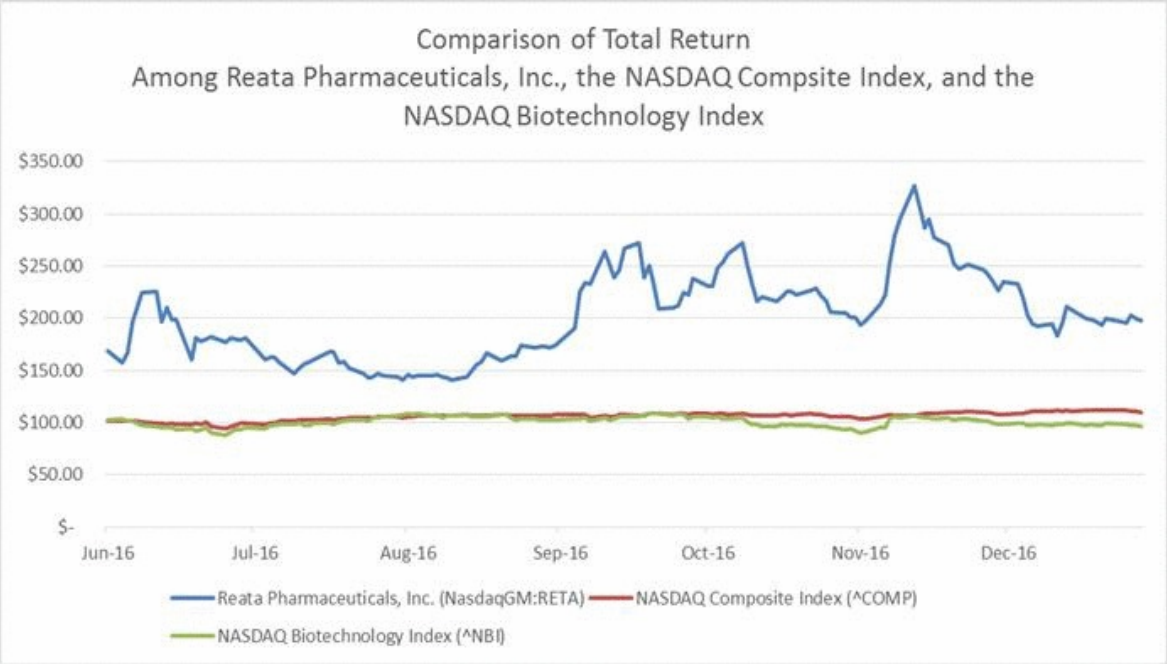
Our Class B common stock is not publicly traded. Our Class B common stock is convertible into Class A common stock on a one-for-one basis at the holder's election at any time. The conversion right of the Class B common stock has no expiration date.

Stockholders

As of February 28, 2017, there were 376 and 213 stockholders of record of our Class A and Class B common stock, respectively. In the case of our Class A common stock, the actual number of holders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. The number of holders of record of Class A common stock also does not include stockholders whose shares may be held in trust by other entities.

Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return for our Class A common stock since May 26, 2016, which is the date our shares began trading, through December 31, 2016, to two indices: the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes an initial investment of $100 on May 26, 2016, in our Class A common stock, the stocks comprising the NASDAQ Composite Index, and the stocks comprising the NASDAQ Biotechnology Index. The comparisons in the table are required by the Securities and Exchange Commission, or SEC, and are not intended to forecast or be indicative of possible future performance of our Class A common stock. This graph shall not be deemed "soliciting material" or be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Securities Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



$100 investment in stock or index	Ticker	May 26, 2016	December 31, 2016
Reata Pharmaceuticals, Inc.	RETA	$ 100.00	$ 197.38
NASDAQ Composite Index	^IXIC	$ 100.00	$ 96.37
NASDAQ Biotechnology Index	^NBI	$ 100.00	$ 109.97

Dividend Policy

We have not paid any dividends on our capital stock within the past two fiscal years. We do not anticipate declaring or paying in the foreseeable future any dividends on our capital stock. We intend to retain all available funds and any future earnings to support operations and to finance the growth and development of our business. Any future determination to pay dividends will be made at the discretion of our board of directors, subject to applicable laws, and will depend upon our results of operations, financial condition, contractual restrictions, capital requirements, and other factors. Our future ability to pay dividends on our capital stock may be limited by the terms of any future debt that we may incur or any preferred securities that we may issue in the future.

Equity Compensation Plans

Information regarding our equity compensation plans is incorporated by reference to Item 12, "Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters—Equity Compensation Plan Information" of Part III of this Annual Report on Form 10-K.

Issuer's Purchases of Equity Securities

None.

Use of Proceeds from Registered Securities

On May 25, 2016, our registration statement on Form S-1 (File No. 333-208843) relating to our initial public offering, or IPO, of our Class A common stock was declared effective by the SEC. The shares began trading on The NASDAQ Global Market on May 26, 2016. The public offering price of the shares sold in the offering was $11.00 per share. The IPO closed on June 1, 2016 and included 6,325,000 shares of Class A common stock, which included 825,000 shares of Class A common stock issued pursuant to the overallotment option granted to the underwriters, for gross proceeds of approximately $69.6 million before deducting underwriters' discounts and commissions and offering-related expenses. Net proceeds, after deducting underwriting discounts and commissions of $4.9 million and offering expenses of approximately $3.8 million, were $60.9 million. Citigroup Global Markets Inc., Cowen and Company, LLC, and Piper Jaffray & Co. acted as joint book-running managers of this offering.

There has been no material change in the planned use of proceeds from our IPO as described in our prospectus dated May 25, 2016, filed with the SEC pursuant to Rule 424(b)(4) of the Securities Act. We invested the funds received in highly liquid money market funds. The net proceeds from the IPO have been used and will be used, together with our cash and cash equivalents, to fund continued advancement of our bardoxolone methyl, omaveloxolone, and other clinical trials and preclinical studies, and to provide funds for working capital and other general purposes. None of the offering proceeds were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates.

Item 6. Selected Financial Data.

The selected consolidated financial data set forth below are derived from our audited consolidated financial statements and may not be indicative of future operating results. The following selected consolidated financial data should be read in conjunction with Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the consolidated financial statements and the notes thereto included elsewhere in this Annual Report. The consolidated selected financial data in this section are not intended to replace our consolidated financial statements and the related notes included elsewhere in this Annual Report. Our historical results are not necessarily indicative of our future results.

	Years Ended December 31			
	2016	2015	2014	2013
	(in thousands, except share and per share data)			
Collaboration revenue				
License and milestone	$ 49,730	$ 50,295	$ 51,368	$ 51,030
Other revenue	126	24	586	170
Total collaboration revenue	49,856	50,319	51,954	51,200
Expenses				
Research and development (1)	39,453	35,141	34,305	45,252
General and administrative (1)	16,603	13,693	11,512	13,403
Depreciation and amortization	682	1,819	2,512	2,927
Total expenses	56,738	50,653	48,329	61,582
Other income				
Investment income	214	32	43	36
Total other income	214	32	43	36
(Loss) income before provision for taxes on income	(6,668)	(302)	3,668	(10,346)
(Benefit) provision for taxes on income	(441)	1,148	2,979	24,759
Net (loss) income	$ (6,227)	$ (1,450)	$ 689	$ (35,105)
Preferred stock dividends	—	—	—	(460)
Net (loss) income attributable to common stockholders	$ (6,227)	$ (1,450)	$ 689	$ (35,565)
Net (loss) income per share—basic (2)	$ (0.31)	$ (0.09)	$ 0.04	$ (0.35)
Net (loss) income per share—diluted (2)	$ (0.31)	$ (0.09)	$ 0.04	$ (0.35)
Weighted-average number of common shares used in net (loss) income per share basic (2)	19,816,635	15,974,974	15,950,023	15,851,838
Weighted-average number of common shares used in net (loss) income per share diluted (2)	19,816,635	15,974,974	15,979,768	15,851,838

(1) Stock-based compensation expense is included in our results of operations as follows:

	Years Ended December 31			
	2016	2015	2014	2013
	(in thousands)			
Research and development	$ 1,121	$ 671	$ 787	$ 992
General and administrative	1,246	1,404	736	1,369
	$ 2,367	$ 2,075	$ 1,523	$ 2,361

(2) See Note 2 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a description of the method used to calculate basic and diluted net (loss) income per share of common stock.

	As of December 31,			
	2016	2015	2014	2013
	(in thousands)			
Condensed Consolidated Balance Sheet Data				
Cash and cash equivalents	$ 84,732	$ 42,008	$ 87,758	$ 176,527
Federal income tax receivable	—	31,926	15,243	10,905
Working capital	27,652	16,439	48,603	77,249
Total assets	89,093	78,954	125,604	229,468
Deferred revenue (including current portion)	291,041	340,771	390,366	441,058
Accumulated deficit	(289,354)	(283,127)	(281,677)	(282,366)
Total stockholders' deficit	$ (215,048)	$ (273,156)	$ (274,246)	$ (277,056)

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes and other financial information appearing in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business, operations, and product candidates, includes forward-looking statements that involve risks and uncertainties. You should review the sections of this Annual Report on Form 10-K captioned "Risk Factors" and "Special Note Regarding Forward-Looking Statements" for a discussion of important factors that could cause our actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical stage biopharmaceutical company focused on identifying, developing, and commercializing product candidates to address rare and life-threatening diseases with few or no approved therapies by targeting molecular pathways that regulate cellular metabolism and inflammation. Our lead product candidates, bardoxolone methyl and omaveloxolone, are Nrf2 activators, previously referred to as antioxidant inflammation modulators, or AIMs, that target Nrf2, an important transcription factor, to restore mitochondrial function, reduce oxidative stress, and resolve inflammation. Bardoxolone methyl is currently being studied in a Phase 3 trial, known as CATALYST, for the treatment of pulmonary arterial hypertension, or PAH, associated with connective tissue disease, or CTD-PAH, as well as a Phase 2 trial, known as LARIAT, for the treatment of pulmonary hypertension due to interstitial lung disease, or PH-ILD, and PAH, each of which are subsets of pulmonary hypertension, or PH. We began enrolling patients in CATALYST in October 2016. In addition, bardoxolone methyl is currently being studied in a single, pivotal Phase 2/3 trial, known as CARDINAL, for the treatment of chronic kidney disease, or CKD, caused by Alport syndrome. We began enrolling patients in CARDINAL on March 2, 2017. Omaveloxolone is being studied in separate two-part Phase 2 trials for the treatment of Friedreich's ataxia, or FA, and mitochondrial myopathies, or MM, known as MOXIe and MOTOR, respectively. We have completed enrollment of part one in MOXIe and are currently dosing patients in part one of MOTOR, which are dose ranging. Data from part two of each of the trials has the potential to be used for registration. Omaveloxolone is also being studied in a Phase 1b/2 for the treatment of metastatic melanoma, known as REVEAL. In addition to our lead product candidates, we are also conducting a Phase 1 clinical trial of RTA 901. Beyond our clinical programs, we have additional promising preclinical development programs. We believe that our product candidates and preclinical programs have the potential to improve clinical outcomes in numerous underserved patient populations.

To date, we have focused most of our efforts and resources on developing our product candidates and conducting preclinical studies and clinical trials. We have historically financed our operations primarily through revenue generated from our collaborations with AbbVie Ltd., or AbbVie, and Kyowa Hakko Kirin Co., Ltd., or KHK, and from sales of our securities. We have not received any payments or revenue from collaborations other than nonrefundable upfront, milestone, and cost sharing payments from our collaborations with AbbVie and KHK and reimbursements of expenses under the terms of our agreement with KHK. We have incurred losses in each year since our inception, other than in 2014. As of December 31, 2016, we had $84.7 million of cash and cash equivalents and an accumulated deficit of $289.4 million. We continue to incur significant research and development and other expenses related to our ongoing operations. Despite contractual product development commitments and the potential to receive future payments from our collaborators, we anticipate that, without taking into account deferred revenue, we will continue to incur losses for the foreseeable future, and we anticipate that our losses will increase as we continue our development of, and seek regulatory approval for, our product candidates. If we do not successfully develop and obtain regulatory approval of our existing product candidates or any future product candidates and effectively manufacture, market, and sell any products that are approved, we may never generate revenue from product sales. Furthermore, even if we do generate revenue from product sales, we may never again achieve or sustain profitability on a quarterly or annual basis. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our failure to become and remain profitable could depress the market price of our Class A common stock and could impair our ability to raise capital, expand our business, diversify our product offerings, or continue our operations.

The probability of success for each of our product candidates and clinical programs and our ability to generate product revenue and become profitable depend upon a variety of factors, including the quality of the product candidate, clinical results, investment in the program, competition, manufacturing capability, commercial viability, and our collaborators' ability to successfully execute our development and commercialization plans. We will also require additional capital through equity or debt financings in order to fund our operations and execute on our business plans, and there is no assurance that such financing will be available to us on commercially reasonable terms or at all. For a description of the numerous risks and uncertainties associated with product development and raising additional capital, see "Risk Factors" included in this Annual Report.

Financial Operations Overview

Revenue

Our revenue to date has been generated primarily from licensing fees received under our collaborative license agreements and reimbursements for expenses. We currently have no approved products and have not generated any revenue from the sale of products to date. In

the future, we may generate revenue from product sales, royalties on product sales, reimbursements for collaboration services under our current collaboration agreements, or license fees, milestones, or other upfront payments if we enter into any new collaborations or license agreements. We expect that our future revenue will fluctuate from quarter to quarter for many reasons, including the uncertain timing and amount of any such payments and sales.

Our license and milestone revenue has been generated primarily from our collaborative licensing agreements with AbbVie and KHK and consists of upfront payments and milestone payments. Under our revenue recognition policy, license revenue associated with upfront, non-refundable license payments received under the collaboration agreements with AbbVie and KHK are recognized ratably over the expected term of the performance obligations under the agreements, which extend through various periods beginning in 2017 and ending in 2026. License revenue recorded with respect to the collaboration agreements with AbbVie consists solely of the recognition of deferred revenue. License revenue recorded with respect to the collaboration agreements with KHK consists of the recognition of deferred revenue and reimbursement of supply costs.

We also have other license revenue, which consists of milestone payments from a disease advocacy organization in 2015, and other revenue, which consists of reimbursements from KHK for expenses incurred to obtain drug supplies.

Research and Development Expenses

The largest component of our total operating expenses has historically been our investment in research and development activities, including the clinical development of our product candidates. From our inception through December 31, 2016, we have incurred a total of $478.2 million in research and development expense, a majority of which relates to the development of bardoxolone methyl and omaveloxolone. We expect our research and development expense to continue to increase in the future as we advance our product candidates through clinical trials and expand our product candidate portfolio. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming and we consider the active management and development of our clinical pipeline to be crucial to our long-term success. The actual probability of success for each product candidate and preclinical program may be affected by a variety of factors, including the safety and efficacy data for product candidates, investment in the program, competition, manufacturing capability, and commercial viability.

