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, 2018

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 every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit such files). YES ☒ NO ☐

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

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

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

Indicate by check mark whether the Registrant 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, 2018, was $554,412,876.

The number of shares of Registrant's Common Stock outstanding as of February 22, 2019 was 24,075,573 shares of Class A Common Stock and 5,702,052 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 12, 2019, are incorporated by reference into Part III of this Report.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. We make such forward-looking statements pursuant to safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. 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, future revenues, projected costs, prospects, 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," "might," "estimate," "continue," "anticipate," "intend," "target," "project," "model," "should," "would," "plan," "expect," "predict," "could," "seek," "goals," "potential," and similar terms or expressions that concern our expectations, strategy, plans, or intentions. These forward-looking statements include, but are not limited to, statements about:

- our expectations regarding the timing, costs, conduct, and outcome of our clinical trials, including statements regarding the timing of the initiation and availability of data from such trials;
- the timing and likelihood of regulatory filings and approvals for our product candidates;
- 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;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use, and the potential market opportunities for commercializing our product candidates;
- 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 maintain and establish relationships with third parties, such as contract research organizations, suppliers, and distributors;
- our ability to maintain and establish 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;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act;
- our expectations related to the use of our available cash;
- our ability to develop, acquire, and advance product candidates into, and successfully complete, clinical trials;

- the initiation, timing, progress, and results of future preclinical studies and clinical trials, and our research and development programs;
- the impact of governmental laws and regulations and regulatory developments in the United States and foreign countries; and
- developments and projections relating to our competitors and our industry.

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 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.

DEFINED TERMS

Unless the context requires otherwise, references to "Reata," "the Company," "we," "us," or "our" in this 2018 Form 10-K refer to Reata Pharmaceuticals, Inc. and its subsidiaries. We also have used several other terms in this 2018 Form 10-K, most of which are explained or defined below.

Abbreviated Term	Defined Term
2017 Tax Act	Tax Cuts and Jobs Act of 2017
6MWD	6-minute walk distance
AbbVie	AbbVie Inc.
ACE	Angiotensin converting enzyme
Actelion	Actelion Pharmaceuticals US, Inc.
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AIA	Leahy-Smith America Invents Act
ANDA	Abbreviated new drug application
ARB	Angiotensin receptor blockers
ASC	Accounting Standards Codification
ASU	Accounting Standards Update
ATP	Adenosine triphosphate
Bard	Bardoxolone methyl
Bayer	Bayer AG
CGMP	Current good manufacturing practice
CKD	Chronic kidney disease
CMO	Contract manufacturing organization
CMS	Center for Medicare and Medicaid Services
Credits	Tax credits
CRO	Contract research organization
CTA	clinical trial application
CTD-PAH	Pulmonary arterial hypertension associated with connective tissue disease
Dartmouth	The Trustees of Dartmouth College
DOJ	United States Department of Justice
DMC	Data monitoring committee
DSCSA	Drug Supply Chain Security Act
DSMB	Data safety monitoring board
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPC	European Patent Convention
ERA	Endothelin receptor antagonist
ESKD	End stage kidney disease
EU	European Union
Exchange Act	Securities Exchange Act of 1934
FA	Friedreich's ataxia
FASB	Financial Accounting Standards Board
FCPA	Foreign Assets Controls, the United States Foreign Corrupt Practices Act of 1977
FDA	United States Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FSGS	Focal segmental glomerulosclerosis
FTC	Federal Trade Commission
GBM	Glomerular basement membrane
GCP	Good clinical practice

Abbreviated Term	Defined Term
GFR	Glomerular filtration rate
Gilead	Gilead Sciences, Inc.
GLP	Good laboratory practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HITECH	Health Information Technology for Economic and Clinical Health Act
IgAN	IgA nephropathy
IND	Investigational new drug
I-PAH	Idiopathic form of PAH
IPO	Initial public offering
IRB	Institutional review board
IRS	Internal Revenue Service
JOBS Act	Jumpstart Our Business Startups Act
KHK	Kyowa Hakko Kirin Co., Ltd.
MAA	Marketing Authorization Application
MD Anderson	The University of Texas MD Anderson Cancer Center
mFARS	Modified Friedreich's Ataxia Rating Scale
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed-model repeated measures
NCE	New chemical entity
NDA	New Drug Application
NOL	Net operating loss
OIG	Office of Inspector General
Omav	Omaveloxolone
PAH	Pulmonary arterial hypertension
PCAOB	Public Company Accounting Oversight Board
PD	Pharmacodynamic
PDMA	Prescription Drug Marketing Act
PH	Pulmonary hypertension
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPACA	Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act of 2010
REMS	Risk evaluation and mitigation strategy
ROS	Reactive oxygen species
SAB	Staff Accounting Bulletin
SAE	Serious adverse event
Sarbanes-Oxley Act	The Sarbanes-Oxley Act of 2002
SEC	Securities and Exchange Commission
Securities Act	Securities Act of 1933
TGA	Therapeutic Goods Administration
T1D CKD	Type 1 diabetic CKD
T2D CKD	Type 2 diabetic CKD
University of Kansas	University of Kansas and the University of Kansas Medical Center
USPTO	The United States Patent and Trademark Office

PART I

Item 1. Business.

Overview

Reata's mission is to develop innovative therapies that change patients' lives for the better. We focus on developing small-molecule therapeutics with novel mechanisms of action for the treatment of severe, life-threatening diseases with few or no approved therapies. Our lead product candidates, bardoxolone methyl (Bard) and omaveloxolone (Omav), activate the transcription factor Nrf2, which plays an important role in regulating the cellular response to injury. By activating Nrf2, Bard and Omav normalize mitochondrial function, restore redox balance, and resolve inflammation. We have fully enrolled two registrational clinical trials: CARDINAL, studying Bard in chronic kidney disease (CKD) caused by Alport syndrome, and MOXIe, studying Omav in Friedreich's ataxia (FA). CKD caused by Alport syndrome and FA are rare, serious diseases with no approved therapy. We designed CARDINAL and MOXIe based on the results of earlier clinical studies and guidance from the FDA on a potential path to approval. We expect to have top-line data from both of these clinical trials in the second half of 2019. If we receive FDA approval based on either of these trials, it may provide expansion opportunities into other related indications. We are also conducting a third registrational trial, CATALYST, studying Bard in patients with a rare and serious form of pulmonary arterial hypertension caused by connective tissue disease (CTD-PAH), and we expect to have top-line data from this trial during the first half of 2020. We expect our current cash to fund our operations through data readouts for these three ongoing registrational clinical trials.

We are developing Bard for the treatment of patients with CKD caused by Alport syndrome, autosomal dominant polycystic kidney disease (ADPKD), and other rare forms of CKD that, in the aggregate, affect more than 700,000 patients in the United States. CKD is characterized by a progressive worsening in the rate at which the kidney filters waste products from the blood, called the glomerular filtration rate (GFR). When GFR gets too low, patients typically develop end-stage kidney disease (ESKD) and require dialysis or a kidney transplant to survive. In 10 separate CKD clinical trials, Bard has been shown to consistently improve estimated GFR (eGFR) in patients with diverse etiologies of CKD. We believe that Bard treatment has the potential to delay or prevent GFR declines that cause the need for dialysis or a transplant in patients with Alport syndrome, ADPKD, and other rare forms of CKD.

We are conducting a Phase 2/3 clinical trial studying Bard in patients with CKD caused by Alport syndrome called CARDINAL. Alport syndrome affects both children and adults and, in patients with the most severe forms of the disease, approximately 50% progress to dialysis by age of 25, 90% by age 40, and nearly 100% by age 60. In the Phase 2 portion of CARDINAL, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 48 weeks of treatment in 25 patients. Available historical data for 22 of these patients showed an average annual decline in eGFR of 4.2 mL/min/1.73 m^2 in the three-year period prior to study entry. Bard also demonstrated a statistically significant increase from baseline in mean eGFR at Week 52 after withdrawal of drug for four weeks. This retained eGFR benefit is important because it provides compelling evidence that drug treatment may delay or prevent the need for dialysis or transplant. The FDA has provided us with written guidance that, in patients with CKD caused by Alport syndrome, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval, and an improvement versus placebo after two years of treatment may support full approval. The Phase 3 portion of CARDINAL is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in 157 Alport syndrome patients randomized one-to-one to active drug or placebo. We have fully enrolled the Phase 3 portion of CARDINAL, and we expect to have one year top-line results available in the second half of 2019. If the trial results are positive, we believe the results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of CKD caused by Alport syndrome.

We are currently initiating a Phase 3 trial studying Bard in patients with ADPKD called FALCON. ADPKD is a rare and serious hereditary form of CKD caused by a genetic defect in genes called PKD1 or PKD2 and is characterized by the formation of fluid-filled cysts in the kidneys. ADPKD is the most common single-gene disorder of the kidneys, and there are an estimated 400,000 patients in the United States, with approximately 140,000 patients diagnosed with the disease. During 2018, we completed a Phase 2 clinical trial studying Bard in patients with ADPKD. In the Phase 2 study, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 12 weeks of treatment in 31 patients. Available historical data for 29 of these patients showed an average annual decline in eGFR of 4.8 mL/min/1.73 m^2 in the three-year period prior to study entry. The FDA has provided us with written

guidance that, in patients with ADPKD, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval, and an improvement versus placebo after two years of treatment may support full approval. FALCON is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in approximately 300 ADPKD patients randomized one-to-one to active drug or placebo. We plan to enroll the first ADPKD patient in FALCON in mid-2019.

We also collected Phase 2 data studying Bard in each of IgA nephropathy (IgAN), type 1 diabetic CKD (T1D CKD), and focal segmental glomerulosclerosis (FSGS). In each of these Phase 2 cohorts, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 12 weeks of treatment in patients whose available historical data showed annual declines in eGFR in the three-year period prior to study entry. We believe that a registrational clinical trial similar to the design of the Phase 3 CARDINAL and FALCON trials with a two-year duration and a retained eGFR benefit endpoint after one and two years of treatment may be acceptable for submission of an NDA for these forms of CKD to the FDA. We plan to pursue each of these rare and serious forms of CKD as commercial indications.

In addition to our CKD development programs, we are conducting a registrational Phase 2 clinical trial, part 2 of MOXIe, studying our second Nrf2 activator, Omav, in patients with FA. FA is a rare, inherited, debilitating, and degenerative neuromuscular disorder caused by mutations in the gene for frataxin, a mitochondrial protein. Patients with FA are typically dependent on wheelchair use 10 to 15 years after disease onset, and their median age of death is in the mid-30s. There are no currently approved therapies for the treatment of FA. In part 1 of MOXIe, at the optimal dose level, Omav demonstrated a statistically significant improvement in modified Friedreich's Ataxia Rating Scale (mFARS) scores of 3.8 points (p=0.0001) versus baseline and a placebo-corrected improvement in mFARS scores of 2.3 points (p=0.06). Part 2 of MOXIe is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Omav in 103 FA patients randomized one-to-one to active drug or placebo. The FDA has provided us with written guidance that the mFARS score is acceptable as the primary endpoint for part 2 of MOXIe and that it may consider either accelerated or full approval based on the overall results of the trial and strength of the data. We have fully enrolled the trial, and we expect to have top-line data from the trial in the second half of 2019. If the trial results are positive, we believe the trial results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Omav for the treatment of FA.