Research and development expenses include:

- expenses incurred under agreements with clinical trial sites that conduct research and development activities on our behalf;
- expenses incurred under contract research agreements and other agreements with third parties;
- employee and consultant-related expenses, which include salaries, benefits, travel, and stock-based compensation;
- laboratory and vendor expenses related to the execution of preclinical and non-clinical studies, and clinical trials;
- the cost of acquiring, developing, manufacturing, and distributing clinical trial materials; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other supply costs.

Research and development costs are expensed as incurred. Costs for certain development activities such as clinical trials are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites.

We base our expense accruals related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple research institutions and contract research organizations, or CROs, that conduct and manage clinical trials on our behalf. The financial terms of these agreements vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing costs, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If we do not identify costs that we have begun to incur or if we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates.

To date, we have not experienced significant changes in our estimates of accrued research and development expenses after a reporting period. However, due to the nature of estimates, we cannot assure you that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical trials and other research activities.

Currently, AbbVie is not participating in the development of bardoxolone methyl for the treatment of PH and CKD caused by Alport syndrome and we are therefore incurring all costs for this program. With respect to our omaveloxolone programs and our collaboration agreement with AbbVie, we were responsible for a certain initial amount in early development costs before AbbVie began sharing development

costs equally. In April 2016, we had incurred all of these initial costs, after which payments from AbbVie with respect to research and development costs incurred by us were recorded as a reduction in research and development expenses. Our expenses were reduced by $1.4 million for AbbVie's share of research and development costs for the year ended December 31, 2016.

In September 2016, we and AbbVie mutually agreed that we would continue unilateral development of omaveloxolone. Therefore, AbbVie no longer co-funds the exploratory development costs of this program, but retains the right to opt back in at certain points in development. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the U.S. or we may be responsible for commercializing the product on a worldwide basis. Upon opting back in, AbbVie would be required to pay an agreed upon amount of all development costs accumulated up to the point of exercising their opt-in right, after which development costs incurred and product revenue worldwide would be split equally.

The following table summarizes our research and development expenses incurred during the years ended December 31:

	2016	2015	2014
		(in thousands)	
Bardoxolone methyl	$ 17,188	$ 5,259	$ 4,429
Omaveloxolone	5,011	11,465	15,270
RTA 901	2,187	6,339	697
Other research and development expenses	15,067	12,078	13,909
Total research and development expenses	$ 39,453	$ 35,141	$ 34,305

The program-specific expenses summarized in the table above include costs that we directly allocate to our product candidates. Our other research and development expenses include research and development salaries, benefits, stock-based compensation and preclinical, research, and discovery costs, which we do not allocate on a program-specific basis.

General and Administrative Expenses

General and administrative expenses consist primarily of employee-related expenses for executive, operational, finance, legal, compliance, and human resource functions. Other general and administrative expenses include personnel expense, facility-related costs, professional fees, accounting and legal services, depreciation expense, other external services, and expenses associated with obtaining and maintaining our intellectual property rights.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research and development and potential commercialization of our product candidates. We have also incurred and anticipate incurring in the future increased expenses associated with being a public company, including exchange listing and Securities and Exchange Commission requirements, director and officer insurance premium, legal, audit and tax fees, compliance with the Sarbanes-Oxley Act of 2002, regulatory compliance programs, and investor relations costs. Additionally, if and when we believe the first regulatory approval of one of our product candidates appears likely, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially for the sales and marketing of our product candidates.

Other Income

Other income represents interest and gains earned on our cash and cash equivalents, which include money market funds.

Provision for Taxes on Income

Provision for taxes on income consists of net loss, taxed at federal tax rates and adjusted for certain permanent differences. We maintain a full valuation allowance against our net deferred tax assets. Changes in this valuation allowance also affect the tax provision.

Results of Operations

Comparison of the Years Ended December 31, 2016, 2015, and 2014

The following table sets forth our results of operations for the years ended December 31:

	2016	Change	2015	Change	2014
	(in thousands, except percentage data)				
Consolidated Statements of Operations Data					
Collaboration revenue					
License and milestone	$ 49,730	(1)%	$ 50,295	(2)%	$ 51,368
Other revenue	126	425%	24	(96)%	586
Total collaboration revenue	49,856	(1)%	50,319	(3)%	51,954
Expenses					
Research and development	39,453	12%	35,141	2%	34,305
General and administrative	16,603	21%	13,693	19%	11,512
Depreciation and amortization	682	(63)%	1,819	(28)%	2,512
Total expenses	56,738	12%	50,653	5%	48,329
Total other income	214	569%	32	(26)%	43
Loss before (benefit) provision for taxes on income	(6,668)	(2108)%	(302)	(108)%	3,668
(Benefit) provision for taxes on income	(441)	(138)%	1,148	(61)%	2,979
Net loss	$ (6,227)	(329)%	$ (1,450)	(310)%	$ 689

Revenue

License revenue represented approximately 100%, 100%, and 99% of total revenue for the years ended December 31, 2016, 2015, and 2014, respectively. License and milestone revenue decreased by 1% during 2016 compared to 2015. The decrease was primarily due to a milestone payment of $0.7 million received from a research collaboration with a disease advocacy organization in 2015. License and milestone revenue decreased by 2% during 2015 compared to 2014. This decrease was due to a decrease in revenue recognized under the KHK agreement due to an extension of KHK's development timeline.

Other revenue increased by 425% during 2016 compared to 2015, primarily due to revenue recognized for reimbursements of expenses from KHK for expenses incurred. Other revenue decreased by 96% during 2015 compared to 2014, primarily due to decreases in rent revenue of $0.4 million recognized from our sublease and revenue of $0.2 million recognized for reimbursements of expenses from KHK for expenses incurred.

The following table summarizes the sources of our revenue for the years ended December 31:

	2016	2015	2014
	(in thousands)		
License and milestone			
AbbVie license agreement	$ 21,470	$ 21,412	$ 21,412
AbbVie collaboration agreement	26,720	26,647	26,647
KHK agreement	1,540	1,536	2,609
Other revenue	—	700	700
Total license and milestone	$ 49,730	$ 50,295	$ 51,368
Other revenue	126	24	586
Total collaboration revenue	$ 49,856	$ 50,319	$ 51,954

Research and Development Expenses

Research and development expenses increased by 12% during 2016 compared to 2015. The increase was primarily due to increases of $11.9 million primarily related to clinical activities for bardoxolone methyl in PAH and PH-ILD, $1.8 million in personnel expense to support growth in our development activities, $0.5 in equity compensation expense, and $0.5 in sponsorship conferences related to PAH, FA and MM, and a net decrease of $6.5 million related to the completion of clinical activities on our topical programs and the upfront startup costs related to the launch of clinical activities for omaveloxolone in FA and MM, and $4.2 million related to delay in preclinical and clinical activities for RTA 901.

Research and development expenses increased by 2% during 2015 compared to 2014. The increase was primarily due to increases of $5.6 million related to manufacturing and preclinical activities for RTA 901 and $0.8 million related to clinical activities for bardoxolone methyl in PAH and PH-ILD, a net decrease of $3.8 million related to the completion of clinical activities on our topical programs and the launch of clinical activities for omaveloxolone in FA and MM and a decrease of $1.8 million related to reduced molecule discovery work in order to focus on preclinical activities for RTA 901.

General and Administrative Expenses

General and administrative expenses increased by 21% during 2016 compared to 2015. The increase was primarily due to $1.4 million in personnel and consulting expense to support growth in our development activities, $0.7 million in insurance coverage in connection with being a public company and in product liability for additional clinical trial activities, and $0.6 million in commercial research consulting activities.

General and administrative expenses increased by 19% during 2015 compared to 2014. The increase was primarily due to $1.0 million in legal and accounting expenses incurred in connection with our preparations for our initial public offering, $0.7 million in stock compensation expense related to the term modification and forgiveness of a board director's promissory note and term modifications of other promissory notes, and $0.5 million in personnel expense to support growth in our development activities.

Investment Income

Investment income increased 569% during 2016 compared to 2015. The increase was primarily due to investment and interest income earned on cash equivalents and shareholder notes receivable. The year-over-year change in investment income was immaterial during 2015.

(Benefit) Provision for Taxes on (Loss) Income

The year-over-year changes in (benefit) provision for taxes on (loss) income during 2016 and 2015 were due to differences in income generated and changes in the valuation allowance.

Liquidity and Capital Resources

Since our inception, we have funded our operations primarily through collaboration and license agreements and the sale of preferred stock. To date, we have raised gross cash proceeds of $476.6 million through the sale of convertible preferred stock and $750.0 million from payments under license and collaboration agreements. We also obtained $60.9 million in net proceeds from our initial public offering of our Class A common stock. We have not generated any revenue from the sale of any products. As of December 31, 2016, we had available cash and cash equivalents of approximately $84.7 million. Our cash and cash equivalents are invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation.

Cash Flows

The following table sets forth the primary sources and uses of cash for the years ended December 31:

	2016	2015	2014
		(in thousands)	
Net cash (used in) provided by:			
Operating activities	$ (19,259)	$ (44,620)	$ (88,630)
Investing activities	(339)	(260)	(140)
Financing activities	62,322	(870)	1
Net change in cash and cash equivalents	$ 42,724	$ (45,750)	$ (88,769)

Operating Activities

Net cash used by operating activities was $19.3 million for the year ended December 31, 2016, consisting primarily of net loss of $6.2 million adjusted for non-cash items including stock-based compensation expense of $2.4 million, depreciation expense of $0.7 million, and a net decrease in operating assets and liabilities of $16.2 million. The significant items in the change in operating assets and liabilities include an increase of prepaid expenses and other current assets of $1.7 million due to prepayments on trial and other operating expenses and reimbursements due from KHK, an increase in accrued direct research and other current liabilities of $3.1 million due to clinical trial activities, a decrease in income tax receivable of $31.9 million due to tax refunds received, and a decrease in deferred revenue of $49.7 million. The decrease in deferred revenue relates to the timing of upfront payments and ratable recognition of revenue over the expected term of the performance obligations under our collaboration agreements with AbbVie and KHK, resulting in recognition of $49.7 million of license and milestone revenue.

Net cash used in operating activities was $44.6 million for the year ended December 31, 2015, consisting primarily of net loss of $1.5 million adjusted for non-cash items including provision of deferred taxes on income of $17.8 million, stock-based compensation of $2.1 million, depreciation expense of $1.8 million, and a net decrease in operating assets and liabilities of $64.8 million. The significant items in the change in operating assets and liabilities include an increase in tax income tax receivable of $17.9 million due to carrying back 2015 losses to realize tax benefits, an increase in accounts payable of $2.8 million due to timing of vendor payments, and a decrease in deferred revenue of $49.6 million. The decrease in deferred revenue related to the timing of upfront payments and ratable recognition of revenue over the expected term of the performance obligations under our collaboration agreements with AbbVie and KHK, resulting in recognition of $49.6 million.

Net cash used in operating activities was $88.6 million for the year ended December 31, 2014, consisting primarily of net income of $0.7 million adjusted for non-cash items including increase in provision for deferred taxes of $18.3 million, depreciation expense of $2.5 million, stock-based compensation expense of $1.5 million, net loss on disposal of fixed assets of $0.2 million and a net decrease in operating assets and liabilities of $111.8 million. The significant items in the change in operating assets and liabilities include a decrease in accrued taxes of $61.1 million and a decrease in deferred revenue of $50.7 million. The decrease in deferred revenue relates to the timing of upfront payments and ratable recognition of revenue over the expected term of the performance obligations under our collaboration agreements with AbbVie and KHK, resulting in recognition of $50.7 million of license and milestone revenue. The decrease in accrued taxes is primarily due to the timing of payments made during 2014.

Investing Activities

Net cash used in investing activities consisted of purchases and sales of property and equipment. Net cash used in investing activities for the years ended December 31, 2016, 2015 and 2014 were $0.3 million, $0.3 million and $0.1 million, respectively.

Financing Activities

Net cash provided in financing activities for the year ended December 31, 2016, primarily consisted of $64.7 million from proceeds of our initial public offering, offset by $2.6 million in payments on deferred offering costs. Net cash used in financing activities for the year ended December 31, 2015, primarily consisted of payments on deferred offering costs of $0.9 million. Net cash provided in financing activities for the year ended December 31, 2014, was not significant.

Operating Capital Requirements

To date, we have not generated any revenue from product sales. We do not know when or whether we will generate any revenue from product sales. We do not expect to generate significant revenue from product sales unless and until we obtain regulatory approval of and commercialize one or more of our current or future product candidates. We anticipate that we will continue to generate losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. We are subject to all the risks related to the development and commercialization of novel therapeutics, and we may encounter unforeseen expenses, difficulties, complications, delays, and other unknown factors that may adversely affect our business. We expect to incur additional costs associated with operating as a public company. We anticipate that we will need substantial additional funding in connection with our continuing operations.

We believe our existing cash and cash equivalents, not including expected receipts from our collaborations, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 months.

Our longer term liquidity requirements are likely to require us to raise additional capital, such as through additional equity or debt financings. Our future capital requirements will depend on many factors, including the receipt of milestones under our current collaboration agreements and the timing of our expenditures related to clinical trials. In addition, we may choose to raise additional capital at any time for the further development of our existing product candidates and may also need to raise additional funds sooner to pursue other development activities related to additional product candidates. Decisions about the timing or nature of any financing will rely on, among other things, our perception of our liquidity and of the market opportunity to raise equity or debt. Additional securities may include common stock, preferred stock, or debt securities.

Until we can generate a sufficient amount of revenue from our product candidates, if ever, we expect to finance future cash needs through public or private equity or debt offerings. Additional capital may not be available on reasonable terms, if at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back, or discontinue the development or commercialization of one or more of our product candidates. If we raise additional funds through the issuance of additional equity or debt securities, it could result in dilution to our existing stockholders or increased fixed payment obligations, and any such securities may have rights senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell, or license intellectual property rights, and other operating restrictions that could adversely affect our ability to conduct our business, and any such debt could be secured by some or all of our assets. Any of these events could significantly harm our business, financial condition, and prospects.

Our forecast of the period through which our financial resources will be adequate to support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements, both near- and long-term, will depend on many factors, including, but not limited to:

- the scope, rate of progress, results and cost of our clinical trials, preclinical testing, and other activities related to the development of our product candidates;
- the number and characteristics of product candidates that we pursue;
- the costs of development efforts for our product candidates that are not subject to reimbursement from our collaborators;
- the costs necessary to obtain regulatory approvals, if any, for our product candidates in the United States and other jurisdictions, and the costs of post-marketing studies that could be required by regulatory authorities in jurisdictions where approval is obtained;
- the continuation of our existing collaborations and entry into new collaborations and the receipt of any collaboration payments;
- the time and unreimbursed costs necessary to commercialize products in territories in which our product candidates are approved for sale;
- the revenue from any future sales of our products for which we are entitled to a profit share, royalties and milestones;
- the level of reimbursement or third-party payor pricing available to our products;
- the costs of obtaining third-party commercial supplies of our products, if any, manufactured in accordance with regulatory requirements;
- the costs associated with being a public company; and
- the costs we incur in the filing, prosecution, maintenance, and defense of our extensive patent portfolio and other intellectual property rights.

If we cannot expand our operations or otherwise capitalize on our business opportunities because we lack sufficient capital, our business, financial condition, and results of operations could be materially adversely affected.

Contractual Obligations and Commitments

Contractual Obligations

As of December 31, 2016, our contractual obligations were as follows:

	Payments due by period			
	Less than 1 year	1 to 2 years	Thereafter	Total
	(in thousands)			
Operating lease obligations	$ 596	$ 509	$ —	$ 1,105
Capital lease obligations	45	—	—	45
Total contractual obligations	$ 641	$ 509	$ —	$ 1,150

Clinical Trials

As of December 31, 2016, we have several on-going clinical trials in various stages. Under agreements with various CROs and clinical trial sites, we incur expenses related to clinical trials of our product candidates and potential other clinical candidates. The timing and amounts of these disbursements are contingent upon the achievement of certain milestones, patient enrollment and services rendered or as expenses are incurred by the CROs or clinical trial sites. Therefore we cannot estimate the potential timing and amount of these payments and they have been excluded from the table above.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to revenue recognition, accrued research and development expenses, income taxes, and stock-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 of Notes to Consolidated Financial Statements appearing elsewhere in this Annual Report, we believe the following accounting policies to be most critical to understanding the judgments and estimates used by management in the preparation of our financial statements.

Revenue Recognition

We currently recognize revenue generated through collaborative licensing agreements with KHK and AbbVie. The KHK agreement and the AbbVie license agreement provide for exclusive licenses to develop and commercialize bardoxolone methyl in certain territories, and participation on respective joint steering committees. The terms of the agreements include payments to us of nonrefundable, up-front license fees; milestone payments; and royalties on product sales. Our collaboration agreement with AbbVie provides for exclusive licenses to collaborate in the research, development, and worldwide commercialization of targeted Nrf2 activators and to participate on respective joint steering committees. The terms of the agreement include a nonrefundable, up-front payment.

We recognize revenue of nonrefundable, up-front license fees and other payments when persuasive evidence that an arrangement exists, services have been rendered or delivery has occurred, the price is fixed and determinable, collection is reasonably assured, and there are no further performance obligations under the agreement. All three of the agreements are multiple-element arrangements. Multiple-element arrangements are analyzed to determine whether the various performance obligations, or elements, can be separated or whether they must be accounted for as a single unit of accounting.

For arrangements entered into prior to January 1, 2011, the following criteria were required to be met in order to separate the elements of the arrangement into different units of accounting:

1. The delivered item or items have value to the customer on a stand-alone basis.
2. There is objective and reliable evidence of fair value of the undelivered item or items.
3. If the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item or items is considered probable and substantially in the control of the vendor.

Both the KHK agreement and the AbbVie license agreement were executed prior to January 1, 2011, and contained both delivered and undelivered elements in the arrangements. We view the key elements of these arrangements as being the exclusive licenses to KHK and AbbVie and participation on joint steering committees. Our involvement in the joint steering committees established under each of these agreements was assessed to determine whether the involvement is an obligation or a right to participate. Based on this assessment, we concluded that involvement in the joint steering committees was a substantive deliverable of the arrangement. We concluded that objective and reliable evidence of the fair value of the undelivered element of these arrangements (participation on joint steering committees) did not exist; therefore, we are accounting for these arrangements as a single unit of accounting.

We are recognizing revenue associated with the nonrefundable, up-front license fees received under the KHK agreement and the AbbVie license agreement ratably over the expected term of the joint steering committee performance obligations, which we estimate will be delivered through December 2021 and November 2017 for the KHK agreement and the AbbVie license agreement, respectively. We continue to participate in regular meetings for the joint steering committees established under the KHK agreement and the AbbVie license agreement. At this time, we believe our participation in these committees continues to be a substantive performance obligation of the agreements and has concluded that no changes in the estimated revenue recognition periods are warranted. Deferred revenue arises from the excess of cash received over cumulative revenue recognized over the terms of our continuing obligations.

Both the KHK agreement and the AbbVie license agreement contain certain clinical development, regulatory, and sales milestones. We evaluated each of these milestones at inception of the respective arrangements and concluded that they were substantive milestones, and accordingly, we will recognize payments related to the achievement of such milestones, if any, when milestones or net sales levels are achieved and collection is reasonably assured. Factors considered in this determination included scientific and regulatory risks that must be overcome to achieve each milestone, the level of effort and investment required to achieve each milestone, and the monetary value attributed to each milestone.

In October 2009, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2009-13, *Multiple-Deliverable Revenue Arrangements*, which amended Accounting Standards Codification, or ASC, 605-25, *Revenue Recognition*, to eliminate the requirement to obtain vendor-specific objective evidence of the fair value of undelivered elements in order to separate the deliverables into different units of accounting. We adopted this revised guidance as of January 1, 2011, and applied this guidance to the collaboration agreement with AbbVie executed in December 2011. This guidance is also required to be applied to any material modifications that may be made to the existing KHK agreement or AbbVie license agreement, of which there were none in 2016 or 2015. We identified the following deliverables within the collaboration agreement with AbbVie:

- The various exclusive, co-exclusive, and non-exclusive license grants to AbbVie by us related to our molecules and to jointly discovered new molecules and to us by AbbVie related to jointly discovered new molecules;
- The substantive participation in the joint research and development incubator committee established by the agreement; and
- The collaboration agreement to jointly develop and commercialize second-generation Nrf2 activators, including participation in the joint executive committee, joint development committees, and joint marketing committees established by the agreement.

We evaluated the deliverables within the collaboration agreement with AbbVie and concluded that the only delivered element of the arrangement, the license grants, does not have value to AbbVie on a stand-alone basis. Accordingly, we concluded that the various elements of the arrangement cannot be separated into different units of accounting. Therefore, we are recognizing revenue associated with the nonrefundable, up-front payment over the estimated 15-year term necessary to execute the joint research, development, and commercialization terms under the agreement.

Research and Development Costs

All research and development costs are expensed as incurred, including costs for drug supplies used in research and development or clinical trials, property and equipment acquired specifically for a finite research and development project, and nonrefundable deposits incurred at the initiation of research and development activities. Research and development costs consist principally of costs related to clinical trials managed directly by the Company and through contract research organizations, manufacture of clinical drug products for clinical trials, preclinical study costs, discovery research expenses, facilities costs, salaries, and related expenses.

As part of the process of recording research and development costs, we are required to estimate and accrue expenses, the largest of which are research and development expenses. This process involves the following:

- communicating with appropriate internal personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost;
- estimating and accruing expenses in our consolidated financial statements as of each balance sheet date based on facts and circumstances known to us at the time; and
- periodically confirming the accuracy of our estimates with service providers and making adjustments, if necessary.

Examples of estimated research and development expenses that we accrue include:

- payments to CROs in connection with preclinical and toxicology studies and clinical trials;
- payments to investigative sites in connection with clinical trials;
- payments to contract manufacturing organizations, or CMOs, in connection with the production of clinical trial materials; and
- professional service fees for consulting and related services.

We base our expense accruals related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple research institutions and CROs that conduct and manage clinical trials on our behalf. The financial terms of these agreements vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing costs, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If we do not identify costs that we have begun to incur or if we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates.

To date, we have not experienced significant changes in our estimates of accrued research and development expenses after a reporting period. However, due to the nature of estimates, we cannot assure you that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical trials and other research activities.

Income Taxes

We account for income taxes and the related accounts under the liability method. Deferred tax assets and liabilities are determined based on differences between the financial statement and tax bases of assets and liabilities, and are measured using the enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. The measurement of a deferred tax asset is reduced, if necessary, by a valuation allowance if it is more likely than not that some portion or all of the deferred tax asset will not be realized.

Realization of deferred tax assets is generally dependent upon future earnings, if any, the timing and amount of which are uncertain. However, with taxable income reported in 2013 and our continued taxable losses in 2014 and 2015, we were able to carry back losses from 2014 and 2015. As of December 31, 2016, based on known factors, the Company cannot conclude that it is more likely than not that the remaining deferred tax assets will be utilized and has recorded a valuation allowance to fully offset its deferred tax assets.

We account for uncertain tax positions in accordance with the provisions of ASC 740, *Income Taxes*. We recognize a tax benefit for uncertain tax positions if we believe it is more likely than not that the position will be upheld on audit based solely on the technical merits of the tax position. We evaluate uncertain tax positions after consideration of all available information.

Stock-Based Compensation

We measure and recognize compensation expense for all stock options and restricted stock awards based on the estimated fair value of the award on the grant date. We use the Black-Scholes option pricing model to estimate the fair value of stock option awards. The fair value is recognized as expense, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award, on a straight-line basis when the only condition to vesting is continued service. If vesting is subject to a market or performance condition, recognition is based on the derived service period of the award. Expense for awards with performance conditions is estimated and adjusted on a quarterly basis based upon the assessment of the probability that the performance condition will be met. Use of the Black-Scholes option-pricing model requires management to apply judgment under highly subjective assumptions. These assumptions include:

- *Expected term* —The expected term represents the period that the stock-based awards are expected to be outstanding and is based on the average period the stock options are expected to be outstanding and was based on our historical information of the options exercise patterns and post-vesting termination behavior.
- *Expected volatility* —Since we are privately held and do not have any trading history for our common stock, the expected volatility was estimated based on the average volatility for comparable publicly traded biopharmaceutical companies. When selecting comparable publicly traded biopharmaceutical companies on which we based our expected stock price volatility, we selected companies with comparable characteristics to us, including enterprise value, risk profiles, position within the industry, and historical share price information sufficient to meet the expected life of the stock-based awards.
- *Risk-free interest rate* —The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.
- *Expected dividend* —We have no plans to pay dividends on our common stock. Therefore, we used an expected dividend yield of zero.

In addition to the assumptions used in the Black-Scholes option-pricing model, we must also estimate a forfeiture rate to calculate the stock-based compensation for our awards. We will continue to use judgment in evaluating the expected volatility, expected terms, and forfeiture rates utilized for our stock-based compensation calculations on a prospective basis.

The weighted-average assumptions used in the Black-Scholes option pricing model were as follows:

	Years Ended December 31		
	2016	2015	2014
Dividend yield	—%	—%	—%
Volatility	72.77%	74.93%	75.21%
Risk-free interest rate	1.76%	1.71%	1.96%
Expected term of options (in years)	6.74	7.28	7.03

Common Stock Valuation

Historically, for all periods prior to our initial public offering, the exercise price of options to purchase shares of our common stock was the estimated fair market value of our common stock as determined by our board of directors. In order to determine the fair market value of our common stock underlying option grants, we considered several objective and subjective factors, including the progress of our research and development efforts, our financial condition, the valuation of other publicly-traded companies in the life sciences and biotechnology sectors at comparable stages of development, equity market conditions, the lack of marketability of our common stock, the economy generally, and timely valuations of our common stock prepared by unrelated third-party valuation firms in accordance with the guidance provided by the American Institute of Certified Public Accountants 2004 Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation* , or the Practice Aid.

Information regarding our stock option grants, along with the estimated fair value per share of the underlying common stock, for stock options granted since January 1, 2014, is summarized in the table below:

Grant date	Number of common shares underlying options granted	Exercise price per common share	Estimated fair value per share of common stock
January 15, 2014	626	$ 12.07	$ 12.07
May 1, 2014	2,388	12.07	12.07
June 1, 2014	14,106	12.07	12.07
September 15, 2014	940	13.08	13.08
November 15, 2014	313	13.08	13.08
March 3, 2015	234	17.43	17.43
April 1, 2015	39,184	17.43	17.43
April 28, 2015	940	17.43	17.43
September 1, 2015	15,085	25.52	25.52

The estimated fair value per share of the common stock in the table above represents the determination of the fair value of our common stock as of the date of the grant.

Common Stock Valuation Methodology

We determined the valuation of our common stock based on a number of factors. In addition, we obtained third-party valuations of our common stock to assist with the determination of the exercise price of our stock options and the fair value of the common stock underlying such options, as of November 30, 2013, May 31, 2014, November 30, 2014, and May 31, 2015. For each of these dates, the third party valuations utilized the probability-weighted expected return method, or the PWERM, in determining the value of the common stock. The PWERM considers various potential liquidity outcomes, including in our case an initial public offering, the sale of our company, and dissolution and assigns probabilities to each outcome to arrive at a weighted equity value. In determining liquidity outcomes and probabilities, we considered a range of objective and subjective factors and assumptions in each of the PWERM scenarios, including:

- progress of our research and development efforts;
- our financial condition, including our levels of available capital resources;
- the valuation of publicly-traded companies in the life sciences and biotechnology sectors at comparable stages of development, as well as recently completed initial public offerings and mergers and acquisitions of similar companies; and
- equity market conditions.

In the November 30, 2013 valuation, we considered three scenarios, an IPO scenario, a sale or merger scenario, and a dissolution scenario. The IPO and sale or merger scenarios were both estimated to occur three years and one month from the time of the valuation with a probability of 25% each. The dissolution scenario was estimated to occur two years from the time of valuation with a probability of 50%. The risk adjusted discount rate was 25% for each scenario.

In the May 31, 2014 valuation, we considered three scenarios, an IPO scenario, a sale or merger scenario, and a dissolution scenario. The IPO and sale or merger scenarios were both estimated to occur two-and-a-half years from the time of the valuation with a probability of 25% each. The dissolution scenario was estimated to occur two years from the time of valuation with a probability of 50%. The risk adjusted discount rate was 25% for each scenario.

In the November 30, 2014 valuation, we considered four scenarios, two IPO scenarios, a sale or merger scenario, and a dissolution scenario. The first IPO scenario was estimated to occur eleven months from the time of the valuation with a probability of 30%. The second IPO scenario was estimated to occur fifteen months from the time of the valuation with a probability of 30%. The merger or sale scenario was estimated to occur eighteen months from the time of the valuation with probability of 20%. The dissolution scenario was estimated to occur a year-and-a-half from the time of the valuation with a probability of 20%. The risk adjusted discount rate was 25% for each scenario.

In the May 31, 2015 valuation, we considered four scenarios, two IPO scenarios, and two sale or merger scenarios. The first IPO scenario was estimated to occur eight months from the time of the valuation with a probability of 35%, and the second IPO scenario was estimated to occur five months from the time of the valuation a probability of 45%. The first merger or sale scenario was estimated to occur thirteen months from the time of the valuation with a probability of 10%, and the second merger or sale scenario was estimated to occur twenty-seven months from the time of the valuation with a probability of 10%. The risk adjusted discount rate was 25% for each scenario.