We are also conducting a Phase 3 trial studying Bard in patients with CTD-PAH called CATALYST. CTD-PAH is a rare, serious and progressive disease that leads to heart failure and death. CTD-PAH patients are less responsive to existing vasodilator therapies than patients with the idiopathic form of PAH (I-PAH) and have a worse prognosis. We have completed a Phase 2 clinical trial called LARIAT in patients with PAH. In LARIAT, Bard demonstrated a statistically significant time-averaged increase in mean 6-minute walk distance (6MWD) at 16 weeks in CTD-PAH patients compared to baseline. Based on discussions with the FDA, the primary endpoint of CATALYST is the change from baseline in 6MWD compared to placebo after 24 weeks of treatment. CATALYST is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in approximately 200 CTD-PAH patients randomized one-to-one to active drug or placebo. We expect to have top-line data from the CATALYST trial in the first half of 2020. If the trial results are positive, we believe the results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of CTD-PAH.

In addition to our lead programs, we are currently exploring a battery of additional clinical and preclinical programs in diseases that may provide meaningful expansion opportunities for Bard and Omav. We also have completed or have ongoing Phase 1 clinical trials with RTA 901, a highly potent and selective C-terminal modulator of Hsp90, and RTA 1701, our lead product candidate from our proprietary series of RORγt inhibitors.

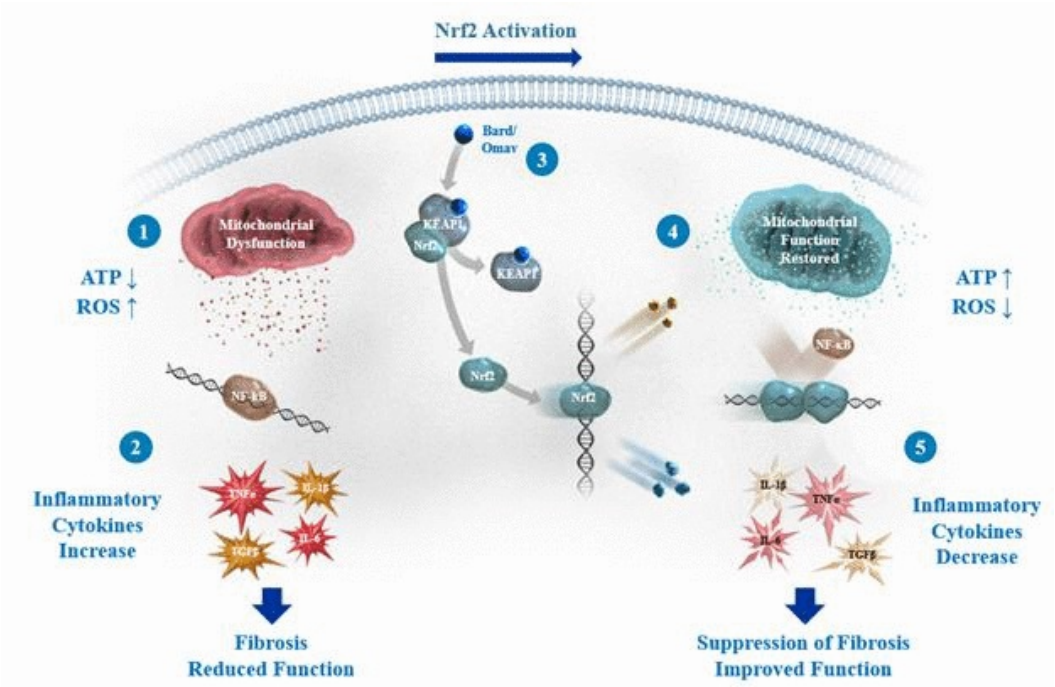
Our Strategy

Our goal is to be a leader in the discovery, development, and commercialization of small-molecule therapies for the treatment of severe and life-threatening diseases. Our strategy includes the following key planned components:

- Announce top-line registrational data from our two lead indications, Alport syndrome and FA, in 2019 and, if successful, seek regulatory approval for both indications in the United States.
- Complete our registrational trial in CTD-PAH in 2020 and, if successful, seek regulatory approval in the United States.

- Continue to build the capabilities to bring Bard and Omav to the market for the treatment of Alport syndrome and FA in the United States, if and when approved.
- Build a franchise in rare CKDs, subject to regulatory approvals, by executing the Phase 3 FALCON trial in ADPKD as the first follow-on indication after Alport syndrome.
- Build the capabilities, or work with current or future collaborators, to internationally commercialize our lead product candidates, Bard and Omav, subject to regulatory approvals.
- Continue to advance our early clinical-stage product candidates, RTA 901 and RTA 1701, into later stage clinical trials and additional preclinical programs through preclinical studies into clinical development.
- Leverage our multiple technologies and relationships to discover new molecules and explore preclinical proof of concept.

Foundational Biology of Our Nrf2 Activators, Our Lead Programs



1 Inflammation and mitochondrial metabolism are closely associated. In many inflammatory diseases, mitochondrial metabolism becomes dysfunctional and is reprogrammed to suppress the production of ATP and increase the production of chemically-reactive molecules called "reactive oxygen species" or ROS.

2 Once released from the mitochondria, ROS amplify pro-inflammatory signaling pathways, such as NF-κB, and increase the production of cytokines such as TNFα, IL-1β, TGFβ, and IL-6. The persistent production of cytokines, impaired redox balance, and mitochondrial dysfunction contribute to chronic inflammation, which can ultimately lead to fibrosis and reduced organ function.

3 By binding to Keap1, Bard and Omav stabilize Nrf2 and increase its activity. Nrf2 is a transcription factor that plays a key role in the resolution of inflammation by regulating the expression of genes involved in mitochondrial metabolism, redox balance, and cytokine production.

4 Nrf2 activation normalizes mitochondrial metabolism and increases ATP production. It also increases the expression of antioxidant enzymes and systems that work together to reduce the levels of ROS and restore redox balance.

5 By normalizing mitochondrial metabolism and restoring redox balance, Nrf2 inhibits proinflammatory signaling. In addition, Nrf2 directly suppresses the expression of proinflammatory cytokine genes by inhibiting their transcription.

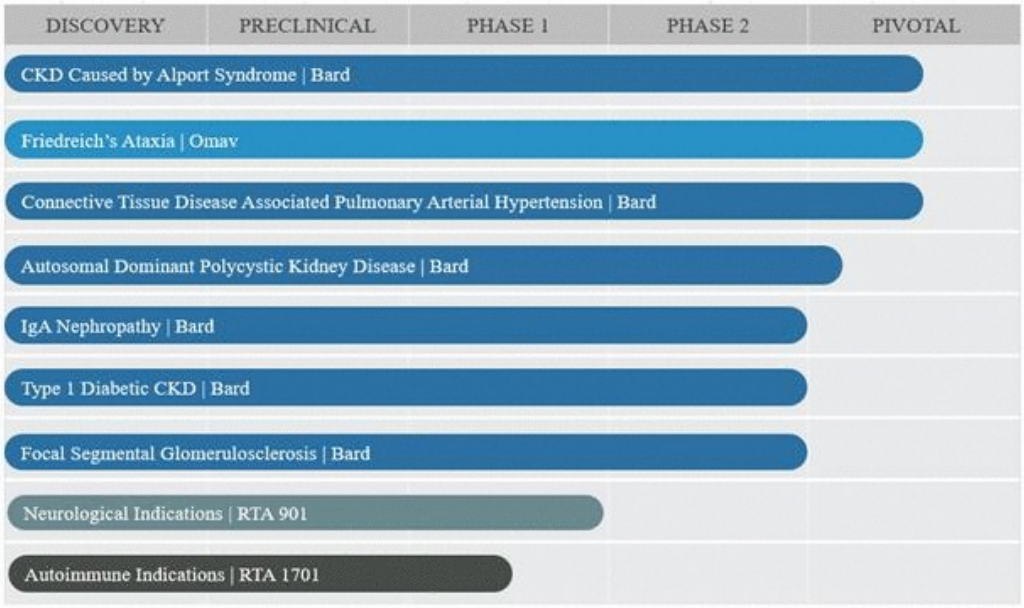
Chronic, unresolved inflammation and impaired cellular metabolism are key features of many diseases. Inflammation is an integral component of the normal immune response that occurs when cells encounter harmful stimuli, such as invading pathogens, damaged cells, or irritants. During inflammation, cells activate inflammatory processes and complexes that increase the production of cytokines, which are proteins that recruit and activate immune cells.

Inflammation and mitochondrial metabolism are closely associated. The mitochondria are often called the "powerhouses" of the cell as they produce the energy that the cell needs to function. This energy is produced by converting fatty acids and glucose into adenosine triphosphate (ATP) by a process called oxidative phosphorylation. During inflammation, mitochondrial metabolism is temporarily reprogrammed to suppress oxidative phosphorylation. Instead of primarily making ATP, the mitochondria divert fatty acids and glucose to increase the production of proinflammatory mediators. During this reprogramming, the mitochondria release chemically-reactive molecules called reactive oxygen species (ROS) that can directly attack pathogens and amplify the production of cytokines.

In a normal immune response, the resolution of inflammation begins after the harmful stimuli have been eliminated. Nrf2 is a protein that plays a key role in the resolution of inflammation by regulating the expression of specific genes involved in mitochondrial metabolism, redox balance, and cytokine production. When activated, Nrf2 promotes the resolution of inflammation by normalizing mitochondrial metabolism, restoring redox balance, and suppressing cytokine production. In many chronic and genetic diseases, Nrf2 activity is suppressed, and the resolution of inflammation fails to occur or is inadequate, leading to persistent mitochondrial dysfunction, excess production of ROS, and production of cytokines. These processes cause chronic inflammation, which can ultimately lead to tissue damage and loss of organ function.