Off-Balance Sheet Arrangements

Since our inception, we have not had any relationships with unconsolidated organizations or financial partnerships, such as structured finance or special purpose entities that would have been established for the purpose of facilitating off-balance sheet arrangements, and we have not engaged in any other off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Recent Accounting Pronouncements

For a discussion of recent accounting pronouncements, please see Note 2 of Notes to Consolidated Financial Statements contained in this Annual Report on Form 10-K.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations. We had cash and cash equivalents of $84.7 million at December 31, 2016, consisting primarily of funds in operating cash accounts. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 1.0% increase in interest rates would have a material effect on the fair market value of our portfolio, and accordingly we do not expect a sudden change in market interest rates to affect materially our operating results or cash flows.

We contract with research, development, and manufacturing organizations and investigational sites globally. Generally, these contracts are denominated in U.S. dollars. However, we may be subject to fluctuations in foreign currency rates in connection with agreements not denominated in U.S. dollars. We do not hedge our foreign currency exchange rate risk.

Item 8. Financial Statements and Supplementary Data.

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report. An index of those financial statements is found in Item 15.

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 the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2016. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financials officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2016, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by the Jumpstart Our Business Startups Act, or JOBS Act, for emerging growth companies.

Changes in Internal Control Over Financial Reporting

There have been no change in our internal control over financial reporting during the year ended December 31, 2016, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 11. Executive Compensation.

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

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

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

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

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 14. Principal Accounting Fees and Services.

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) The following documents are filed as a part of the report:

(1) Financial Statements
Report of Independent Registered Public Accounting Firm
Consolidated Balance Sheets
Consolidated Statements of Operations
Consolidated Statements of Stockholders' Deficit
Consolidated Statements of Cash Flows
Notes to Consolidated Financial Statements

(2) Schedules have been omitted as all required information has been disclosed in the financial statements and related footnotes.

(3) The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following our consolidated financial statements. The Exhibit Index is incorporated herein by reference.

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, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

REATA PHARMACEUTICALS, INC.

Date: March 2, 2017

By: /s/ J. Warren Huff
J. Warren Huff
President and Chief Executive Officer

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

Name	Title	Date
/s/ J. Warren Huff J. Warren Huff	President, Chief Executive Officer and Chairman of the Board of Directors (*Principal Executive Officer*)	March 2, 2017
/s/ Jason D. Wilson Jason D. Wilson	Chief Financial Officer (*Principal Financial Officer*)	March 2, 2017
/s/ Elaine Castellanos Elaine Castellanos	Vice President, Finance and Accounting (*Principal Accounting Officer*)	March 2, 2017
/s/ James E. Bass James E. Bass	Member of the Board of Directors	March 2, 2017
/s/ William D. McClellan, Jr. William D. McClellan, Jr.	Member of the Board of Directors	March 2, 2017
/s/ R. Kent McGaughy, Jr. R. Kent McGaughy, Jr.	Member of the Board of Directors	March 2, 2017
/s/ Jack B. Nielsen Jack B. Nielsen	Member of the Board of Directors	March 2, 2017
/s/ William E. Rose William E. Rose	Member of the Board of Directors	March 2, 2017

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Reata Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Reata Pharmaceuticals, Inc. (the "Company") as of December 31, 2016 and 2015, and the related consolidated statements of operations, stockholders' deficit and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Reata Pharmaceuticals, Inc. at December 31, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP
Dallas, Texas
March 2, 2017

Reata Pharmaceuticals, Inc.

Consolidated Balance Sheets
(in thousands, except share data)

	December 31,	
	2016	2015
Assets		
Cash and cash equivalents	$ 84,732	$ 42,008
Federal income tax receivable	—	31,926
Prepaid expenses and other current assets	2,551	3,325
Total current assets	87,283	77,259
Property and equipment, net	819	1,142
Other assets	991	553
Total assets	$ 89,093	$ 78,954
Liabilities and stockholders' deficit		
Accounts payable	$ 3,830	$ 3,531
Accrued direct research liabilities	6,151	3,975
Other current liabilities	3,047	3,584
Current portion of deferred revenue	46,603	49,730
Total current liabilities	59,631	60,820
Other long-term liabilities	72	249
Deferred revenue, net of current portion	244,438	291,041
Total noncurrent liabilities	244,510	291,290
Commitments and contingencies		
Stockholders' deficit:		
Common stock A, $0.001 par value: 500,000,000 shares authorized; issued and outstanding – 11,687,974 and 0 shares at December 31, 2016 and December 31, 2015, respectively	12	—
Common stock B, $0.001 par value: 150,000,000 shares authorized; issued and outstanding – 10,656,920 and 15,998,106 shares at December 31, 2016 and December 31, 2015, respectively	11	16
Additional paid-in capital	74,298	10,036
Shareholder notes receivable	(15)	(81)
Accumulated deficit	(289,354)	(283,127)
Total stockholders' deficit	(215,048)	(273,156)
Total liabilities and stockholders' deficit	$ 89,093	$ 78,954

See accompanying notes.

Reata Pharmaceuticals, Inc.

Consolidated Statements of Operations
(in thousands, except share and per share data)

	Years Ended December 31		
	2016	2015	2014
Collaboration revenue			
License and milestone	$ 49,730	$ 50,295	$ 51,368
Other revenue	126	24	586
Total collaboration revenue	49,856	50,319	51,954
Expenses:			
Research and development	39,453	35,141	34,305
General and administrative	16,603	13,693	11,512
Depreciation and amortization	682	1,819	2,512
Total expenses	56,738	50,653	48,329
Other income:			
Investment income	214	32	43
Total other income	214	32	43
(Loss) income before provision for taxes on income	(6,668)	(302)	3,668
(Benefit) provision for taxes on income	(441)	1,148	2,979
Net (loss) income	$ (6,227)	$ (1,450)	$ 689
Net (loss) income per share—basic	$ (0.31)	$ (0.09)	$ 0.04
Net (loss) income per share—diluted	$ (0.31)	$ (0.09)	$ 0.04
Weighted-average number of common shares used in net (loss) income per share basic	19,816,635	15,974,974	15,950,023
Weighted-average number of common shares used in net (loss) income per share diluted	19,816,635	15,974,974	15,979,768

See accompanying notes.

Reata Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Deficit
(in thousands, except share and per share data)

	Common Stock A		Common Stock B		Additional Paid-In	Shareholder Notes	Total Accumulated	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Receivable	Deficit	(Deficit) Equity
Balance at January 1, 2014	—	$ —	15,994,877	$ 16	$ 5,601	$ (307)	$ (282,366)	$ (277,056)
Compensation expense related to stock option and restricted stock	—	—	—	—	1,523	—	—	1,523
Exercise of options	—	—	82	—	1	—	—	1
Vesting of prepaid restricted stock	—	—	—	—	597	—	—	597
Net income	—	—	—	—	—	—	689	689
Balance at December 31, 2014	—	—	15,994,959	16	7,722	(307)	(281,677)	(274,246)
Compensation expense related to stock option and restricted stock	—	—	—	—	1,331	—	—	1,331
Cancelation and modification of shareholder notes receivable	—	—	—	—	480	226	—	706
Exercise of options	—	—	3,147	—	39	—	—	39
Vesting of prepaid restricted stock	—	—	—	—	464	—	—	464
Net loss	—	—	—	—	—	—	(1,450)	(1,450)
Balance at December 31, 2015	—	—	15,998,106	16	10,036	(81)	(283,127)	(273,156)
Compensation expense related to stock option and restricted stock	—	—	—	—	2,367	—	—	2,367
Exercise of options	—	—	21,788	1	4	—	—	5
Vesting of prepaid restricted stock	—	—	—	—	464	—	—	464
Proceeds from payments of shareholder promissory notes	—	—	—	—	199	66	—	265
Initial public offering of common stock, net of offering costs	6,325,000	6	—	—	61,228	—	—	61,234
Conversion of common stock Class B to Class A	5,362,974	6	(5,362,974)	(6)	—	—	—	—
Net loss	—	—	—	—	—	—	(6,227)	(6,227)
Balance at December 31, 2016	11,687,974	$ 12	10,656,920	$ 11	$ 74,298	$ (15)	$ (289,354)	$ (215,048)

See accompanying notes.

Reata Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Years Ended December 31		
	2016	2015	2014
Operating activities			
Net (loss) income	$ (6,227)	$ (1,450)	$ 689
Adjustments to reconcile net (loss) income to net cash used in operating activities:			
Depreciation and amortization	682	1,819	2,512
Stock-based compensation expense	2,367	2,075	1,523
Provision for deferred taxes on income	—	17,802	18,316
Loss on disposal of property and equipment	—	2	203
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(1,218)	81	(791)
Other assets	(438)	281	(532)
Accounts payable	299	2,754	(1,656)
Accrued direct research and other current liabilities	3,080	(486)	2,925
Federal income tax receivable/payable	31,926	(17,903)	(61,127)
Deferred revenue	(49,730)	(49,595)	(50,692)
Net cash used in operating activities	(19,259)	(44,620)	(88,630)
Investing activities			
Sales/disposals of fixed assets	1	12	43
Purchases of property and equipment	(340)	(272)	(183)
Net cash used in investing activities	(339)	(260)	(140)
Financing activities			
Proceeds from issuance of common stock from initial public offering, net of issuance costs	64,705	—	—
Payments on deferred offering costs	(2,607)	(864)	—
Exercise of options and related tax withholdings	4	39	1
Proceeds from payments of shareholder promissory notes	265	—	—
Payment of capital lease obligation	(45)	(45)	—
Net cash provided by (used in) financing activities	62,322	(870)	1
Net increase (decrease) in cash and cash equivalents	42,724	(45,750)	(88,769)
Cash and cash equivalents at beginning of year	42,008	87,758	176,527
Cash and cash equivalents at end of period	$ 84,732	$ 42,008	$ 87,758
Supplemental disclosures			
Income taxes paid	$ —	$ 1,249	$ 59,500
Purchases of equipment in accounts payable and other current liabilities	$ 20	$ 187	$ —
Accrued deferred offering costs	$ —	$ 1,129	$ —
Equipment acquired under capital lease	$ —	$ —	$ 135

See accompanying notes.

1. Description of Business

Reata Pharmaceuticals, Inc., or the Company, is a clinical stage biopharmaceutical company located in Irving, Texas focused on identifying, developing, and commercializing product candidates to address rare and life-threatening diseases with few or no approved therapies by targeting molecular pathways that regulate cellular metabolism and inflammation. The Company operates as a single segment of business.

The Company's lead product candidates, bardoxolone methyl and omaveloxolone, are Nrf2 activators, previously referred to as antioxidant inflammation modulators, or AIMs, that target Nrf2, an important transcription factor, to restore mitochondrial function, reduce oxidative stress, and resolve inflammation. Bardoxolone methyl is in Phase 3 clinical development for the treatment of pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH), and Phase 2 clinical development for the treatment of pulmonary hypertension due to interstitial lung disease and pulmonary arterial hypertension, each of which are subsets of pulmonary hypertension (PH). The Company began enrolling patients in its Phase 3 trial in CTD-PAH in October 2016. In addition, bardoxolone methyl is being studied in a single, pivotal Phase 2/3 trial in chronic kidney disease caused by Alport syndrome, in which the Company began enrolling patients on March 2, 2017. Omaveloxolone is being studied in separate two-part Phase 2 trials for the treatment of Friedreich's ataxia, or FA, and mitochondrial myopathies, or MM, known as MOXIe and MOTOR, respectively. The Company has completed enrollment of part one in MOXIe and is currently dosing patients in part one of MOTOR, which are dose ranging. Data from part two of each of the trials has the potential to be used for registration. Omaveloxolone is also being studied in a Phase 1b/2 for the treatment of metastatic melanoma, known as REVEAL. In addition to its lead product candidates, the Company is in Phase 1 development for RTA 901. Beyond our clinical programs, the Company has additional promising preclinical development programs. The Company believes its product candidates and preclinical programs have the potential to improve clinical outcomes in numerous underserved patient populations.

The Company's consolidated financial statements include the accounts of all majority-owned subsidiaries that are required to be consolidated. Accordingly, the Company's share of net earnings and losses from these subsidiaries is included in the consolidated statements of operations. Intracompany profits, transactions, and balances have been eliminated in consolidation.

On January 6, 2016, the Company effected a 4.4-to-1 reverse split of its common stock, and an automatic conversion of its common stock into Class B common stock. Upon the effectiveness of the reverse stock split and conversion, (i) every 4.4 shares of outstanding common stock were combined into one share of Class B common stock, (ii) the number of shares of common stock for which each outstanding option to purchase common stock is exercisable was proportionally decreased on a 4.4-to-1 basis and converted into an option to purchase Class B common stock, and (iii) the exercise price of each outstanding option to purchase common stock was proportionately increased on a 4.4-to-1 basis. All of the outstanding common stock share numbers, common stock options, share prices, exercise prices, and per share amounts have been adjusted in these consolidated financial statements, on a retroactive basis, to reflect this 4.4-to-1 reverse stock split for all periods presented. The par value per share was not adjusted as a result of the reverse stock split.

On May 11, 2016, the Company effected a 1.45-to-1 reverse split of its common stock. Upon the effectiveness of the reverse stock split, (i) every 1.45 shares of outstanding common stock were combined into one share of common stock of the same class, (ii) the number of shares of common stock for which each outstanding option to purchase common stock is exercisable was proportionally decreased on a 1.45-to-1 basis, and (iii) the exercise price of each outstanding option to purchase common stock was proportionately increased on a 1.45-to-1 basis. All of the outstanding common stock share numbers, common stock options, share prices, exercise prices, and per share amounts have been adjusted in these consolidated financial statements, on a retroactive basis, to reflect this 1.45-to-1 reverse stock split for all periods presented. The par value per share was not adjusted as a result of the reverse stock split.

On May 25, 2016, the Company's registration statement on Form S-1 (File No. 333-208843) relating to its initial public offering (IPO), of its common stock was declared effective by the U.S. Securities and Exchange Commission (SEC). The shares began trading on The NASDAQ Global Market on May 26, 2016. The public offering price of the shares sold in the offering was $11.00 per share. The IPO closed on June 1, 2016 for 6,325,000 shares of its Class A common stock, which included 825,000 shares of its Class A common stock issued pursuant to the over-allotment option granted to the underwriters. The Company received total proceeds from the offering of $60.9 million, net of underwriting discounts and commissions and offering expenses.

2. Summary of Significant Accounting Policies

Revenue Recognition

The Company has license agreements with AbbVie Inc. (AbbVie) (the AbbVie License Agreement) and Kyowa Hakko Kirin Co., Ltd. (KHK) (the KHK Agreement), under which AbbVie and KHK were granted exclusive licenses to develop and commercialize bardoxolone methyl in the Territory (as defined in the KHK Agreement) and the Licensed Territory (as defined in the AbbVie License Agreement). The terms of the agreements include payments to the Company of nonrefundable, up-front license fees; milestone payments; and royalties on product sales.