Bard and Omav are Nrf2 activators that selectively bind to Keap1, a protein that governs the activity of Nrf2 in response to cellular stress. By binding to Keap1, Bard and Omav stabilize Nrf2 and increase its activity. Since mitochondrial dysfunction, oxidative stress, and inflammation are features of many diseases, Nrf2 activators, such as Bard and Omav, may have many potential clinical applications. Bard and Omav have been extensively studied by many investigators. Their tissue protective and therapeutic effects have been observed in many preclinical models and are associated with meaningful improvements in hallmarks of disease progression, such as inflammation, tissue remodeling, and fibrosis. Our Nrf2 activators are the subject of over 400 peer-reviewed publications, and have been studied in over 50 preclinical animal models in which they have demonstrated anti-inflammatory, tissue protective, or anti-fibrotic effects in the kidney, heart, brain, liver, lungs, vasculature, fat tissue, pancreas, bone marrow, intestines, eyes, spinal cord, prostate, inner ear, and skin.

Our Programs



Bard for the Treatment of Rare CKD

We are developing Bard for the treatment of patients with five rare forms of CKD that, in the aggregate, affect more than 700,000 patients in the United States. CKD is characterized by a progressive worsening in GFR, the rate at which the kidney filters waste products from the blood. When GFR falls too low, patients typically develop ESKD and require dialysis or a kidney transplant to survive. Dialysis leads to a reduced quality of life and increases the likelihood of serious and life-threatening complications. The five-year survival rate for hemodialysis patients is only approximately 42%. The number of patients with kidney failure in the United States has nearly doubled in the last two decades with an estimated 725,000 patients as of 2016. Approximately 30% of these patients suffer from a rare form of CKD. Other than tolvaptan, which is approved for ADPKD, the only approved therapies in the United States that affect disease progression for any form of CKD are blood pressure medications, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) approved for diabetic kidney disease, that modestly slow the rate of kidney function loss. There are no other approved therapies in the United States for Alport syndrome or the four additional rare forms of CKD addressed by our program.

The initiating events that promote CKD can be quite different, but a substantial body of evidence has emerged that inflammation is a final common pathway promoting progression in most forms of CKD. Bard has been evaluated in many preclinical models of CKD and, unlike blood pressure medications, it addresses inflammation in the kidney. In preclinical studies that are the subject of more than 40 recent peer-reviewed publications, Bard and related analogs have been shown to reduce inflammation, improve kidney function, or prevent injury, remodeling, or fibrosis of the kidney in many animal models of kidney disease. Bard has been evaluated in multiple clinical trials enrolling over 2,000 patients exposed to active drug and has been shown to consistently improve kidney function as measured by eGFR and other markers of kidney function. As a consequence, we believe that Bard treatment has the potential to delay or prevent the loss of kidney function that causes the need for dialysis or a transplant in patients with Alport syndrome and other rare forms of CKD.

Our lead clinical program in rare forms of CKD is studying the safety and efficacy of Bard treatment in patients with Alport syndrome in a registrational Phase 3 study called CARDINAL. We designed CARDINAL based on guidance from the FDA on a potential path to approval. We have fully enrolled CARDINAL, and we expect to have one-year top-line results available in the second half of 2019. We have completed our Phase 2 trial PHOENIX, studying Bard in each of ADPKD, IgAN, T1D CKD, and FSGS. In each of these Phase 2 studies, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 12 weeks of treatment in patients whose available historical data showed annual declines in eGFR in the three-year period prior to study entry. Based on these results, we are currently initiating a Phase 3 trial studying Bard in patients with ADPKD called FALCON. We designed FALCON based on the results of our Phase 2 program and guidance from the FDA on a potential path to approval. We plan to enroll the first ADPKD patient in FALCON in mid-2019. Based on the Phase 2 results, we plan to pursue IgAN, T1D CKD, and FSGS as commercial indications.

Background on Rare Forms of CKD, eGFR, and the Burden of ESKD and Dialysis

CKD is characterized by a progressive loss in the rate at which the kidney is filtering blood, called GFR. CKD generally results from diabetic complications, hypertension, obesity, genetic defects, or autoimmunity. The initiating events that promote CKD can be quite different, but a substantial body of evidence has emerged that inflammation is a common underlying feature for most forms of CKD.

Declining kidney function leads to the buildup of high levels of waste products in the blood that causes the patient to suffer symptoms, such as nausea and fatigue, and to develop complications including high blood pressure, anemia, weak bones, poor nutritional health, and nerve damage. eGFR is an estimate of GFR that nephrologists use to track the decline in kidney function and progression of CKD. Normal individuals have an eGFR of approximately 120 mL/min/1.73 m^2. When eGFR declines to approximately 15 mL/min/1.73 m^2 or below, patients generally develop ESKD and require dialysis or a kidney transplant to survive.

Dialysis leads to a reduced quality of life, and most patients must spend several hours at a dialysis clinic three times a week for the remainder of their life and may suffer side effects due to dialysis. Dialysis also increases the likelihood of serious and life-threatening complications, such as cardiovascular disease, and the five-year survival rate for hemodialysis patients is only approximately 42%. The number of patients with ESKD in the United States has nearly doubled in the last two decades with an estimated 725,000 patients as of 2016. Approximately 30% of these patients suffer from a rare form of CKD. In 2015, Medicare spending for CKD was $98 billion, of which $34 billion was spent on patients with ESKD. Other than tolvaptan, which is approved for ADPKD, the only approved therapies in the United States that affect disease progression for any form of CKD are blood pressure medications, ACE inhibitors, and ARBs, approved for diabetic kidney disease, that modestly slow the rate of kidney function loss. There are no other approved therapies in the United States for Alport syndrome or the four additional rare forms of CKD addressed by our program.

Bard Targets Inflammatory Pathways that Contribute to GFR Loss and ESKD

Inflammatory processes initiated by a variety of pathogenic stimuli, including diabetes, systemic hypertension, IgA deposition, and genetic mutations drive declining kidney function. At the molecular level, these pathogenic stimuli activate pro-inflammatory signaling pathways that normally detect cellular damage or pathogens. These signals induce mitochondrial dysfunction in which production of ATP is impaired in favor of production of pro-inflammatory mitochondrial ROS. ROS production activates pro-inflammatory signaling complexes including NF-κB to produce TNFα, IL-6, IL-1, IFNγ, angiotensin II, and other cytokines that initiate inflammatory pathways in glomerular endothelial cells, mesangial cells, and podocytes, while also recruiting activated macrophages and other inflammatory effector cells to the renal interstitium. At the physiological level, chronic activation of pro-inflammatory pathways in these kidney cells promotes GFR loss. Glomerular endothelial dysfunction and mesangial cell contraction are dynamic processes that impair GFR by reducing the glomerular surface area for filtration. Chronic activation of inflammatory pathways also leads to GFR loss through GBM thickening and glomerular sclerosis.

Bard targets inflammatory pathways that contribute to kidney function loss. The activity of Nrf2, the target of Bard, has been shown to protect the kidney in preclinical studies that are the subject of many peer-reviewed manuscripts. Nrf2 gene ablation intensifies inflammation, oxidative stress, and kidney injury, remodeling, and fibrosis in multiple animal models of kidney disease. Nrf2-knockout mice exhibit a lupus-like autoimmune nephritis, and histologic analyses of kidney tissue show impaired antioxidant activity and increased oxidative damage including enlarged glomeruli, mesangial cell proliferation, GBM thickening, and glomerulosclerosis. Kidney function is compromised in these animals, as evidenced by a significant decrease in creatinine clearance and survival. Similarly, Nrf2-knockout mice are more susceptible to nephrotoxic insults and develop more severe kidney impairment in multiple animal models of kidney disease.

In a large biopsy study of 157 patients representing nine different types of CKD, patients' biopsy samples were analyzed to determine genes and mutations associated with kidney function, as assessed clinically by eGFR. Etiologies of CKD included thin basement membrane nephropathy, of which most are now considered patients with Alport syndrome, IgAN, diabetes, FSGS, hypertension, lupus, and others. Eighteen genes and 97 molecular pathways were identified that affect eGFR. Two clusters of pathways were identified that comprise inflammation and metabolic pathways, and Nrf2 was identified as a central link. Collectively, these data establish that Nrf2 plays an important role in maintaining the function and structure of the kidney. They also demonstrate that Nrf2 affects a final common pathway of progression across diverse etiologies of CKD.

Bard is an Nrf2 activator that selectively binds to Keap1, a protein that governs the activity of Nrf2 in response to cellular stress. By binding to Keap1, Bard stabilizes Nrf2 and increases its activity. Through Nrf2, Bard activates molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signaling. Bard and closely related structural analogs have been shown to improve kidney function, reduce inflammation, and prevent injury, remodeling, and fibrosis in a number of preclinical models of kidney injury and disease. In particular, Bard and related analogs have been shown to reduce hyperfiltration-mediated fibrosis and glomerular sclerosis in the pressure overload model of CKD, to reduce tubulointerstitial inflammation and fibrosis in a high protein model of CKD, and to reverse endothelial dysfunction and mesangial cell contraction in response to angiotensin II, thereby improving glomerular function and GFR. Thus, Bard and analogs have been shown to be protective in several animal models of kidney disease and have been demonstrated to preserve kidney function and prevent structural remodeling and fibrosis in the kidney.

Filtration of blood in the kidney is governed by intraglomerular pressure and surface area of the glomerular capillaries, and reductions in GFR therefore directly correlate with decreases in glomerular surface area. Activation of pro-inflammatory pathways in the kidney promotes GFR loss by at least three mechanisms. Two of these mechanisms, glomerular endothelial dysfunction and mesangial cell contraction, are dynamic processes that decrease glomerular surface area and GFR. Inflammation-associated processes deplete vasodilatory nitric oxide, resulting in loss of glomerular endothelial function. Mesangial cells regulate blood flow by their contractile activity, and inflammation and oxidative stress induces mesangial cell contraction to reduce the surface area for filtration and the single nephron GFR. Chronic activation of inflammatory pathways also leads to long-term structural alterations in the mesangium, which results in reduced glomerular surface area and GFR.

Overview of Clinical Trials of Bard in CKD

Bard has been evaluated in multiple clinical trials enrolling over 2,000 patients exposed to active drug, including those with CKD caused by Alport syndrome, ADPKD, IgAN, T1D CKD, type 2 diabetic CKD (T2D CKD), and FSGS. Bard has been shown to consistently improve kidney function as measured by eGFR and other markers of kidney function in numerous clinical trials. Key findings from clinical trials of Bard's effects on kidney function are summarized below.

Bard Demonstrated Improvements in Kidney Function as Assessed by eGFR, Measured GFR (Inulin Clearance), Creatinine Clearance, and other Measures

Bard's effects on kidney function have been assessed using the "gold standard" inulin clearance method of directly measuring GFR. In TSUBAKI, a double-blind, randomized, placebo-controlled Phase 2 trial conducted by our licensee, KHK, Bard demonstrated statistically significant and clinically meaningful increases in directly-measured GFR. Moreover, directly-measured GFR increases were significantly and positively correlated with improvements in eGFR. In several studies, Bard significantly increased creatinine clearance, another assessment of kidney function. These increases were not associated with a change in total 24-hour excretion of creatinine, which demonstrates that Bard does not affect creatinine metabolism. In other CKD studies, Bard has been shown to significantly reduce blood waste products in inverse correlation to eGFR increases and to numerically reduce kidney serious adverse events (SAEs) and ESKD events. Taken together, these data demonstrate that the increases in eGFR observed in multiple CKD studies of Bard treatment reflect improvements in kidney function and support the use of eGFR as a reliable marker of kidney function.

Bard Demonstrated Improvement in Kidney Function in Diverse Types of CKD and in a High Percentage of Treated Patients within Each Subtype of CKD

The safety and efficacy of Bard treatment have been studied in clinical trials of patients with six different types of CKD. Bard has produced statistically significant improvements in eGFR versus baseline or placebo in patients Alport syndrome, ADPKD, IgAN, T1D CKD, T2D CKD, and FSGS. A high percentage of patients, called responders, in each subtype of CKD treated with Bard experienced improvements in kidney function. The observed broad and consistent improvements in kidney function demonstrated with Bard treatment suggest that Bard's mechanism is targeting a common pathogenic feature of many types of CKD.

Patients with CKD have been treated with Bard for one year or longer in three prior trials, with no evidence of an increased risk of kidney toxicity, as assessed by kidney SAEs, ESKD events, or the proportion of patients with clinically meaningful loss of eGFR. Additionally, there has been no evidence of kidney injury based on validated markers of kidney injury (urinary neutrophil gelatinase-associated lipocalin (NGAL) and N-acetyl-beta-d-glucosaminidase (NAG)). Apart from the patient-specific fluid overload events observed in advanced T2D CKD patients (discussed below), Bard was well-tolerated and appears to possess a favorable clinical safety profile. The most common AEs associated with Bard treatment in previous trials included muscle spasms (34%), pain (18%), nausea (18%), hypomagnesemia (15%), fatigue (15%), decreased appetite (14%), and weight loss (13%).

Bard Treatment Produced Sustained eGFR Improvements and Reduced the Risk of Adverse Kidney Outcomes

In three separate clinical trials, Bard treatment produced increases in eGFR in CKD patients treated for one year or longer. In the Phase 2 portion of CARDINAL, Bard demonstrated a statistically significant increase from baseline in mean eGFR of 10.4 mL/min/1.73 m^2 ($p<0.0001$) after 48 weeks of treatment. Historical data available for 22 of the patients showed eGFR declined an average of 4.2 mL/min/1.73 m^2 per year in the three-year period prior to enrolling in the trial. This magnitude of improvement in mean eGFR represents the recovery of over two years of average decline in kidney function in Alport syndrome patients in this trial.

In BEACON, a large, international Phase 3 trial in patients with T2D CKD, Bard-treated patients had increases in mean eGFR through Week 48 of 5.6 mL/min/1.73 m^2. In contrast, placebo-treated patients experienced a decline in mean eGFR of 1.2 mL/min/1.73 m^2, corresponding to a statistically significant relative difference between groups of 6.8 mL/min/1.73 m^2 ($p<0.001$). In BEAM, a randomized, placebo-controlled 52-week Phase 2 trial in patients with T2D CKD, Bard-treated patients at the mid- and high doses had increases in mean eGFR through Week 48 of 14.9 mL/min/1.73 m^2. In contrast, placebo-treated patients experienced a decline in mean eGFR of 1.1 mL/min/1.73 m^2, corresponding to a statistically significant relative difference between groups of 16.0 mL/min/1.73 m^2 ($p<0.001$).

In BEACON, post-hoc analysis showed that patients randomized to Bard were significantly less likely to experience adverse kidney outcomes as defined by a composite endpoint consisting of ≥30% decline from baseline in eGFR, eGFR <15 mL/min/1.73 m^2, or ESKD events (HR=0.48, $p<0.0001$). This composite endpoint has recently been validated by a joint FDA, European Medicines Agency (EMA), and the National Kidney Foundation working group. Furthermore, Bard treatment resulted in a decreased number of kidney-related SAEs and ESKD events. The data suggest that Bard treatment preserves kidney function and may delay the onset of kidney failure in patients with T2D and stage 4 CKD.

Bard Treatment Produced a Retained eGFR Benefit after Withdrawal of Drug Suggesting Bard Modified the Course of CKD

The FDA has provided guidance to us and other sponsors that clinical trials with a retained eGFR benefit analysis may support approval in certain rare forms of CKD. The retained eGFR benefit is the patient's eGFR change compared to baseline after long-term treatment of approximately one year and withdrawal of active drug. We believe measuring eGFR after withdrawal of active drug isolates, and allows the measurement of, the functional improvement associated with the effect of the drug on the underlying structure of the kidney. If the drug produces an improvement in retained eGFR versus placebo, it is strong evidence that the drug has modified the course of the disease and may delay or prevent the need for dialysis or a transplant.

The duration of withdrawal varies by drug and is based on the drug's pharmacokinetic (PK)/pharmacodynamics (PD) profile, including the time it takes for a drug to reach sub-therapeutic concentrations and the reversal of PD markers. Bard is eliminated from the system within 10 days after cessation of drug treatment, and the FDA has indicated that a four-week withdrawal period, which represents approximately 17 half-lives of the drug, is appropriate for Bard in the Phase 3 CARDINAL and FALCON studies.

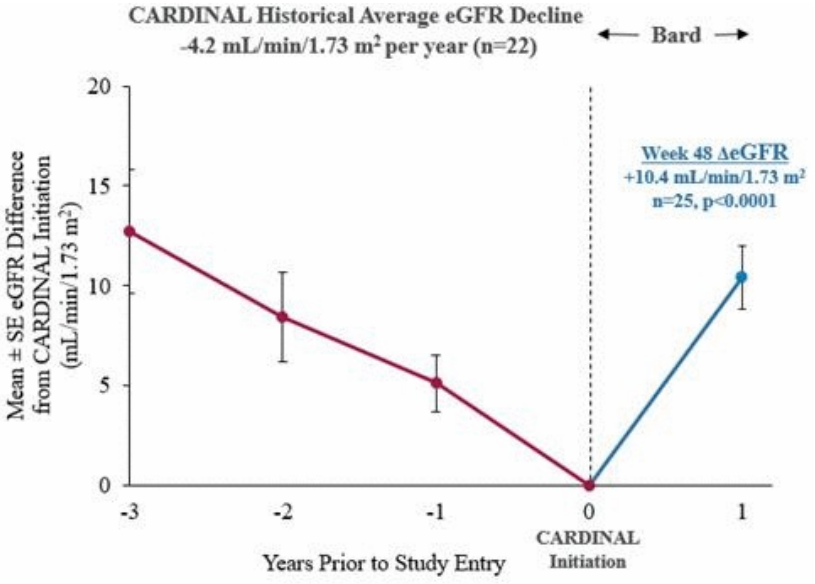
We assessed retained eGFR benefit in three clinical trials: BEAM, BEACON, and the Phase 2 portion of CARDINAL. In each of those trials, after patients had been treated with Bard for approximately one year, the drug was withdrawn for four weeks, and the post-withdrawal eGFR was compared to the patient's baseline eGFR. In each of these trials, Bard treatment produced a statistically significant improvement in retained eGFR versus baseline after withdrawal of drug. To our knowledge, Bard is the first therapy to produce a retained eGFR benefit that is above baseline in a long-term CKD trial. We believe the retained eGFR benefit observed in these clinical trials demonstrates that Bard treatment improved the structure of the kidney, modified the course of the disease, and may prevent or delay kidney failure and the need for dialysis or a kidney transplant. The FDA has provided us with written guidance that, in patients with CKD caused by Alport syndrome or ADPKD, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval and an improvement versus placebo after two years of treatment may support full approval.

Bard Development Program for the Treatment of CKD Caused by Alport Syndrome

Alport syndrome is a rare and serious hereditary disease caused by a genetic defect in type IV collagen, a component of the glomerular basement membrane (GBM) in the kidney, which results in alterations to the GBM structure and impairs its function. Compromised GBM, along with other disease factors, contributes to chronic inflammation, which results in glomerular scarring, interstitial fibrosis, and progressive loss of kidney function. Patients with Alport syndrome experience an average annual decline in eGFR of 3 to 4 mL/min/1.73 m^2. In patients with the most severe forms of Alport syndrome, approximately 50% progress to dialysis by age of 25, 90% by age 40, and nearly 100% by age 60. Currently, there are no 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 ACE inhibitors or ARBs, which are intended to reduce the rate of kidney function loss.

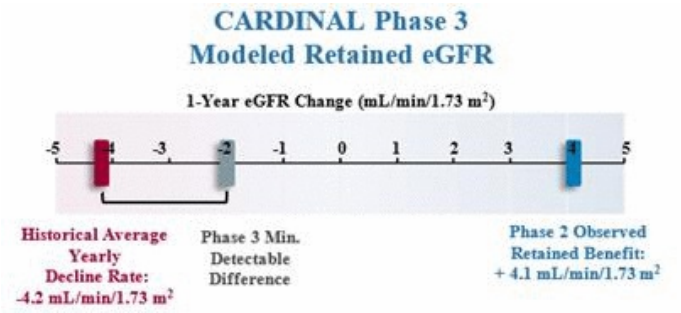
The Phase 3 portion of CARDINAL is an international, multi-center, randomized trial, which is double-blind and placebo-controlled, that studies the safety and efficacy of Bard in patients with CKD caused by Alport syndrome. We have completed enrollment of CARDINAL with 157 patients, randomized one-to-one to either Bard or placebo, at approximately 50 sites in the United States, Europe, Japan, and Australia. We will assess on-treatment eGFR at 48 weeks and retained eGFR at 52 weeks. After 52 weeks, patients will be restarted on study drug with their original treatment assignments and will continue on study drug for a second year. The second-year on-treatment eGFR will be measured after 100 weeks and the retained eGFR will be measured at Week 104. All patients who complete the treatment period are eligible to continue into an extension trial to evaluate the intermediate and long-term safety of Bard. Those patients who had been receiving placebo will be converted to Bard in the extension trial. One-year top-line results from the Phase 3 portion of CARDINAL are expected to be available in the second half of 2019. The trial is being overseen by a data monitoring committee (DMC) that reviews all data, including SAE and AE data, on an unblinded basis, to assess safety. The DMC has not reported any safety concerns to date.

In the Phase 2 portion of CARDINAL, Bard demonstrated a sustained eGFR improvement in patients whose disease was actively progressing on standard of care. In 25 patients, Bard demonstrated a statistically significant increase from baseline in mean eGFR of 10.4 mL/min/1.73 m^2 ($p<0.0001$) after 48 weeks of treatment. Historical data available for 22 of the patients showed eGFR declined an average of 4.2 mL/min/1.73 m^2 per year in the three-year period prior to enrolling in the trial. This magnitude of improvement in eGFR represents the recovery of over two years of average decline in kidney function in Alport syndrome patients in this trial. Further, all patients in the Phase 2 portion of CARDINAL had an increase in eGFR from baseline at Week 12, and these increases in eGFR translated to an improvement in CKD stage for approximately 73% of patients. No treatment-related SAEs were reported, and the reported AEs have generally been mild to moderate in intensity.