The Company has a collaboration agreement with AbbVie (the AbbVie Collaboration Agreement) that provides for exclusive licenses to collaborate in the research, development, and worldwide commercialization of targeted Nrf2 activators and to participate on respective joint steering committees. The terms of the agreements include a nonrefundable, up-front payment.

The Company recognizes revenue of nonrefundable, up-front license fees and other payments when persuasive evidence that an arrangement exists, services have been rendered or delivery has occurred, the price is fixed and determinable, collection is reasonably assured, and there are no further performance obligations under the agreement.

The AbbVie License Agreement, the AbbVie Collaboration Agreement, and the KHK Agreement are all multiple-element arrangements. Multiple-element arrangements are analyzed to determine whether the various performance obligations, or elements, can be separated or whether they must be accounted for as a single unit of accounting.

For arrangements entered into prior to January 1, 2011, the following criteria were required to be met in order to separate the elements of the arrangement into different units of accounting:

1. The delivered item or items have value to the customer on a stand-alone basis.
2. There is objective and reliable evidence of fair value of the undelivered item or items.
3. If the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item or items is considered probable and substantially in the control of the vendor.

Both the AbbVie License Agreement and the KHK Agreement were executed prior to January 1, 2011, and contained both delivered and undelivered elements in the arrangements. The Company views the key elements of these arrangements as being the exclusive licenses to AbbVie and KHK and participation on joint steering committees. The Company's involvement in the joint steering committees established under each of these agreements was assessed to determine whether the involvement is an obligation or a right to participate. Based on this assessment, the Company concluded that involvement in the joint steering committees was a substantive deliverable of the arrangement. The Company concluded that objective and reliable evidence of the fair value of the undelivered element of these arrangements (participation on joint steering committees) did not exist; therefore, the Company is accounting for these arrangements as a single unit of accounting.

The Company is recognizing revenue associated with the nonrefundable, up-front license fees received under the AbbVie License Agreement and the KHK Agreement ratably over the expected term of the joint steering committee performance obligations, which the Company estimates will be delivered through December 2021 and November 2017 for the KHK Agreement and the AbbVie Agreement, respectively. The Company continues to participate in regular meetings for the joint steering committees established under the AbbVie License Agreement and the KHK Agreement. At this time, the Company believes its participation in these committees continues to be a substantive performance obligation of the agreements and has concluded that no changes in the estimated revenue recognition periods are warranted. Deferred revenue arises from the excess of cash received over cumulative revenue recognized over the terms of the Company's continuing obligations.

Both the AbbVie License Agreement and the KHK Agreement contain certain clinical development, regulatory, and sales milestones. The Company evaluated each of these milestones at inception of the respective arrangements and concluded that they were substantive milestones, and accordingly, the Company will recognize payments related to the achievement of such milestones, if any, when milestones or net sales levels are achieved and collection is reasonably assured. Factors considered in this determination included scientific and regulatory risks that must be overcome to achieve each milestone, the level of effort and investment required to achieve each milestone, and the monetary value attributed to each milestone.

In October 2009, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2009-13, *Multiple-Deliverable Revenue Arrangements* , which amended Accounting Standards Codification (ASC) 605-25, *Revenue Recognition* , to eliminate the requirement to obtain vendor-specific objective evidence of the fair value of undelivered elements in order to separate the deliverables into different units of accounting. The Company adopted this revised guidance as of January 1, 2011, and applied this guidance to the AbbVie Collaboration Agreement executed in December 2011. This guidance is also required to be applied to any material modifications that may be made to the existing AbbVie License Agreement or KHK Agreement, of which there were none in 2016, 2015, and 2014. The Company identified the following deliverables within the AbbVie Collaboration Agreement:

- The License Grants, including various exclusive, co-exclusive, and non-exclusive license grants to AbbVie by the Company related to the Company's molecules and to jointly discovered new molecules and to the Company by AbbVie related to jointly discovered new molecules;
- The Research and Exploratory Development Collaboration, including substantive participation in the Joint Research and Development Incubator Committee established by the agreement; and
- The Collaboration Agreement to jointly develop and commercialize second-generation Nrf2 activators, including participation in the Joint Executive Committee, Joint Development Committees, and Joint Marketing Committees established by the agreement.

The Company evaluated the deliverables within the AbbVie Collaboration Agreement and concluded that the only delivered element of the arrangement, the License Grants, does not have value to AbbVie on a stand-alone basis. Accordingly, the Company concluded that the various elements of the arrangement cannot be separated into different units of accounting. Therefore, the Company is recognizing revenue associated with the nonrefundable, up-front payment over the estimated 15-year term necessary to execute the joint research, development, and commercialization terms under the agreement.

The Company follows ASC 605-28, *Revenue Recognition—Milestone Method* to evaluate whether each milestone under a license agreement is substantive. This evaluation includes an assessment of whether (i) the consideration is commensurate with either (a) the entity's performance to achieve the milestone, or (b) the enhancement of the value of the delivered item as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company evaluates factors such as the preclinical, clinical, regulatory, commercial and other risks that must be overcome to achieve the respective milestone, the level of effort and investment required and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment. If a substantive milestone is achieved, the Company would recognize revenue related to the milestone in its entirety in the period in which the milestone was achieved, assuming all other revenue recognition criteria were met. Commercial milestones would be accounted for as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria were met.

In June 2013, the Company entered into a research collaboration with a disease advocacy organization. Under the agreement, the Company may be provided milestone payments to fund research and development activities estimated over a two-year period. The Company recorded collaboration revenue totaling $0, $700,000 and $700,000 related to milestone payments during the years ended December 31, 2016, 2015, and 2014, respectively.

Cash and Cash Equivalents

The Company considers all investments in highly liquid financial instruments with a maturity of three months or less when purchased to be cash equivalents. Investments qualifying as cash equivalents primarily consist of money market funds. The carrying amount of cash equivalents approximates fair value. Investment income consists primarily of interest income on our cash and cash equivalents, which include money market funds.

Research and Development Costs

All research and development costs are expensed as incurred, including costs for drug supplies used in research and development or clinical studies, property and equipment acquired specifically for a finite research and development project, and nonrefundable deposits incurred at the initiation of research and development activities. Research and development costs consist principally of costs related to clinical studies managed directly by the Company and through contract research organizations, manufacture of clinical drug products for clinical studies, preclinical study costs, discovery research expenses, facilities costs, salaries, and related expenses.

AbbVie is not currently participating in the development of bardoxolone methyl for the treatment of PH and the Company is therefore incurring all costs for this program. With respect to its omaveloxolone programs and its collaboration agreement with AbbVie, the Company was

responsible for a certain initial amount in early development costs before AbbVie began sharing development costs equally. As of April 2016, the Company had incurred all of these initial costs, after which payments from AbbVie with respect to research and development costs incurred by the Company were recorded as a reduction in research and development expenses. The Company's expenses were reduced $1,434,000 for AbbVie's share of research and development costs for the twelve months ended December 31, 2016.

In September 2016, the Company and AbbVie mutually agreed that the Company would continue unilateral development of omaveloxolone. Therefore, AbbVie no longer co-funds the exploratory development costs of this program, but retains the right to opt back in at certain points in development. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the U.S. or the Company may be responsible for commercializing the product on a worldwide basis. Upon opting back in, AbbVie would be required to pay an agreed upon amount of all development costs accumulated up to the point of exercising their opt-in right, after which development costs incurred and product revenue worldwide would be split equally.

The Company bases its expense accruals related to clinical trials on its estimates of the services received and efforts expended pursuant to contracts with multiple research institutions and contract research organizations that conduct and manage clinical trials on its behalf. The financial terms of these agreements vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing costs, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the Company does not identify costs that it has begun to incur or if the Company underestimates or overestimates the level of services performed or the costs of these services, its actual expenses could differ from its estimates.

To date, the Company has not experienced significant changes in its estimates of accrued research and development expenses after a reporting period. However, due to the nature of estimates, the Company cannot assure that it will not make changes to its estimates in the future as the Company becomes aware of additional information about the status or conduct of its clinical trials and other research activities.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation is computed using the straight-line method over the following estimated useful lives:

Computer equipment	2–5 years
Software	3 years
Laboratory equipment	5–7 years
Office furniture	5 years
Office equipment	5 years

Leasehold improvements are amortized on the straight-line method over the shorter of the lease term or the estimated useful life of the equipment or improvement. Such amortization is included in depreciation and amortization expense in the consolidated statements of operations.

Impairment of Long-Lived Assets

The Company periodically evaluates its long-lived assets for potential impairment in accordance with ASC Topic 360, *Property, Plant and Equipment*. Potential impairment is assessed when there is evidence that events or changes in circumstances indicate that the carrying amount of an asset may not be recovered. Recoverability of these assets is assessed based on undiscounted expected future cash flows from the assets, considering a number of factors, including past operating results, budgets and economic projections, market trends, and product development cycles. If impairments are identified, assets are written down to their estimated fair value. The Company has not recognized any impairment charges in 2016, 2015, and 2014.

Licenses and Patents

License and sublicense costs are expensed as incurred and are classified as research and development expenses. Costs associated with filing, prosecuting, enforcing, and maintaining patent rights are expensed as incurred and are classified as general and administrative expenses.

Income Taxes

The Company accounts for income taxes and the related accounts under the liability method. Deferred tax assets and liabilities are determined based on differences between the financial statement and tax bases of assets and liabilities, and are measured using the enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. The measurement of a deferred tax asset is reduced, if necessary, by a valuation allowance if it is more likely than not that some portion or all of the deferred tax asset will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740, *Income Taxes*. The Company recognizes a tax benefit for uncertain tax positions if the Company believes it is more likely than not that the position will be upheld on audit based solely on the technical merits of the tax position. The Company evaluates uncertain tax positions after consideration of all available information. During November 2015, the FASB issued ASU 2015-17, *Balance Sheet Classification of Deferred Taxes* (ASU 2015-17), which simplifies the presentation of deferred income taxes. The Company early adopted ASU 2015-17 effective December 31, 2015 on a prospective basis.

Stock-Based Compensation

The Company accounts for its stock-based compensation in accordance with ASC 718 *Compensation—Stock Compensation* (ASC 718). ASC 718 requires companies to measure and recognize compensation expense for all stock options and restricted stock awards based on the estimated fair value of the award on the grant date. The Company uses the Black-Scholes option pricing model to estimate the fair value of stock option awards. The fair value is recognized as expense, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award, on a straight-line basis when the only condition to vesting is continued service. If vesting is subject to a market or performance condition, recognition is based on the derived service period of the award. Expense for awards with performance conditions is estimated and adjusted on a quarterly basis based upon the assessment of the probability that the performance condition will be met. Use of the Black-Scholes option-pricing model requires management to apply judgment under highly subjective assumptions. These assumptions include:

- Expected term—The expected term represents the period that the stock-based awards are expected to be outstanding and is based on the average period the stock options are expected to be outstanding and was based on our historical information of the options exercise patterns and post-vesting termination behavior.
- Expected volatility—Since the Company was privately held and did not have any trading history for its common stock until its IPO, the expected volatility was estimated based on the average volatility for comparable publicly traded biopharmaceutical companies. When selecting comparable publicly traded biopharmaceutical companies on which the Company based its expected stock price volatility, the Company selected companies with comparable characteristics to the Company, including enterprise value, risk profiles, position within the industry, and historical share price information sufficient to meet the expected life of the stock-based awards.
- Risk-free interest rate—The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.
- Expected dividend—The Company has no plans to pay dividends on its common stock. Therefore, the company used an expected dividend yield of zero.

In addition to the assumptions used in the Black-Scholes option-pricing model, the Company must also estimate a forfeiture rate to calculate the stock-based compensation for its awards. The Company will continue to use judgment in evaluating the expected volatility, expected terms, and forfeiture rates utilized for its stock-based compensation calculations on a prospective basis.

Options to purchase shares of the Company's common stock, and restricted common stock with certain repurchase rights, have been granted or sold to nonemployees at fair value, in connection with research and consulting services provided to the Company, and to employees at fair value, in connection with Stock Purchase and Restriction Agreements. Equity awards generally vest over terms of four or five years. For awards to employees, stock-based compensation expense is recorded ratably through the vesting period for each option award or tranche of restricted stock.

The stock purchase amounts for sales of restricted common stock have been loaned by the Company to the nonemployees and employees, and the promissory notes are secured by Stock Pledge and Security Agreements. The notes are bifurcated into 75% non-recourse and 25% fully recourse portions. The Company included the following considerations in determining its treatment of the 25% portion as recourse:

- the legal provisions, which allow full recourse to shareholders' other assets, in the note,
- the Company's historical pattern of collecting payments on notes utilized to purchase restricted stock,

- the Company's historical pattern in not converting any recourse portions to nonrecourse, and
- the shareholders' having the wherewithal to pay the recourse portions of the notes.

The recourse portion of the notes and the related shares are accounted for as substantive issuances of stock, and the loans totaling $15,000 and $81,000 as of December 31, 2016 and 2015, respectively, are recorded on the consolidated balance sheet as a reduction to stockholders' equity. The remaining 75% portion of the notes is nonrecourse to the Company and is accounted for as substantive grants of stock options recorded in accordance with ASC 718. Accordingly, this portion of the notes is not recorded on the consolidated balance sheet; rather, consistent with the accounting for stock options, the Company utilized the Black-Scholes option pricing model to estimate the fair value of the award on the grant date and recognized the fair value as stock-based compensation expense over the vesting period. The carrying value of shareholder notes receivable that are treated as options and not recorded on the balance sheet was $45,000 and $244,000 at December 31, 2016 and 2015, respectively. The decreases from December 31, 2015 to December 31, 2016 in the balance of the recourse portion of the notes on the consolidated balance sheet and the carrying value of the nonrecourse portion of the notes were directly due to repayment of shareholder notes during 2016.

Risks and Uncertainties

The Company has experienced losses and negative operating cash flows for many years since inception and has no marketed drug or other products. The Company's ability to generate future revenue depends upon the results of its development programs, whose success cannot be guaranteed. The Company may need to raise additional equity capital in the future in order to fund its operations.

Use of Estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Deferred Offering Costs

Deferred offering costs, consisting of legal, accounting, and filing fees relate to the initial public offering, are capitalized. The deferred offering costs were offset against proceeds from the initial public offering. The Company capitalized $0 and $1,993,000 of deferred offering costs as of December 31, 2016 and 2015, respectively.

Net Income (Loss) per Share

Basic and diluted net income (loss) per common share is calculated by dividing net income (loss) attributable to common stockholders by the weighted average number of common shares outstanding during the period, without consideration for common stock equivalents. The Company's potentially dilutive shares, which include unvested restricted stock, and options to purchase common stock, are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive. For periods in which the Company reports a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

The Company uses the two-class method to compute net income (loss) per common share attributable to common stockholders because the Company has issued securities, other than common stock, that contractually entitle the holders to participate in dividends and earnings of the Company. The two-class method requires earnings for the period to be allocated between common stock and participating securities based upon their respective rights to receive distributed and undistributed earnings. Holders of restricted common stock are entitled to the dividend amount paid to common stockholders on an as-if-converted-to-common stock basis when declared by the Company's Board of Directors. As a result, all restricted common stock are considered to be participating securities.