In the Phase 2 portion of CARDINAL, Bard also demonstrated a statistically significant increase from baseline in mean retained eGFR of 4.1 mL/min/1.73 m^2 ($p<0.05$) at Week 52. To our knowledge, Bard is the first therapy to produce a retained eGFR benefit that is above baseline in a long-term CKD trial. As noted above, we believe measuring eGFR after withdrawal of active drug isolates, and allows the measure of, the functional improvement associated with the effect of the drug on the underlying structure of the kidney. We believe the retained eGFR benefit observed in the Phase 2 portion of CARDINAL provides evidence that Bard treatment improved the structure of the kidney, modified the course of the disease, and may prevent or delay kidney failure and the need for dialysis or a kidney transplant.

As shown in the figure below, Phase 3 modeling[1] based on this one year retained eGFR benefit and the annual average historical eGFR decline of 4.2 mL/min/1.73 m^2 suggests a potential placebo-corrected retained benefit of 8.3 mL/min/1.73 m^2. The Phase 3 portion of CARDINAL, at 157 patients, is conservatively powered to detect a placebo-corrected retained benefit of 2.2 mL/min/1.73 m^2.



[1]Modeled changes are not intended as a forecast of probable results. No assurance is given about the results that will be obtained.

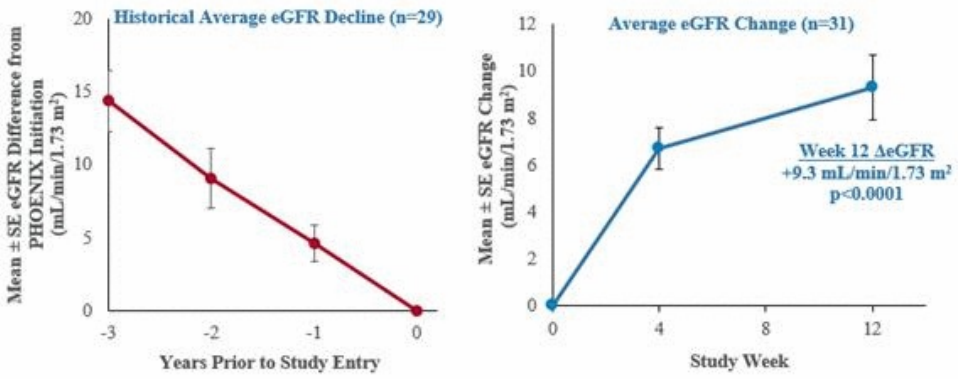
The FDA has provided us with written guidance that, in patients with CKD caused by Alport syndrome, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval and an improvement versus placebo after two years of treatment may support full approval. If the results of the Phase 3 portion of CARDINAL are positive, we believe the results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of CKD caused by Alport syndrome. We have received orphan drug designation from the FDA for Bard for the treatment of Alport syndrome.

Bard Development Program for the Treatment of ADPKD

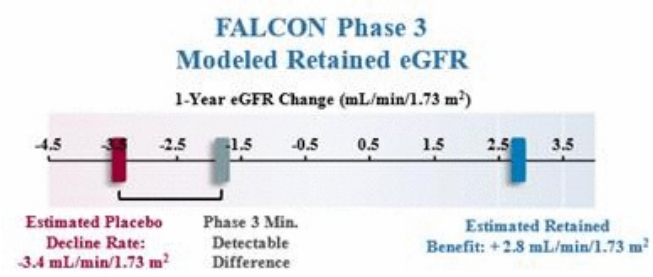
ADPKD is an inherited, rare form of CKD caused by a genetic defect in PKD1 or PKD2 and is characterized by formation of fluid-filled cysts in the kidneys. Inflammation appears to play a role in cyst growth and is associated with disease progression in ADPKD. PKD1 is the most common mutation, causing about 85% of ADPKD cases and patients with the PKD1 mutation to progress to ESKD, on average, by age 54. ADPKD is the most common single-gene disorder of the kidneys, and there are an estimated 400,000 patients in the United States, with approximately 140,000 diagnosed. The only therapy currently approved for ADPKD is tolvaptan, which was approved in the United States during 2018.

We are initiating a pivotal Phase 3 trial called FALCON in patients with ADPKD. FALCON is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in approximately 300 ADPKD patients randomized one-to-one to active drug or placebo. We plan to enroll the first ADPKD patient in FALCON during mid-2019. We will measure the retained eGFR benefit at 52 weeks. After 52 weeks, patients will be restarted on study drug with their original treatment assignments and will continue on study drug for a second year. The second-year retained eGFR benefit will be measured at Week 104.

FALCON was designed and powered based on data from the ADPKD cohort of the Phase 2 PHOENIX trial. In PHOENIX, Bard demonstrated a statistically significant increase in eGFR of 9.3 mL/min/1.73 m^2 ($p<0.0001$) after 12 weeks of treatment in 31 patients with ADPKD. Historical data available for 29 of the patients showed that their eGFR declined an average of 4.8 mL/min/1.73 m^2 per year in the three-year period prior to enrolling in the trial. The magnitude of improvement in eGFR observed with Bard represents the recovery of approximately two years of average decline in kidney function in the patients in this trial. The ADPKD patients showed a high response rate, with all but one patient showing improvement at Week 12. No drug-related serious adverse events were reported, and reported adverse events were generally mild to moderate in intensity.



As shown in the figure below, Phase 3 modeling[1] estimates a retained eGFR of 2.8 mL/min/1.73 m^2 in the Bard group relative to baseline. The modeled retained eGFR benefit is based on 30% of the Week 12 eGFR benefit of 9.3 mL/min/1.73 m^2. In BEAM, BEACON, and the Phase 2 portion of CARDINAL, Bard treatment produced a statistically significant improvement in retained eGFR versus baseline or placebo after withdrawal of drug. The acute increase in eGFR from Bard treatment observed at 12 weeks was predictive of the on-treatment eGFR change after one year of treatment and associated with a retained eGFR benefit. In addition, a placebo decline of 3.4 mL/min/1.73 m^2 (less than the annual eGFR decline observed prior to study entry in ADPKD patients in PHOENIX) has been estimated based on several recently published ADPKD trials, which suggests a potential placebo-corrected retained benefit of 6.2 mL/min/1.73 m^2. FALCON is powered to detect a placebo-corrected retained benefit of 1.6 mL/min/1.73 m^2.



[1] *Modeled changes are not intended as a forecast of probable results. No assurance is given about the results that will be obtained.*

The FDA has provided us with written guidance that, in patients with ADPKD, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval and an improvement versus placebo after two years of treatment may support full approval. If the trial results are positive, we believe the results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of ADPKD.

Bard Development Program for the Treatment of Other Rare Kidney Diseases

We believe the mechanism of action of Bard addresses a final common pathway of kidney function loss, and we have observed significant increases in eGFR in patients with declining kidney function from a variety of diseases. As a consequence, we conducted a Phase 2 trial called PHOENIX to assess whether Bard treatment can improve kidney function in patients with four rare forms of CKD: ADPKD, IgAN, T1D CKD, and FSGS. IgAN is a rare form of CKD caused by deposition of IgA complexes in the kidney and is estimated to affect 120,000 patients in the United States. CKD is a common complication of T1D and is estimated to affect 20% of the approximately one million T1D patients in the United States. FSGS is a rare form of CKD that results from the chronic inflammation and scarring of the glomeruli and affects an estimated 40,000 patients in the United States.

PHOENIX was an open-label, multi-center Phase 2 trial evaluating the safety and efficacy of Bard in patients with ADPKD, IgAN, T1D CKD, or FSGS. A total of 103 patients were enrolled in the study in four separate cohorts, including 31 patients with ADPKD, 26 with IgAN, 28 with T1D CKD, and 18 with FSGS. Patients were treated with Bard for 12 weeks in all four cohorts, and all four cohorts showed statistically significant increases in mean eGFR, as shown in the table below.

	Week 12 ΔeGFR (Mean ± SE)	**P-value vs. Baseline**
ADPKD (n=31)	9.3 ± 1.4	P < 0.0001
IgAN (n=26)	8.0 ± 1.6	P < 0.0001
T1D (n=28)	5.5 ± 2.3	P = 0.02
FSGS (n=18)	7.8 ± 2.2	P = 0.003
All (n=103)	7.8 ± 0.9	P < 0.0001

Each cohort achieved a statistically significant increase in mean eGFR at Week 12, and there was a consistent response across cohorts. Of the patients that reached Week 12, 88% experienced increases in eGFR at Week 12. Bard significantly reduced mean systolic blood pressure by 3.8 mmHg (n=103; p=0.002) and mean diastolic blood pressure by 2.8mmHG (n=103; p=0.0009). Urinary albumin excretion was low upon study entry and remained unchanged by Bard treatment (n-103; p=0.6). The most commonly reported AE across all cohorts was muscle spasms, which were not associated with clinical signs or symptoms of muscle injury. No SAEs were reported as related to Bard.

Based on the eGFR improvements observed in PHOENIX patients, we plan to pursue IgAN, T1D CKD, and FSGS as commercial indications. We believe that a registrational clinical trial similar to the design of the Phase 3 CARDINAL and FALCON trials with a two-year duration and a retained eGFR benefit endpoint after one and two years of treatment would be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of these forms of CKD.

Commercial and Manufacturing Preparations for Bard in Rare CKD

We are in the process of preparing for a potential commercial launch of Bard in Alport syndrome in the United States. Our ability to launch Bard is dependent on a successful outcome of the Phase 3 portion of CARDINAL, the successful filing and defense of an NDA, and approval by the FDA. We have hired commercial and medical affairs leaders, and we are building the teams, infrastructure, systems, and processes necessary for the launch of Bard in the United States, including sales, marketing, market access, patient support, medical affairs, distribution, quality, and compliance functions.

If we receive approval for Bard in Alport syndrome, we plan to utilize a specialty pharmacy distribution model to support product availability to patients, with a patient-centered hub to support on-label utilization, ease of access, and patient education and compliance. We have completed preliminary field force sizing and structure for sales and access teams. The trade naming process is underway. We have launched disease awareness campaigns to educate physicians about Alport syndrome.

Our manufacturing and quality teams are in place for the current stage of program development with plans to grow as needed to support commercial supply and distribution. We have made good progress to establish a robust supply chain to adequately support clinical and near-term commercial demand after launch. We have completed process validation batches for drug substance and registration batches for drug product. A three-year, room temperature shelf life is currently established for clinical-image Bard capsules at multiple doses, which is anticipated to reflect commercial product. In addition, our synthesis process from regulatory starting material to drug substance results in a reasonable cost of goods.

Bard Development Program for the Treatment of Type 2 Diabetic CKD

Early Termination of BEACON Study

Prior to initiating the current clinical development programs, Bard was evaluated in six Phase 1 and 2 studies in patients with T2D CKD that demonstrated significant improvements in kidney function as evidenced by increases in eGFR and other markers of kidney function as discussed above. Based on the Phase 2 results, we conducted BEACON, a large, international Phase 3 trial in patients with T2D CKD. In 2010, when the study was initiated, guidance from the FDA required the study to demonstrate that Bard treatment significantly reduce the risk of ESKD and death events for approval. Because CKD patients' kidney function declines very slowly over a long period of time, BEACON enrolled only severe or Stage 4 CKD patients that had baseline eGFR values close to the threshold for ESKD.

During October 2012, BEACON was terminated in response to the independent DMC's recommendation to stop the trial for safety concerns. 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.

Development of Risk Mitigation Plan for Fluid Retention

Further investigation, including additional preclinical studies, indicated that Bard modulates the endothelin pathway. In patients with Stage 4 and 5 diabetic CKD, 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 kidney 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 diabetic CKD treated with other therapies, including endothelin receptor antagonists (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 in patients with Stage 4 diabetic CKD identified two major risk factors as predictors of fluid overload events: prior hospitalization for heart failure and baseline elevation in B-type natriuretic peptide (BNP), a clinical chemistry measure of fluid status. Bard-treated patients that experienced heart failure events in BEACON had mean BNP values at baseline, and before receiving study drug, of approximately 550 pg/mL. Normal BNP levels are less than 100 pg/mL, suggesting many of the patients with fluid overload were in heart failure prior to randomization. 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 diabetic CKD 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.

Safety Experience Using Risk Mitigation Plan and Results of TSUBAKI Trial

Based on these findings, we resumed clinical development of Bard, excluding at-risk patients by using these identified risk factors and closely monitoring trial participants for signs and symptoms of fluid retention during the first few weeks after treatment initiation. Risk mitigation features have been implemented in all clinical trials of Bard

in CKD patients including CARDINAL, our global Phase 2/3 study of patients with Alport syndrome, and PHOENIX, a study in patients with CKD due to FSGS, T1D CKD, IgAN, or ADPKD. We have also implemented risk mitigation procedures in CATALYST, our global Phase 3 study of patients with CTD-PAH, and LARIAT, our Phase 2 study of patients with PAH. The risk mitigation strategies adopted for Bard are similar to those adopted by developers of ERAs. For example, the inclusion/exclusion criteria for trials studying AbbVie's ERA atrasentan and Retrophin's ERA/ARB drug sparsentan utilize a patient's prior history of heart failure, current heart failure, and elevated BNP as key components of their exclusion criteria.

Our licensee, KHK, implemented risk mitigation features in TSUBAKI, their clinical study of Bard in patients with Stage 3 and 4 diabetic CKD in Japan. TSUBAKI used the risk mitigation plan to exclude patients at risk for fluid retention and carefully monitored cardiac status. Results from TSUBAKI demonstrated that Bard was not associated with any evidence of cardiotoxicity, based on assessments of serial measurements of troponin T and cardiac function by echocardiography. Moreover, while eGFR improved, there were no associated changes in blood pressure or other signs of overt volume retention. Further, urine volume and sodium excretion were unchanged relative to placebo patients. The trends observed in safety parameters were similar between patients with Stage 3 and 4 diabetic CKD and there were no fluid overload hospitalizations reported in the study. Thus, data from TSUBAKI demonstrate that by prospectively enrolling patients who were not at risk for fluid retention, Bard appeared well-tolerated in patients with Stages 3 and 4 diabetic CKD.

To date, none of these studies has shown an increased risk for acute fluid overload AEs with Bard treatment. The absence of overt fluid overload or subclinical measures of heart failure, including meaningful increases in blood pressure, BNP, or body weight, in these studies demonstrate that prospectively enrolling patients who are not at risk for heart failure may mitigate the risk for fluid retention with Bard previously seen in patients with late-stage diabetic CKD.

AYAME Trial in Diabetic CKD Conducted by KHK

Upon completion of TSUBAKI and successful discussions with the Japanese PMDA, KHK finalized the design of a Phase 3 outcomes trial in patients with diabetic kidney disease, which is named AYAME. This trial is being conducted in Japan and is enrolling patients with Stage 3 or 4 diabetic CKD. This trial uses the same risk mitigation strategy to avoid overt fluid retention that was used in TSUBAKI. The primary endpoint is time to onset of a $\geq$ 30% decrease in eGFR from baseline or ESKD. The trial is expected to be completed in the first half of 2022.

Omav for the Treatment of Neuromuscular Diseases

In addition to our CKD development programs, we are conducting a registrational Phase 2 clinical trial, part 2 of MOXIe, studying our second Nrf2 activator, Omav, in patients with a rare neuromuscular disorder called FA. Neuromuscular diseases are commonly driven by mitochondrial dysfunction that impairs ATP production, due to the high energy demand of the nervous system. Impaired ATP production likely accounts for the decreased coordination, progressive muscle weakness, exercise intolerance, and fatigue observed in patients with FA, as well as other disease manifestations. All components of the neuromuscular system, including muscle, the neuromuscular junction, peripheral nerves, spinal cord, and the brain, can be affected. These diseases include ataxias, stroke, Parkinson's disease, multiple sclerosis, Huntington's disease, and many others. These diseases can strike as early as infancy, and symptoms can include poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, neurological problems, autonomic dysfunction, and dementia.

Because mitochondrial dysfunction is a key feature of many neuromuscular diseases, we believe Omav may be broadly applicable to treat neuromuscular diseases by activating Nrf2 to normalize and improve mitochondrial function and ATP production. In preclinical models, Omav reduced seizure frequency in refractory, progressive epilepsy models and restored mitochondrial function in biopsy samples from FA, ALS, and familial Parkinson's disease patients. Omav has also been shown *in vitro* to restore mitochondrial activity in fibroblasts isolated from FA patients. In clinical trials, improvements in neuromuscular function have been observed in FA patients treated with Omav as assessed by mFARS rating scale, and improvements in mitochondrial function, as measured by reductions in blood lactate and heart rate, have been observed in patients with primary mitochondrial disease. Accordingly, we believe that Omav has the potential to treat a number of neuromuscular diseases with few or no effective therapies.

Omav Development Program for the Treatment of Friedreich's Ataxia

Friedreich's Ataxia

FA is an inherited, life-shortening, debilitating, and degenerative neuromuscular disorder, which is normally diagnosed during adolescence and is caused by a mutation in the frataxin gene. 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 mitochondrial iron overload and poor cellular iron regulation, increased sensitivity to oxidative stress, and impaired mitochondrial ATP production. 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.

FA is usually diagnosed by genetic testing, with approximately 75% of people with FA diagnosed between six and 20 years of age. Childhood-onset FA can occur as early as age five, is more common than later-onset FA, and normally involves more rapid disease progression. Most 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 mean age of death for FA patients is 35 years. Currently, there are no approved therapies for the treatment of FA. Patients are usually given guidelines for certain lifestyle habits and are recommended to follow a diet that is low in iron and encouraged to take vitamins and supplements.

Rationale for Omav in FA

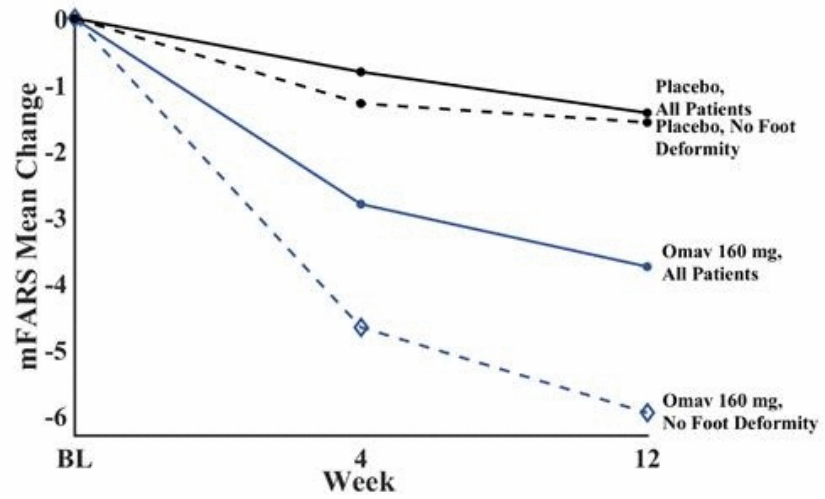
Because impaired ATP production in FA patients likely accounts for the decreased coordination, progressive muscle weakness, exercise intolerance, and fatigue observed in these patients, as well as other disease manifestations, we believe that Omav may be effective in treating this indication. In FA patients, mitochondrial function is correlated with measures of 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, Omav has been shown *in vitro* to restore mitochondrial activity in fibroblasts isolated from FA patients. Accordingly, we believe that Nrf2 activation by Omav may result in a clinical benefit to FA patients.

Clinical Development of Omav in FA

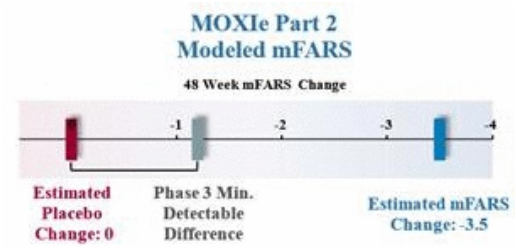
We are evaluating Omav in MOXIe, a two-part international, multi-center, randomized, placebo-controlled, double-blind, dose-escalation, registrational Phase 2 trial. Part 1 of MOXIe evaluated a broad dose range of Omav. Part 2 of MOXIe is evaluating the efficacy and safety of a single dose level of Omav in FA patients. We have fully enrolled part 2 of MOXIe across 11 sites in the United States, Europe, and Australia with 103 FA patients, randomized evenly to either Omav or placebo. The primary endpoint of part 2 of the trial is the change from baseline in mFARS score, a neurological and functional assessment tool, in patients treated with Omav compared to placebo at 48 weeks. Additional endpoints will include the change from baseline in peak work during maximal exercise testing, Patient Global Impression of Change, and Clinical Global Impression of Change. The FDA has provided us with written guidance that mFARS score is acceptable as the primary endpoint for part 2 of MOXIe and may consider either accelerated or full approval based on the overall results of the trial and strength of the data. All patients who complete the treatment period are eligible to continue in the MOXIe trial to evaluate the intermediate and long-term safety of Omav. Those patients who had been receiving placebo will be converted to Omav.