Fair Value of Financial Instruments

Assets and liabilities that are carried at fair value are to be classified and disclosed in one of the following three categories:

Level 1: Observable quoted market prices in active markets for identical assets or liabilities;

Level 2: Observable inputs other than Level 1, such as quoted prices in active markets for similar assets or liabilities, quoted prices for identical or similar assets or liabilities in markets that are not active, or inputs other than quoted prices that are observable for the asset or liability; and.

Level 3: Unobservable inputs for the asset or liability that are significant to the fair value of the assets or liabilities.

At December 31, 2016 and 2015, the Company had no assets or liabilities that are required to be carried at fair value. The book values of the Company's cash and cash equivalents and other working capital financial assets and liabilities approximate their fair values due to their short term nature. The fair values of the Company's shareholder notes receivable were approximately $28,000 and $138,000 at December 31, 2016 and 2015, respectively. One shareholder note, with fair value of $372,000 at December 31, 2014, was forgiven during 2015, which is discussed in Note 12. There were no other changes in shareholder notes receivable other than repayments on shareholder notes and the change in fair value, which was calculated using an income approach to estimate the present value of expected future cash flows to be received under the notes. The measurement is considered to be based primarily on Level 3 inputs used in the calculation, including the discount rate applied and the estimate of future cash flows.

Comprehensive Income (Loss)

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions, and other events and circumstances from non-owner sources and includes all components of net income (loss) and other comprehensive income (loss). The Company had no items of other comprehensive income (loss) for the years ended December 31, 2016, 2015, and 2014.

Recent Accounting Pronouncements

The Company is an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. The Company has irrevocably elected not to avail itself of this exemption from new or revised accounting standards, and, therefore, will be subject to the same new or revised accounting standards as public companies that are not emerging growth companies.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* (Topic 606) (ASU 2014-09), which supersedes the revenue recognition requirements in ASC 605, *Revenue Recognition*. The FASB has subsequently issued a number of amendments to ASU 2014-09. The new standard, as amended, provides a single comprehensive model based on the principle that revenue is recognized to depict the transfer of goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. To achieve this principle, ASU 2014-09 defines a five-step process, which may include more judgment and estimates than are required under existing GAAP, including identifying performance obligations in a contract, estimating the amount of variable consideration to include in the transaction price, and allocating the transaction price to each performance obligation.

The new standard is effective for interim and annual periods beginning after December 15, 2017, with early application for interim and annual periods beginning after December 15, 2016 permitted, and allows two methods of adoption: the full retrospective method, which requires the standard to be applied to each prior period presented, or the modified retrospective method, which requires the cumulative effect of adoption to be recognized as an adjustment to opening retained earnings in the period of adoption. The Company has begun an initial review of its existing contracts with AbbVie and KHK and has not yet determined what, if any, effect ASU 2016-09 will have on its consolidated results of operations or financial position.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements—Going Concern* (Subtopic 205-40) (ASU 2014-15), which requires management to assess an entity's ability to continue as a going concern by incorporating and expanding upon certain principles that are currently in U.S. auditing standards. Specifically, ASU 2014-15 provides a definition of the term substantial doubt and requires an assessment for a period of one year after the date that the financial statements are issued (or available to be issued). It also requires certain disclosures when substantial doubt is alleviated as a result of consideration of management's plans and requires an express statement and other disclosures when substantial doubt is not alleviated. ASU 2014-15 is effective for the annual period ending after December 15, 2016, and for annual and interim periods thereafter. The Company adopted the guidance and disclosure provisions of ASU 2014-15, and the adoption did not have any impact on its consolidated results of operations or financial position.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* (Topic 842) (ASU 2016-02), which supersedes the leases in ASC 840, Leases. ASU 2016-02 requires the recognition of lease assets and lease liabilities by lessees for those leases previously classified as operating leases. The standard is effective for public companies for fiscal years, and for interim periods within those fiscal years, beginning after December 15, 2018. Early adoption is permitted. The Company will apply the guidance and disclosure provisions of the new standard upon adoption. The Company is currently evaluating this standard and has not yet determined what, if any, effect ASU 2016-02 will have on its consolidated operations or financial position but anticipates the recognition of additional assets and corresponding liabilities related to leases on its balance sheet.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation - Stock Compensation: Improvements to Employee Share-Based Payment Accounting* (Topic 718) (ASU 2016-09). ASU 2016-09 modifies U.S. GAAP by requiring the following, among others: (1) all excess tax benefits and tax deficiencies are to be recognized as income tax expense or benefit on the income statement (excess tax benefits are recognized regardless of whether the benefit reduces taxes payable in the current period); (2) excess tax benefits are to be classified along with other income tax cash flows as an operating activity in the statement of cash flows; (3) in the area of forfeitures, an entity can still follow the current U.S. GAAP practice of making an entity-wide accounting policy election to estimate the number of awards that are expected to vest or may instead account for forfeitures when they occur; and (4) classification as a financing activity in the statement of cash flows of cash paid by an employer to the taxing authorities when directly withholding shares for tax withholding purposes. ASU 2016-09 is effective for annual periods beginning after December 15, 2016, and early adoption is permitted. The Company has evaluated this standard and does not believe that the new standard will have a material impact on its consolidated results of operations or financial position.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments* (Topic 230) (ASU 2016-15). This update addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. The ASU is effective for public companies for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2017. The Company is currently evaluating this standard and has not yet determined what, if any, effect ASU 2016-15 will have on its consolidated results of operations or financial position.

Reclassifications

Certain prior year amounts have been reclassified to conform to the current year presentation. The Company reclassified approximately $446,000 in other current liabilities to accrued direct research liabilities as of December 31, 2015.

3. Collaboration Agreements

AbbVie

In December 2011, the Company entered into the AbbVie Collaboration Agreement to jointly research, develop, and commercialize the Company's portfolio of second and later generation oral Nrf2 activators. The terms of the agreement include payment to the Company of a nonrefundable, up-front payment of $400,000,000. The Company is also participating with AbbVie on joint steering committees.

The up-front payment and the Company's collaboration on research, development, and commercialization are accounted for as a single unit of accounting. Revenue is being recognized ratably through December 2026, which is the estimated minimum period that is needed to complete the deliverables under the terms of the AbbVie Collaboration Agreement. The Company began recognizing revenue related to the up-front payment upon execution of the agreement and, accordingly, recognized approximately $26,720,000, $26,647,000, and 26,647,000 as collaboration revenue during the years ended December 31, 2016, 2015, and 2014, respectively. As of December 31, 2016 and 2015, the Company recorded deferred revenue totaling approximately $264,939,000 and $291,659,000, respectively, of which approximately $26,647,000 and $26,720,000, respectively, is reflected as the current portion of deferred revenue.

In September 2010, the Company entered into the AbbVie License Agreement for an exclusive license to develop and commercialize bardoxolone methyl in the Licensee Territory (as defined in the AbbVie License Agreement). The terms of the agreement include payment to the Company of a nonrefundable, up-front license fee of $150,000,000 and additional development and commercial milestone payments. As of December 31, 2016, the Company has received $150,000,000 related to clinical development milestone payments from AbbVie and has the potential in the future to achieve another $50,000,000 from one remaining non-substantive commercial milestone. The AbbVie License Agreement includes additional potential milestones for new compounds other than bardoxolone methyl in cardiovascular and metabolic programs, none of which is planned at this time. The Company also has the potential to achieve tiered royalties ranging from 15 percent to the high 20 percent range, depending on the amount of annual net sales, on net sales by AbbVie in the Licensee Territory. Under certain terminations, the Company may be obligated to pay reverse royalties on net sales in the terminated territory. The Company is participating with AbbVie on joint steering committees to oversee the development and commercialization activities, respectively, related to bardoxolone methyl.

The up-front license fee and the Company's participation on joint steering committees are accounted for as a single unit of accounting, and accordingly, revenue is being recognized ratably through November 2017, which is the term of the joint steering committees. The Company began recognizing revenue related to the up-front license fee upon transfer of the license of bardoxolone methyl to AbbVie, which occurred in November 2010 and, accordingly, recognized approximately $21,470,000, $21,412,000, and $21,412,000 in collaboration revenue during the years ended December 31, 2016, 2015, and 2014, respectively. As of December 31, 2016 and 2015, the Company recorded deferred revenue totaling approximately $18,420,000 and $39,890,000 respectively, of which approximately $18,420,000 and $21,470,000, respectively, is reflected as the current portion of deferred revenue.

KHK

In December 2009, the Company entered into the KHK Agreement for an exclusive license to develop and commercialize bardoxolone methyl in the KHK Licensed Territory. The terms of the agreement include payment to the Company of a nonrefundable, up-front license fee of $35,000,000 and additional development and commercial milestone payments. As of December 31, 2016, the Company received $5,000,000 related to regulatory development milestone payments and $10,000,000 related to clinical development milestone payments from KHK and has the potential in the future to achieve another $82,000,000 from eight non-substantive regulatory milestones and $140,000,000 from four non-substantive commercial milestones. The Company also has the potential to achieve tiered royalties ranging from the low teens to the low 20 percent range, depending on the country of sale and the amount of annual net sales, on net sales by KHK in the KHK Licensee Territory. The Company is participating on a joint steering committee with KHK to oversee the development and commercialization activities related to bardoxolone methyl. Any future milestones and royalties received are subject to mid to lower single digit percent declining tiered commissions to certain consultants as compensation for negotiations of the KHK Agreement.

The up-front license fee and the Company's participation on the joint steering committee are accounted for as a single unit of accounting, and accordingly, revenue was initially being recognized ratably through March 2014, which was the Company's estimate of its substantive performance obligation period related to the joint steering committee. During 2014, the Company agreed to a change to KHK's timeline to develop and commercialize bardoxolone methyl, which modified the Company's estimate of its substantive performance obligation period related to the joint steering committee to December 2021. The Company deemed that this was not a material modification to the KHK Agreement because no payment terms or deliverables were changed and has adjusted its revenue recognition prospectively as of October 2014.

The Company began recognizing revenue related to the up-front payment upon transfer of the license and technical knowledge of bardoxolone methyl to KHK, which occurred in December 2009, and, accordingly, recognized approximately $1,540,000, $1,536,000, and $2,609,000 as collaboration revenue during the years ended December 31, 2016, 2015, and 2014, respectively. As of December 31, 2016 and 2015, the Company recorded deferred revenue totaling approximately $7,682,000 and $9,222,000, respectively, of which approximately $1,536,000 and $1,540,000 respectively, is reflected as the current portion of deferred revenue.

Under the KHK Agreement, the Company will provide KHK with a sufficient supply of bardoxolone methyl to support its development and commercialization efforts. Products provided during development will be charged to KHK at the Company's direct cost without markup for profit.

The Company will report amounts received from these product transactions, net of direct costs incurred, as a component of collaboration revenue. The Company expects the net profit or loss on these product transactions will not be material. Products during commercialization will be charged to KHK with a markup and will be reported as product sales revenue.

4. Property and Equipment

Property and equipment consisted of the following as of December 31(in thousands):

	2016	2015
Computer equipment and software	$ 2,928	$ 3,106
Laboratory equipment	4,530	4,531
Office furniture	1,273	1,273
Office and other equipment	273	271
Leasehold improvements	4,976	4,926
	13,980	14,107
Less accumulated depreciation and amortization	(13,161)	(12,965)
Property and equipment, net	$ 819	$ 1,142

5. Income Taxes

The provision for taxes on income consists of the following at December 31 (in thousands):

	2016	2015	2014
Current	$ (441)	$ (16,654)	$ (15,337)
Deferred	—	17,802	18,316
Total provision for taxes on income	$ (441)	$ 1,148	$ 2,979

The following table reconciles the Company's effective income tax rate from continuing operations to the federal statutory tax rate of 35%:

	2016	2015	2014
U.S. federal income taxes	35%	35%	35%
Stock-based compensation	(2)	(80)	17
Change in valuation allowance	(25)	(310)	30
Other	(1)	(25)	(1)
Recorded federal income tax benefit (provision)	7%	(380)%	81%

Deferred tax assets and liabilities reflect the net effects of net operating loss and tax credit carryovers and temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of the Company's net deferred tax assets as of December 31 are as follows (in thousands):

	2016	2015
Deferred tax assets:		
Deferred revenue	$ 101,864	$ 119,270
Net operating loss	19,159	152
Stock-based compensation	1,362	762
Depreciation	608	695
Other	392	821
Subtotal	123,385	121,700
Less: Valuation allowance	(123,385)	(121,700)
Net deferred tax asset	$ —	$ —

Deferred tax assets are regularly reviewed for recoverability and valuation allowances are established based on historical and projected future taxable losses and the expected timing of the reversals of existing temporary differences. The Company cannot currently conclude that it is more likely than not that the remaining deferred tax assets will be utilized. Therefore, the Company's deferred tax assets have been fully offset by a valuation allowance in 2016. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income (including reversals of deferred tax liabilities) during the periods in which those temporary differences will become deductible. For 2016 and 2015, the valuation allowance increased by approximately $1,685,000 and $935,000, respectively.

As of December 31, 2016, the Company had accumulated net operating losses of approximately $54,741,000 of which $315,000 are subject to an annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended (Section 382). Approximately $434,000 of the net operating loss carryforwards expire between fiscal years 2023 and 2024, with the remaining $54,307,000 expiring in fiscal year 2036.

As of December 31, 2016, the Company has federal research and development tax credit carryforwards of $123,000. These credits expire beginning in 2024.

As of December 31, 2016, there were no unrecognized tax benefits that, if recognized, would have an impact on the Company's effective tax rate. The Company currently has a full valuation allowance against its deferred tax assets. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease within the next 12 months. The Internal Revenue Service (IRS) completed an examination of the Company's U.S. income tax returns for 2009, 2011, and 2012, with no significant adjustments, and has commenced an examination of the Company's U.S. income tax returns for 2013 and 2014. The Company anticipates that this audit will conclude within the next twelve months. As of February 28, 2017, the Company has not been notified of any significant

proposed adjustments by the IRS. All other tax years remain open to federal tax examination. The Company will classify interest and penalties related to unrecognized tax benefits as part of the income tax provision.

6. Patents

Business intellectual property protection is critical to the Company's ability to successfully commercialize its product innovations. The potential for litigation regarding the Company's intellectual property rights always exists and may be initiated by third parties attempting to abridge the Company's rights, as well as by the Company in protecting its rights. There were no patent matters outstanding at December 31, 2016, 2015, or 2014.