Part 2 of MOXIe, the registrational portion of the trial, was designed and powered based on data from part 1 of MOXIe. In part 1 of MOXIe, all dose groups had small sample sizes and were not powered to demonstrate statistical significance. Data from part 1 demonstrated that the maximum effect on mFARS scores was observed at the 160-mg dose level administered to a total of 12 patients for 12 weeks. At the 160-mg dose, Omav treatment produced a statistically significant improvement in mFARS scores of 3.8 points versus baseline (p=0.0001) and of 2.3 points relative to placebo (which approached statistical significance, p=0.06). We also observed that Omav produced greater improvements in mFARS scores in patients that did not have a preexisting musculoskeletal foot deformity that causes high arched feet, called *pes cavus*. Excluding *pes cavus* patients, at the 160-mg dose, Omav treatment produced a statistically significant improvement in mFARS scores of 6.0 points versus baseline (p<0.0001) and of 4.4 points relative to placebo (p=0.01). The observed improvement in mFARS scores for the seven placebo patients without *pes cavus* of 1.6 points was similar to that observed in all 17 placebo patients of 1.4 points. Data from the 160-mg dose are shown in the graph below. No safety concerns were identified by the DSMB in part 1 of MOXIe and only two SAEs were reported, with both events occurring in placebo-treated patients. The most common AEs in excess to placebo in the Omav group were upper respiratory tract infections and nasopharyngitis, which were generally mild in severity.

mFARS Improved with 160-mg Dose



Based on results from part 1 of MOXIe, Phase 3 modeling[1] limits *pes cavus* patients to 20% of the sample size for the trial and assumes minimal effect in patients with *pes cavus*. An increase of 4.4 points in 80% of the population and minimal effect in *pes cavus* patients would suggest a potential placebo-corrected improvement of 3.5 points in mFARS. The MOXIe registrational trial is conservatively powered to detect a placebo-corrected improvement in mFARS scores of 1.2 (p<0.05) to 1.7 (p<0.01).



[1] *Modeled changes are not intended as a forecast of probable results. No assurance is given about the results that will be obtained.*

We expect to complete part 2 of MOXIe and have top-line data available in the second half of 2019. We have received orphan drug designation from the FDA for Omav for the treatment of FA. 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. If successful, we believe the results from the registrational portion of MOXIe, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval for Omav in the United States.

Market Opportunity for Omav 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 . FA impacts children and young adults, leading to wheelchair use and severely shortened life expectancy. Although there is no approved therapy, treatment for FA patients is concentrated in 21 neurology ataxia centers.

Patients with FA are often undiagnosed or are misdiagnosed with a different cerebellar ataxia, and sometimes correct diagnosis may take years. Omav has the potential to be the first therapy for the treatment of FA, and, if approved and marketed, more patients may be diagnosed earlier for treatment to preserve or improve neurologic function measured by mFARS scores.

Commercial and Manufacturing Preparations for Omav in Friedreich's Ataxia

We are in the process of preparing for a potential commercial launch of Omav in FA in the United States. Our ability to launch Omav is dependent on a successful outcome of MOXIe, the successful filing and defense of an NDA, and approval by the FDA. We have hired commercial and medical affairs leadership and are building the teams, infrastructure, systems, and processes necessary for the launch of Omav in the United States, including in sales, marketing, market access, patient support, medical affairs, distribution, quality, compliance, and other areas.

If we receive approval for Omav in FA, we plan to utilize a specialty pharmacy distribution model to support product availability to patients, with a patient-centered hub to support on-label utilization, ease of access, and patient education and compliance. We have completed preliminary field force sizing and structure for sales and access teams. The trade naming process is underway. We have launched disease awareness campaigns to educate physicians about FA.

Manufacturing and quality teams are in place for the current stage of program development with plans to grow as needed to support commercial supply and distribution. We are on track for planned NDA and commercial launch drug supplies, with an identified supply chain to adequately support near-term clinical and commercial demand. We have completed registration batches for drug substance and drug product. A three-year, room temperature, shelf life has been established for clinical-image Omav capsules at the target commercial dose. In addition, our synthesis from regulatory starting material to drug substance results in a reasonable cost of goods.

In addition to our efforts in the United States, we are refining our strategy and market assessments with respect to a potential launch in the EU. We also plan to continue to evaluate market opportunities for Omav in FA in other global markets.

Bard Development Program for the Treatment of CTD-PAH

Connective Tissue Disease Associated Pulmonary Arterial Hypertension

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. CTD-PAH is a subset of PAH, which results in a progressive increase in pulmonary vascular resistance, ultimately leading to right ventricular heart failure and death. Female PAH patients outnumber males by a factor of two to one, and the onset of PAH generally occurs between the ages of 40 and 60, with the average age of onset being 53. In comparison to patients with I-PAH, CTD-PAH patients generally have a worse prognosis and experience a higher occurrence of small vessel fibrosis and pulmonary veno-obstructive diseases. CTD-PAH represents approximately 30% of the overall PAH population and approximately 10-15% of patients with scleroderma or lupus erythematosus. 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.

PAH is a systemic disease affecting tissues beyond the cardiopulmonary system. Inflammation and oxidative stress contribute to metabolic dysfunction, which promotes bioenergetic deficits and mitochondrial dysfunction. The resulting reduction in glucose uptake, lipid oxidation, and cellular energy production translate to dyspnea, fatigue, and impaired functional activity in PAH patients despite optimal vasodilator therapy. Mitochondrial dysfunction has also been connected with a phenotype in pulmonary arterial smooth muscle cells that may accelerate disease progression in PAH. Mitochondrial dysfunction in PAH patients is characterized by, not only decreased Nrf2 activity, but also increased NF-kB activity.

Three classes of drugs are currently used to treat all etiologies of PAH: ERAs, PDE-5 inhibitors, and prostacyclins. These agents are all systemic vasodilators that do not address the role of mitochondrial dysfunction and inflammation in PAH. Furthermore, their systemic hemodynamic effects can result in hypotension and syncope, or fainting, headache, flushing, and jaw pain, which generally limit their clinical effectiveness and can be exacerbated by clinically significant drug-drug interactions when used in combination.

In comparison to patients with I-PAH, CTD-PAH patients are generally less responsive to existing therapies; therefore, vasodilators approved for PAH generally do not yield as significant functional improvements in CTD-PAH patients. A meta-analysis of 11 registrational trials comprised of more than 2,700 PAH patients demonstrated that CTD-PAH patients benefit less from vasodilator therapies than I-PAH patients when measured by clinical worsening and improvements in 6MWD, with a response in CTD-PAH patients (9.6 meters) of approximately one-third of the response in I-PAH patients (30 meters). Therefore, vasodilators provide a poor risk-benefit for CTD-PAH patients given minimal treatment effect and AEs.

Rationale for Bard in CTD-PAH

Bard directly targets the bioenergetic and inflammatory components of PAH. PAH patients experience mitochondrial dysfunction, increased NF-kB activity, and related inflammatory pathways involved in ROS-mediated signaling, cellular proliferation, and fibrosis. Bard, 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 proteins related to fibrosis and tissue remodeling, and increase cellular respiration and ATP production. Bard targets multiple cell types relevant to PAH, including endothelial cells, smooth muscle cells, and macrophages. Additionally, unlike current therapies, Bard does not cause systemic hemodynamic effects or drug-drug interactions in PAH patients. Therefore, by addressing a novel pathway in PAH, we believe that Bard may provide additional benefits beyond current PAH therapies, including increased functional capacity, effects beyond functional improvements, broader applicability, and as a combination therapy.

Clinical Development for Bard in CTD-PAH

We are conducting CATALYST, a multi-center, international, randomized, double-blind, placebo-controlled Phase 3 trial examining the safety and efficacy of Bard 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 evenly to either Bard or placebo, and the study drug will be administered once daily for 24 weeks. Patients randomized to Bard will start at 5 mg and will dose-escalate to 10 mg at Week 4 unless contraindicated clinically. Based on discussion with the FDA, the primary endpoint of the study is the change from baseline in 6MWD relative to placebo at Week 24. The trial is conservatively powered to enroll approximately 200 patients, and all patients who complete the treatment period are eligible to continue into an extension trial to evaluate the intermediate and long-term safety of Bard. Those patients who had been receiving placebo will be converted to Bard in the extension trial.

CATALYST was designed based on data from LARIAT, a Phase 2 trial in PAH. The primary endpoint in CATALYST, which will be analyzed using the mixed-model repeated measures (MMRM) statistical analysis method, is the placebo-corrected change in 6MWD from baseline to the end-of-treatment at 24 weeks. As part of the planning to determine sample size for CATALYST, 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. The LARIAT end-of-treatment analysis at Week 16 shows placebo-corrected change in 6MWD of 48.5 m (p=0.005) in patients without anemia and 21 m (p=0.037) in initial cohorts at doses of 2.5, 5 and 10 mg. A clinically meaningful improvement of 28.4 m (p=0.07) was observed across all patients. The summary of our analysis using the change at the end of the treatment period on all patients and patients without anemia is shown in the table below.

Dataset	Treatment	N	Time-Averaged Δ6MWD (m)		Week 16 Δ6MWD (m)	
			Change from Baseline	Placebo-corrected	Change from Baseline	Placebo-corrected
All	Placebo	7	0.6 p=0.96	-	9.8 p=0.44	-
	BARD	15	26.7 p<0.001	26.1 p=0.06	38.2 p<0.001	28.4 p=0.07
Without Anemia	Placebo	5	-10.1 p=0.39	-	-5.8 p=0.68	-
	BARD	14	30.2 p<0.001	40.3 p=0.009	42.7 p<0.001	48.5 p=0.005

Patients with anemia at baseline demonstrated larger variability and are excluded in CATALYST. 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. Overall, Bard was well tolerated in the LARIAT trial. Among all PAH patients in Part 1, the most common adverse events that were reported with higher incidence in the Bard group compared with the placebo group included dyspnea (12.7% of patients), urinary tract infection (15.5%), decreased appetite (14.1%), and muscle spasm (16.9%). Among all PAH patients in the placebo-controlled portion of the trial, one serious adverse event of moderate pneumonia was considered by the investigator to be possibly drug related. After completing 16 weeks of treatment, all patients in LARIAT were eligible to receive Bard in an open-label extension study.

Data from CATALYST are expected to be available during the first half of 2020, and, if successful, may support an NDA submission for approval of Bard for the treatment of CTD-PAH. No safety concerns have been reported by the DSMB that oversees the trial and reviews all data, including SAE and AE data, on an unblinded basis to assess safety. We have received orphan drug designation from the FDA for the treatment of PAH.