7. Licenses

The proprietary rights and technical information covered by various patent and patent applications, which are discussed in more detail below, have been licensed by the Company from third parties, including stockholders. These licenses will continue for the life of the respective patent or until terminated by either party. Certain agreements call for the payment of royalties on product sales over the life of the patents. The term of all agreements is through the useful lives of the licensed patents or for a period of 15 to 20 years for technology rights, for which there are no applicable patent rights.

Bardoxolone Methyl and Nrf2 Activators

In July 2004, the Company entered into an exclusive technology and patent license agreement (the 2004 CDDO License Agreement) with two academic institutions for certain patents and patent applications, known as the CDDO Patents. The Company has the right to sublicense these patents. In the event of a sublicense, the terms of the contract require the Company to pay the licensors sublicense fees based on a percentage of total compensation received that varies depending on the phase of development of a drug candidate as of the time of the sublicense. The Company agreed to pay a royalty on net sales of any products developed as a result of the license, an annual license fee, and various milestone fees, and issued shares of its common stock as consideration for the license.

In January 2009, the Company filed a patent application claiming the use of bardoxolone methyl and related compounds in treating chronic kidney disease, endothelial dysfunction, cardiovascular disease, and related disorders. Several of the original inventors of these compounds at an academic institution were named as co-inventors on this application, along with several company employees. Consequently, the Company and the academic institution are co-owners of this patent application. In December 2009, the Company entered into an agreement with the academic institution (the 2009 Method of Use License Agreement) that provides the Company with an exclusive worldwide license to the academic institution's rights in these applications and any resulting patents. The Company agreed to pay a limited super-royalty on product sales that occur during the effective term of the original patents (as discussed above), a royalty on product sales that occur after the effective term of the original patents, a sublicense fee, an annual license fee, and various milestone fees.

Other Technologies

In September 2014, the Company entered into two exclusive technology and patent license agreements with the University of Kansas for certain patents and patent applications related to small molecule modulators of heat shock proteins. The Company has the right to sublicense these patents. In the event of a sublicense, the terms of the contract require the Company to pay the licensors sublicense fees based on a percentage of total compensation received that varies depending on the phase of development of a drug candidate as of the time of the sublicense. The Company paid non-refundable license issue fees and agreed to pay royalties on net sales of any products developed as a result of the licenses, annual license fees, various milestone fees, including reimbursement of sunk-in patent expenses, and fees for sponsored research performed by the University of Kansas as consideration for the licenses.

The Company also has various exclusive technology and patent license agreements with private and academic institutions for certain patents and patent applications. The Company has the right to sublicense these patents. The licenses contain provisions for payments to the licensors of sublicense fees based on a percentage of total compensation received by the Company for such sublicenses, that varies depending on the phase of development of a drug candidate as of the time of the sublicenses. The Company agreed to pay royalties on net sales of any products developed as a result of the licenses, annual license fees, and various milestone fees as consideration for the licenses.

8. Common Stock

The Company records all issued shares of common stock at fair value on the dates of issuance.

Reserved Shares

At December 31, 2016, common stock reserved for issuance is as follows:

Outstanding common stock options under the 2007 Long Term Incentive Plan	2,279,800
Outstanding common stock options under standalone option agreements	31,346
Common stock available for future grant under the 2007 Long Term Incentive Plan	436,638
Total common shares reserved for future issuance	2,747,784

9. Convertible Preferred Stock

The authorized shares of convertible preferred stock as of December 31 are as follows:

	Shares Authorized	
	2016	2015
Undesignated shares	100,000,000	9,528,487
Series H	—	9,799,474
Series G2	—	19,602,523
Series G1	—	6,041,936
Series F	—	11,360,675
Series E	—	10,957,445
Series D	—	10,770,911
Series C	—	6,856,302
Series B	—	3,331,247
Series A	—	1,751,000
Total	100,000,000	90,000,000

As of December 31, 2016 and 2015, there were no shares of convertible preferred stock issued and outstanding.

On January 4, 2016, the Company filed its Tenth Amended and Restated Certificate of Incorporation, which removed all previous designations and authorized 100,000,000 undesignated shares of convertible preferred stock.

10. Stock-Based Compensation

The 2007 Long Term Incentive Plan (the 2007 LTIP), which is the successor equity incentive plan to the Amended and Restated 2002 Stock Option and Incentive Plan (the 2002 Plan), provides for awards of restricted stock, both nonstatutory stock options and incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended, and other incentive awards and rights to purchase shares of the Company's common stock. On September 23, 2015, the Board of Directors suspended any further grants from being awarded under the 2002 Plan. A total of 436,638 and no shares of common stock have been reserved for issuance under the 2007 LTIP and the 2002 Plan, respectively.

As of December 31, 2016, no shares of restricted stock are outstanding under the 2007 LTIP, and options to purchase 2,311,146 shares and no options have been granted and are outstanding under the 2007 LTIP and the 2002 Plan, respectively. These options vest over the stated periods through 2021. Additional detail on stock compensation costs can be found below.

Stock Options

Stock options are granted to employees at exercise prices equal to the estimated fair market value of the Company's stock at the dates of grant. Stock options under the 2007 LTIP generally vest over four or five years and have a term of ten years. Compensation cost is recognized, net of estimated forfeitures of approximately 7.87% as of December 31, 2016, over the vesting period of the options using the straight-line attribution method.

The following table summarizes stock-based compensation expense reflected in the consolidated statements of operations (in thousands):

	Years Ended December 31		
	2016	2015	2014
Research and development	$ 1,121	$ 671	$ 787
General and administrative	1,246	1,404	736
	$ 2,367	$ 2,075	$ 1,523

The following table summarizes stock option activity as of December 31, 2016, and changes during the years ended December 31, 2016 under the 2007 LTIP and standalone option agreements:

	Number of Options	Weighted-Average Exercise Price
Outstanding at January 1, 2016	550,675	16.11
Granted	1,834,520	17.24
Exercised	(35,207)	9.94
Forfeited	(19,133)	11.55
Expired	(19,709)	11.50
Outstanding at December 31, 2016	2,311,146	17.18
Exercisable at December 31, 2016	444,862	16.46

At December 31, 2016, the outstanding stock options have a weighted-average outstanding term of 8.92 years.

At December 31, 2016, 2,029,932 stock options are fully vested or are expected to vest and have a weighted-average outstanding term of 8.83 years and a weighted-average exercise price of $17.03. Exercisable stock options have a weighted-average outstanding term of 6.52 years.

Restricted Stock

Restricted and unvested stock has occasionally been sold or granted to employees of the Company under the 2007 LTIP and the 2002 Plan. The fair value of restricted stock is determined based on the estimated fair value of the Company's common stock at the date of grant. Restricted stock generally vests straightline over a period of four or five years, provided the employee remains in the service of the Company. Compensation cost is recognized on a straight-line basis over the vesting period. Shares of restricted and unvested stock purchased by employees are released from their restriction at each vesting date; however, these shares remain pledged to the Company and are nontransferable until the related shareholder note receivable has been paid. The shareholder notes receivable related to the restricted stock sold to employees are usually due in full one year after the final release date of the stock. At December 31, 2016 and 2015, a total of 1,193,780 shares of restricted stock had been issued through the 2007 LTIP and the 2002 Plan.

Details of unvested and vested restricted common stock for the year ended December 31, 2016 and 2015 can be seen in the table below:

	Restricted Shares of Stock	Weighted-Average Purchase Price	Shares of Stock Released From Restriction	Weighted-Average Purchase Price
Outstanding at January 1, 2016	14,800	41.79	1,126,514	8.19
Granted	—	—	—	—
Vested	(14,800)	41.79	14,800	41.79
Canceled or expired	—	—	—	—
Repurchased	—	—	—	—
Outstanding at December 31, 2016	—	—	1,141,314	8.63

At December 31, 2016, no shares of restricted stock are outstanding. The fair value of restricted stock vested in fiscal 2016 and 2015 was $356,000 and $369,000, respectively.

Fair Value Estimates

The Company's determination of the fair value of stock-based payment awards on the date of grant using the Black-Scholes option pricing model is affected by many factors, including the stock price and a number of highly complex and subjective variables. These variables include, but are not limited to, the Company's stock price volatility over the expected term of the awards, and estimates of the expected option term.

The weighted-average assumptions used in the Black-Scholes option pricing model were as follows:

	Years Ended December 31		
	2016	2015	2014
Dividend yield	—%	—%	—%
Volatility	72.77%	74.93%	75.21%
Risk-free interest rate	1.76%	1.71%	1.96%
Expected term of options (in years)	6.74	7.28	7.03

Expected volatility is based on the Company's own historical volatility since its IPO and benchmarked public companies during fiscal years 2016, 2015 and 2014. The risk-free interest rate, ranging from 1.24% to 2.07% during the year ended December 31, 2016, is based on the U.S. Treasury yield curve in effect at the time of grant for periods corresponding with the expected life of the options. The expected term of options represents the weighted-average period of time that options granted are expected to be outstanding based on historical data.

The total intrinsic value (the difference between market value and exercise prices of in-the-money options) of all outstanding options at December 31, 2016, 2015, and 2014, was $12,951,000, $6,360,000 and $2,823,000, respectively. The total intrinsic value of exercisable options at December 31, 2016, 2015, and 2014, was $3,841,000, $3,586,000 and $1,258,000, respectively. In 2016, 2015 and 2014, 35,207, 3,147 and 82 options were exercised, respectively. As of December 31, 2016, total unrecognized compensation expense of $20,906,000 related to equity awards is expected to be recognized over a weighted average of 4.18 years.

11. Commitments and Contingencies

Lease Commitments

The Company leases certain office and laboratory space under a non-cancelable operating lease. During 2010, the Company renewed and amended the lease agreement to include additional space. This lease contains a renewal option and has an increasing payment schedule. Rent is expensed on a straight-line basis, and an accrued rent liability of approximately $120,000 and $162,000 is recorded in other accrued liabilities on the accompanying consolidated balance sheets at December 31, 2016 and 2015, respectively. The lease contains a construction allowance from the landlord that must be repaid upon early termination of the lease. At December 31, 2016, the leasehold incentive liability associated with this allowance was approximately $159,000, which is being amortized on a straight-line basis as a reduction of rent expense over the remaining lease term.

Future minimum lease payments under non-cancelable operating leases are as follows at December 31, 2016 (in thousands):

2017	$ 596
2018	509
Thereafter	—
	$ 1,105

For the years ended December 31, 2016, 2015, and 2014, the Company recorded total rent expense of approximately $463,000, $523,000 and $694,000, respectively.

The Company has a capital lease for equipment with an outstanding balance of $45,000 as of December 31, 2016.

Indemnifications

ASC 460, *Guarantees,* requires that, upon issuance of a guarantee, the guarantor must recognize a liability for the fair value of the obligations it assumes under that guarantee.

As permitted under Delaware law and in accordance with the Company's bylaws, officers and directors are indemnified for certain events or occurrences, subject to certain limits, while the officer or director is or was serving in such capacity. The maximum amount of potential future indemnification is unlimited; however, the Company has obtained director and officer insurance that limits its exposure and may enable recoverability of a portion of any future amounts paid. The Company believes the fair value for these indemnification obligations is minimal. Accordingly, the Company has not recognized any liabilities relating to these obligations as of December 31, 2016.

The Company has certain agreements with licensors, licensees, and collaborators that contain indemnification provisions. In such provisions, the Company typically agrees to indemnify the licensor, licensee, and collaborator against certain types of third-party claims. The Company accrues for known indemnification issues when a loss is probable and can be reasonably estimated. There were no accruals for expenses related to indemnification issues for any period presented.

12. Related-Party Transactions

The Company paid approximately $946,000, $1,295,000, and $2,300,000, to certain stockholders, primarily academic institutions, for sponsored research, research and development consulting services, contract manufacturing services, regulatory and medical consulting services, data management services, license fees, and clinical trial services in 2016, 2015, and 2014, respectively. These amounts are recorded in research and development expense in the accompanying consolidated statements of operations.

Approximately $318,000, $140,000 and $5,000 were due to stockholders and included in accounts payable and other current liabilities for services related to sponsored research, contract manufacturing services, and data management at December 31, 2016, 2015, and 2014 respectively.

On September 23, 2015, the Company's Board of Directors resolved to forgive a board director's promissory note principal and accrued interest, totaling $1,056,000, effective October 19, 2015. The value of the 25% recourse portion of the note and related accumulated interest was $264,000. The value of the 75% nonrecourse portion of the note required calculation based on the incremental value of the stock award prior to the forgiveness compared to subsequent to the forgiveness. The fair value of the Company's stock, as determined by the board of directors, at this time was $25.52, and this value was utilized in calculating the value of the nonrecourse portion of the note which totaled $272,000. The total of $536,000 was charged to stock-based compensation expense as of December 31, 2015.

13. Net (Loss) Income per Share

The computation of basic and diluted net (loss) income per share attributable to common stockholders the Company for the years ended December 31 is summarized in the following table:

	2016	2015	2014
Numerator			
Net (loss) income (in thousands)	$ (6,227)	$ (1,450)	$ 689
Denominator			
Weighted-average number of common shares used in net (loss) income per share – basic	19,816,635	15,974,974	15,950,023
Dilutive potential common shares	—	—	29,745
Weighted-average number of common shares used in net (loss) income per share – diluted	19,816,635	15,974,974	15,979,768
Net (loss) income per share – basic	(0.31)	(0.09)	0.04
Net (loss) income per share – diluted	(0.31)	(0.09)	0.04

The number of weighted average options that were not included in the diluted earnings per share calculation because the effect would have been anti-dilutive represented 2,311,146, 550,675, and 491,668 shares for the years ended 2016, 2015, and 2014, respectively.

14. Selected Quarterly Financial Data

The following table contains quarterly financial information for 2016 and 2015. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period (in thousands except per share data).

	2016			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total collaboration revenue	$ 12,438	$ 12,366	$ 12,551	$ 12,501
Total expenses	12,701	13,791	13,509	16,737
Total other income	23	28	62	101
Provision (benefit) for taxes on income	18	(461)	1	1
Net (loss) income	(258)	(936)	(897)	(4,136)
Net (loss) income per share – basic	(0.02)	(0.05)	(0.04)	(0.19)
Net (loss) income per share – diluted	$ (0.02)	$ (0.05)	$ (0.04)	$ (0.19)

	2015			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total collaboration revenue	$ 12,929	$ 12,365	$ 12,500	$ 12,525
Total expenses	11,965	13,586	12,016	13,086
Total other income	8	8	9	7
(Benefit) provision for taxes on income	(386)	482	(140)	1,192
Net income (loss)	1,358	(1,695)	633	(1,746)
Net income (loss) per share – basic	0.08	(0.11)	0.04	(0.11)
Net income (loss) per share – diluted	$ 0.08	$ (0.11)	$ 0.04	$ (0.11)

15. Subsequent Events

The Company has evaluated events and transactions occurring subsequent to December 31, 2016, but prior to the issuance of the consolidated financial statements, for recognition or disclosure in its consolidated financial statements. During this period, there were no subsequent events requiring either recognition in the consolidated financial statements or nonrecognized subsequent events requiring disclosure.

Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
3.1	Thirteenth Amended and Restated Certificate of Incorporation.	S-1	333-208843	3.7	05/16/2016	
3.2	Second Amended and Restated Bylaws.	8-K	001-37785	3.1	12/07/2016	
4.1	Form of Class A Common Stock Certificate of the Registrant.	S-1	333-208843	4.1	02/08/2016	
4.2	Eighth Amended and Restated Investors' Rights Agreement, by and among the Registrant and certain of its stockholders, dated as of December 6, 2011, as amended.	S-1	333-208843	4.2	01/04/2016	
4.3	Seventh Amended and Restated Registration Rights Agreement by and among the Registrant and certain of its stockholders, dated as of November 10, 2010.	S-1	333-208843	4.3	01/04/2016	
10.1+	Indemnification Agreement by and between the Registrant and J. Warren Huff, together with a schedule identifying other substantially identical agreements between the Registrant and the persons identified on the schedule and identifying the material differences between each of the agreements and the filed Indemnification Agreement.	S-1	333-208843	10.1	05/20/2016	
10.2+	Indemnification Agreement by and between the Registrant and Dawn C. Bir dated September 6, 2016.	10-Q	001-37785	10.1	11/14/2016	
10.3+	Reata Pharmaceuticals, Inc. Amended and Restated 2007 Long Term Incentive Plan and forms of award agreements and grant notices.	S-1	333-208843	10.2	03/22/2016	
10.4+	Employment Agreement by and between the Registrant and J. Warren Huff, dated September 23, 2015.	S-1	333-208843	10.3	01/04/2016	
10.5+	Employment Agreement by and between the Registrant and Keith W. Ward, Ph.D., dated September 23, 2015.	S-1	333-208843	10.4	01/04/2016	
10.6+	Employment Agreement by and between the Registrant and Colin Meyer, M.D., dated September 23, 2015.	S-1	333-208843	10.5	01/04/2016	
10.7+	Employment Agreement by and between the Registrant and Jason D. Wilson dated September 23, 2015.	10-Q	001-37785	10.2	11/14/2016	
10.8+	Employment Agreement by and between the Registrant and Michael D. Wortley dated September 23, 2015.	10-Q	001-37785	10.3	11/14/2016	
10.9+	Employment Agreement by and between the Registrant and Dawn C. Bir dated September 6, 2016.	10-Q	001-37785	10.4	11/14/2016	
10.10	Lease by and between the Registrant and SDCO Gateway Commerce I & II, Inc., dated as of May 25, 2006, as amended.	S-1	333-208843	10.6	01/04/2016	

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.11#	Exclusive Patent License Agreement among the Board of Regents of The University of Texas System, The University of Texas M.D. Anderson Cancer Center, and the Trustees of Dartmouth College and the Registrant, dated as of July 15, 2004, as amended.	S-1	333-208843	10.7	01/04/2016	
10.12#	Exclusive License Agreement between the Trustees of Dartmouth College and the Registrant, dated as of December 16, 2009, as amended.	S-1	333-208843	10.8	01/04/2016	
10.13#	Exclusive License Agreement between the KU Center for Technology Commercialization, Inc. and the Registrant, dated as of September 26, 2014.	S-1	333-208843	10.9	01/04/2016	
10.14#	Exclusive License Agreement between the KU Center for Technology Commercialization, Inc. and the Registrant, dated as of September 26, 2014.	S-1	333-208843	10.10	01/04/2016	
10.15#	Exclusive License and Supply Agreement between the Registrant and Kyowa Hakko Kirin Co. Ltd., dated as of December 24, 2009.	S-1	333-208843	10.11	01/04/2016	
10.16#	License Agreement between the Registrant and Abbott Pharmaceuticals PR Ltd., dated as of September 21, 2010.	S-1	333-208843	10.12	02/08/2016	
10.17#	Collaboration Agreement between the Registrant and Abbott Pharmaceuticals PR Ltd., dated as of December 9, 2011.	S-1	333-208843	10.13	02/08/2016	
10.18	Supplement to Exclusive License and Supply Agreement between the Registrant and Kyowa Hakko Kirin Co., Ltd., dated as of March 4, 2016.	S-1	333-208843	10.14	03/22/2016	
10.19+	Non-Employee Director Compensation Policy					X
10.20+	Indemnification Agreement by and between the Registrant and William D. McClellan dated March 1, 2017.	8-K	001-37785	10.1	03/02/2017	
21.1	List of subsidiaries.	S-1	333-208843	21.1	01/04/2016	
23.1	Consent of Ernst & Young LLP, an Independent Registered Public Accounting Firm.					X
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					X
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					X
32.1	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					*
32.2	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					*

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
101.INS	XBRL Instance Document.					X
101.SCH	XBRL Taxonomy Extension Schema Document.					X
101.CAL	XBRL Taxonomy Calculation Linkbase Document.					X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.					X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.					X
101.PRE	Taxonomy Extension Presentation Linkbase Document.					X

+ Indicates management contract or compensatory plan.

Confidential information has been omitted from this Exhibit and has been filed separately with the SEC pursuant to a confidential treatment request under Rule 406 of the Securities Act of 1933 and Rule 24b-2 of the Securities Exchange Act of 1934.

* Furnished herewith.

Exhibit 10.19

REATA PHARMACEUTICALS, INC.
NON-EMPLOYEE DIRECTOR COMPENSATION POLICY

Each member of the Board of Directors (the ***"Board"***) who is not also serving as an employee of or consultant to Reata Pharmaceuticals, Inc. (***"Reata"***) or any of its subsidiaries (each such member, an ***"Eligible Director"***) will receive the compensation described in this Non-Employee Director Compensation Policy (the "***Policy***") for his or her Board service or service on a committee of the Board ("***Committee***"). This Policy is effective as of December 7, 2016 (the "***Effective Date***") and may be amended at any time in the sole discretion of the Board or the Compensation Committee of the Board.

Annual Cash Compensation

The annual cash compensation amount set forth below is payable in equal quarterly installments, payable after each regular quarterly Board meeting, beginning with the Board meeting currently scheduled to be held on March 1, 2017 (collectively, the "***Annual Cash Fees***"). All Annual Cash Fees are vested upon payment.

1. Annual Board Service Retainer:
    a. All Eligible Directors: $37,250
    b. Lead Independent Director Service Retainer (in addition to Annual Board Service Retainer): $20,000
2. Annual Committee Member Service Retainer:
    a. Member of the Audit Committee: $7,500
    b. Member of the Compensation Committee: $6,375
    c. Member of the Nominating and Corporate Governance Committee: $4,500
3. Annual Committee Chair Service Retainer (in addition to Annual Committee Member Service Retainer):
    a. Chairman of the Audit Committee: $25,000
    b. Chairman of the Compensation Committee: $5,875
    c. Chairman of the Nominating and Corporate Governance Committee: $3,000

Equity Compensation

The equity compensation set forth below will be granted under the Reata's Amended and Restated 2007 Long Term Incentive Plan (the "***Plan***"). All stock options granted under this Policy will be nonstatutory stock options to purchase shares of Class B common stock of Reata ("***Common Stock***"), with (a) an exercise price per share equal to 100% of the Fair Market Value (as defined in the Plan) of the underlying Common Stock on the date of grant, which shall be the closing price on the date of grant (or, if not a business day, the first business day thereafter) of a share of Reata's Class A common stock on the Nasdaq Global Market, and (b) a term of ten years from the date of grant. The other terms and provisions of the stock options, including

vesting on termination of service, Disability (as defined in the form stock option agreement), death and Change in Control (as defined in the Plan) will be in conformity with the Plan and the form of stock option agreement and notice of grant previously approved by the Board for members of the Board, as the Plan or any such form may be amended from time to time. The terms and provisions of the stock options as set forth in this paragraph are referred to herein as the "***Terms***".

1. Initial Grant: On the date of the Eligible Director's initial election or appointment to the Board (or, if such date is not a market trading day, the first market trading day thereafter), the Eligible Director will automatically, and without further action by the Board or Compensation Committee of the Board, be granted a stock option to purchase 12,000 shares of Common Stock (the ***"Initial Grant"***). The stock option constituting each Initial Grant will vest in equal annual installments over a three-year period so that the Initial Grant will become fully vested on the third anniversary of the date of grant, subject to the Terms.

2. Annual Grant: On the date of the first regular Board meeting held after each Reata annual stockholder meeting, for each Eligible Director who continues to serve as a non-employee member of the Board (or who is first elected to the Board at such annual stockholder meeting), the Eligible Director will automatically, and without further action by the Board or Compensation Committee of the Board, be granted a stock option to purchase 6,000 shares of Common Stock (the ***"Annual Grant"***). In addition, each Eligible Director who is first elected or appointed to the Board other than at the first regular Board meeting held after a Reata annual stockholder meeting will automatically, and without further action by the Board or Compensation Committee of the Board, be granted an Annual Grant on the date of the Eligible Director's initial election or appointment to the Board, prorated by multiplying 6,000 by a fraction (1) the numerator of which is the number of subsequent regular Board meetings remaining until (and including) the first regular Board meeting held after Reata's next annual stockholder meeting and (2) the denominator of which is four. Subject to the Terms, the stock options constituting the Annual Grant will vest in the number of equal quarterly installments that is the number of regular quarterly Board meetings scheduled to be held following the date of grant to and including Reata's regular Board meeting scheduled to be held after Reata's next annual stockholder meeting following the date of grant. An example of the above proration procedures follows: if an Eligible Director is appointed to the Board on January, 5, 2017, then the Eligible Director would receive an Annual Grant of 3,000 shares on January 5, 2017, which Annual Grant would vest 50% on April 5, 2017, and 50% on July 5, 2017, subject to the Terms; the new Eligible Director and all other Eligible Directors would receive an Annual Grant of 6,000 shares on the date of the June regular Board meeting (held after the June annual stockholder meeting) following the January date of grant, which would vest in four equal quarterly installments, subject to the Terms.

3. Interim Grants: On the Effective Date, each Eligible Director will automatically, and without further action by the Board or Compensation Committee of the Board, be granted a stock option to purchase 6,000 shares of Common Stock (the "***Interim Annual Grant***").

The shares subject to the Interim Annual Grant will vest 50% on March 7, 2017, and 50% on June 7, 2017, subject to the Terms.

Election to Receive Stock Options in Lieu of Cash Compensation

An Eligible Director may elect to receive a grant of stock options pursuant to the Equity Compensation provisions of this Policy in lieu of receiving future cash compensation payments, or any portion thereof, of the Annual Board Service Retainer, the Lead Independent Director Service Retainer, the Annual Committee Member Service Retainer, and/or the Annual Committee Chair Service Retainer (the "***Election Grant***"). This election to receive an Election Grant may be made by an Eligible Director on the date of Reata's first regular Board meeting held after an annual stockholder meeting by submitting an executed election form (the "***Election Form***") to Reata's chief legal counsel in the form and pursuant to procedures established by the Company. The stock options granted pursuant to an Election Grant will be granted on the day of Reata's first regular Board meeting held after each annual stockholder meeting, will have a Black-Scholes value equal to the annual amount of the applicable Retainer, and will otherwise be subject to the Terms. In addition, each Eligible Director serving as of the Effective Date, and each Eligible Director who is first elected or appointed to the Board following the Effective Date and not at an annual stockholder meeting, may execute an Election Form on a date other than the date of Reata's first regular Board meeting held after an annual stockholder meeting, in which case, in addition to receiving a grant of stock options pursuant to an Election Grant on the day of Reata's first regular Board meeting held after each annual stockholder meeting, such Eligible Director will also be granted on the date of execution of the Election Form a prorated Election Grant with a Black-Scholes value equal to the Black-Scholes value of the applicable Retainer multiplied by a fraction (1) the numerator of which is the number of subsequent regular Board meetings that will be held after the date of grant to, and including, the first regular Board meeting held after Reata's next annual stockholder meeting, and (2) the denominator of which is 4, and will otherwise be subject to the Terms. The stock options constituting Election Grants will vest in the number of equal quarterly installments that is the number of regular quarterly Board meetings scheduled to be held following the date of grant to and including Reata's regular Board meeting scheduled to be held after Reata's next annual stockholder meeting following the date of grant, subject to the Terms. Any election to receive an Election Grant will be irrevocable until the third anniversary of such election. Once an Election Form has been executed and delivered to Reata, no additional Election Form is required to be executed, unless (1) an Eligible Director has revoked an election to receive an Election Grant and thereafter determines to again receive an Election Grant or (2) an Eligible Director becomes entitled to receive a Retainer which the Eligible Director was not entitled to receive at the time of the execution of an Election Form. If the amount of any Retainer is changed, no additional Election Form is required to be executed if it included an election as to that type of Retainer.

Fractions

Stock options granted pursuant to an Election Grant shall be for a number of whole shares of Common Stock. Any fractional share of Common Stock shall be rounded down to the nearest whole share of Common Stock. Fractions of shares of Common Stock subject to a stock option shall not vest on a vesting date of an Initial Grant, an Annual Grant, an Interim Annual Grant, or an Election Grant, and the shares of Common Stock that do vest on a vesting date shall be

rounded down to the nearest whole share of Common Stock; provided, however, that such fractions of shares of Common Stock shall be added to the number of shares of Common Stock that vest on the final vesting date or that otherwise vest due to the vesting acceleration (with any resulting fraction of a share of Common Stock being rounded down to the nearest whole share of Common Stock).

Waiver

An Eligible Director may, at any time and from time to time, waive receipt of any or all cash or equity compensation payable to such Eligible Director pursuant to the Policy (a "***Waiver***"). After a Waiver, the Eligible Director may, at any time and from time to time, withdraw the Waiver and begin receiving future cash and equity compensation pursuant to the Policy. Any Waiver or withdrawal of a Waiver shall be made by providing written notice to an officer of Reata.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in Registration Statement (Form S-8 No. 333-211682) pertaining to the Reata Pharmaceutical, Inc. 2007 Long Term Incentive Plan, of our report dated March 2, 2017, with respect to the consolidated financial statements of Reata Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2016.

/s/ Ernst & Young LLP

Dallas, Texas
March 2, 2017

Exhibit 31.1

CERTIFICATIONS

I, J. Warren Huff, certify that:

1. I have reviewed this Annual Report on Form 10-K of Reata Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations, and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the small business issuer and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 2, 2017

By: /s/ J. Warren Huff

J. Warren Huff
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, Jason D. Wilson, certify that:

1. I have reviewed this Annual Report on Form 10-K of Reata Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 2, 2017

By: /s/ Jason D. Wilson

Jason D. Wilson
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Reata Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ending December 31, 2016 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, J. Warren Huff, as Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 2, 2017

By: /s/ J. Warren Huff

J. Warren Huff
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Reata Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ending December 31, 2016 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I Jason D. Wilson, certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 2, 2017

By: /s/ Jason D. Wilson

Jason D. Wilson
Chief Financial Officer
(Principal Financial Officer)