Market Opportunity for Bard in CTD-PAH

We believe there is significant opportunity for once-daily, orally administered Bard to address, not only the overall PAH market currently served only by the existing vasodilator therapies, but, significantly, CTD-PAH patients who receive limited efficacy and have a more severe form of PAH with high morbidity and mortality. In 2017, global sales of approved PAH treatments were approximately $5.3 billion. In addition, recently approved treatments such as Opsumit® and Uptravi® have shown rapid uptake in the PAH market and, based on industry reports, are 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.

Other Clinical Programs

In addition to our lead programs, we are currently exploring a battery of additional programs in diseases that may include meaningful expansion opportunities. Once we have received data on all of our earlier stage programs, we plan to evaluate all data to determine which indications to prioritize and move forward.

RTA 901 Development Program for the Treatment of Orphan Neurological Indications

RTA 901 is the lead product candidate from our Hsp90 modulator program. Our Hsp90 modulators, including RTA 901, are highly potent and selective C-terminal modulators of Hsp90. Modulation of Hsp90 may induce expression 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, neural inflammation, and neuropathic pain. 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. We have completed a Phase 1 trial to evaluate the safety, tolerability, and PK profile of RTA 901 in healthy adult volunteers. No safety or tolerability concerns were reported. We are the exclusive licensee of RTA 901 and have worldwide commercial rights.

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 (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.

RTA 1701 is the lead product candidate from our proprietary series of RORγt inhibitors for the potential treatment of a broad range of autoimmune, inflammatory, and fibrotic diseases. RTA 1701 is an orally-bioavailable, RORγt-selective allosteric inhibitor that suppresses Th17 differentiation in vitro and demonstrates strong efficacy in rodent disease models of autoimmune disease. RTA 1701 also potently suppresses production of IL-17A, a clinically important cytokine, in human immune cells and when dosed orally to non-human primates. We are currently conducting a Phase 1 trial to evaluate the safety, tolerability, and PK profile of RTA 1701, administered orally once-daily, in healthy adult volunteers, with initial results expected in the first half of 2019. We retain all rights to our RORγt inhibitors, which are not subject to any existing commercial collaborations.

Collaborations

KHK Agreement

In December 2009, we entered into an agreement with KHK, under which we provided KHK the right to develop and commercialize Bard 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 PAH. Total consideration under this agreement could reach $272.0 million in upfront and milestone payments, of which we have received $80.0 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% range depending on the country of sale and the amount of annual net sales.

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 Bard in PAH, ADPKD, or other rare kidney diseases at this time but is reimbursing us the majority of the costs for our registrational trial in CKD caused by Alport syndrome in Japan. 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 commercial supply agreements with KHK.

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 Bard 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 Bard or other molecules for renal, metabolic, and cardiovascular indications, including CKD and PAH, 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 Bard in the United States. Also, both parties are obligated to use commercially reasonable efforts to develop Bard in accordance with agreed-upon joint development plans. The aggregate amount of such consideration received through December 31, 2018 totaled $300.0 million in upfront and milestone payments, with a potential $50.0 million milestone related to commercial sales remaining. Additionally, AbbVie is required to pay us tiered royalties on net sales of licensed product sold by AbbVie, its affiliates and sublicensees in its territory ranging from 15% to the high 20% range depending on the amount of annual net sales.

At present, AbbVie has not opted into the development program in CTD-PAH, CKD caused by Alport syndrome, or other rare kidney diseases, and therefore is not co-funding our development programs in these indications. AbbVie has the right to opt-in to these programs at any time. 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 would be 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 Bard, transfer and assign to us the regulatory filings for Bard 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 Bard in the terminated territory.

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 Bard 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. Payments to us under this agreement include a $400.0 million upfront payment received upon execution of the AbbVie collaboration agreement, $1.4 million in shared development costs prior to our continuing development of Omav unilaterally, and potential future payments including development cost reimbursement, profit share, and royalty payments.

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 EU, or Japan, in which case the costs and profits will be shared 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.

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 Omav, 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 Omav indications.

With respect to joint development, commercialization territory rights are divided on a molecule-by-molecule basis. We have the primary right to commercialize Omav in the United States, and AbbVie has the primary right to commercialize Omav in the rest of the 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 Omav. Therefore, AbbVie no longer co-funds the exploratory development costs of this program but retains the right to opt back in. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the United States, 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.

Competition

Bard in Rare Forms of CKD

The development and commercialization of new pharmaceutical products is highly competitive. Our future commercial success depends on our ability to achieve and maintain a competitive advantage. We are aware of several advanced drug development programs in the rare forms of CKD for which we are developing Bard.

Bard in CKD Caused by Alport Syndrome

Currently, there are no approved therapies for CKD caused by Alport syndrome and patients are commonly treated off-label with ACE inhibitors or ARBs. If Bard is approved and launched commercially, it will likely be the first treatment on the market in the United States. We are aware of one therapy, RG-012 (lademirsen), which is in Phase 2 clinical development for male patients with CKD caused by Alport syndrome. Additionally, several inhibitors of the sodium-glucose Cotransporter-2 protein, such as empagliflozin and dapagliflozin by Boehringer Ingelheim and Johnson and Johnson, are in development for inflammatory and inherited forms of CKD, and TRC101 is in development for the treatment of CKD patients with metabolic acidosis, a complication which may occur in patients with various forms of CKD including some of the diseases for which we are developing Bard.

Bard in ADPKD

Currently, there is one drug approved and multiple therapies in late stage clinical development for the treatment of ADPKD. In 2018, Otsuka Pharmaceuticals Co., Ltd. received approval by the FDA to market tolvaptan (Jynarque®) to slow kidney function decline in adults at risk of rapidly progressing ADPKD. Additional therapies reported to be in clinical development include venglustat, which is currently in Phase 2/3 clinical development in ADPKD patients by Sanofi Genzyme, tesevatinib, which is in Phase 2 development by Kadmon Holdings, Inc., and lixivaptan, which is in Phase 2 development by Palladio Biosciences.

Bard in IgAN

There are currently no therapies approved for IgAN, and patients are commonly treated off-label with ACE inhibitors, ARBs, or immunosuppressant therapy. We are aware of multiple drugs in advanced clinical development for IgAN, including OMS-721, nefecon, and sparsentan, which are in Phase 3 clinical development by Omeros Corporation, Calliditas Therapeutics AB, and Retrophin, Inc., respectively. Additionally, LNP023, atacicept, and APL-2 are reported to be in Phase 2 clinical development by Novartis AG, Merck KgaA, and Apellis Pharmaceuticals Inc., respectively.

Bard in FSGS

There are currently no therapies approved for FSGS, and patients are commonly treated off-label with ACE inhibitors, ARBs, or immunosuppressant therapy. There are multiple drugs in advanced clinical development for FSGS, including sparsentan, which is in Phase 3 clinical development by Retrophin, Inc., and CCX140, CXA-10, DMX-200, voclosporin, PF-06730512, and abatacept, which are reported to be in Phase 2 clinical development by ChemoCentryx, Inc., Complexa, Inc., Dimerix Bioscience Ltd., Aurinia Pharmaceuticals Inc., Pfizer Inc., and Bristol-Myers Squibb Company, respectively.

Bard in T1D CKD

There are currently no therapies approved to treat T1D CKD, and patients are commonly treated off-label with ACE inhibitors or ARBs. We are aware of two drugs in advanced clinical development, including empagliflozin, which is in Phase 3 development by Boehringer Ingelheim and Eli Lilly and Company, and GKT831, which is in Phase 2 clinical development by GenKyoTex SA.

Omav in FA

If Omav is approved for the treatment of FA, it has the potential to be the first treatment on the market for this indication, but it currently faces pipeline competition. Pipeline competition for this orphan disease results in competition for patient recruitment as well as investigators' time and resources. Several competitor product candidates are in Phase 1 or 2 clinical development for FA, including TAK831, epicatechin, RT001, vatiquinone, and JOT101 from Takeda Pharmaceutical Company Limited, Cardero Therapeutics Inc., Retrotope Inc., BioElectron Technology Corporation, and Jupiter Orphan Therapeutics, Inc., respectively.

Bard in CTD-PAH

If Bard is approved for the treatment of patients with CTD-PAH for use in conjunction with currently approved therapies for PAH, such as ERAs, prostacyclins, and PDE-5 inhibitors, it will face competition with those current treatments such as macitentan, marketed by Actelion Pharmaceuticals US, Inc. (Actelion) as Opsumit®; riociguat, marketed by Bayer AG (Bayer) as Adempas®; oral treprostinil, marketed by United Therapeutics Corporation as Orenitram®; ambrisentan, marketed by Gilead Sciences, Inc. (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, United Therapeutics Corporation, Gilead, Bial-Portela & Ca., SA, 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.

Manufacture and Supply

We rely on multiple third-party manufacturers for the manufacture of our product candidates for preclinical and clinical testing, as well as for planned commercial manufacture if our product candidates receive marketing approval. We believe there are reliable 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 and continue to strategically build redundancy in suppliers to fulfill and secure the ongoing and planned preclinical, clinical, and, if our product candidates are approved for marketing, commercial supply needs for ourselves and our collaborators.

Sales and Marketing

We currently intend to build, and are in the process of building, the commercial infrastructure in the United States necessary to effectively support the commercialization of all of our product candidates if and when regulatory approval of such product candidates in the United States appears imminent. We are in the process of preparing for a potential commercial launch of Bard in Alport syndrome in the United States. Our ability to launch Bard is dependent on a successful outcome of the CARDINAL trial, the successful filing and defense of an NDA, and obtaining FDA approval. We have hired commercial and medical affairs leadership and are building the teams, infrastructure, systems, and processes necessary for launch of Bard in the United States, including sales, marketing, market access, patient support, medical affairs, distribution, quality, compliance, and other areas.

If we receive approval for Bard in Alport syndrome, we plan to utilize a specialty pharmacy distribution model to support product availability to patients, with a patient-centered hub to support on-label utilization, ease of access, and patient education and compliance. We have completed preliminary field force sizing and structure for sales and access teams.

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 commercialize 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 DOJ or other governmental entities.

United States Product Approval Process

In the United States, the FDA regulates drugs under the FFDCA. Pharmaceutical products are also subject to regulation by other governmental agencies, such as the FTC, the OIG of the United States Department of Health and Human Services, the Consumer Product Safety Commission, the EPA, and the DOJ. 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 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 GCPs;
- The submission to the FDA of an 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 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 SAEs and unexpected AEs, any clinically important increase in the rate of serious suspected AEs 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 PD and PK 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, the manufacturer of an investigational drug in a Phase 2 or Phase 3 clinical trial 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.

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, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial may be sufficient in rare instances, including (1) 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 or (2) in conjunction with confirmatory evidence. 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 approximately $2.6 million for fiscal year 2019. 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 (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, 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 (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. Unless otherwise required by regulation, PREA generally does not apply to a drug for an indication for which orphan designation has been granted; however, beginning in 2020, PREA will apply to NDAs for orphan-designated drugs if the drug is a molecularly targeted cancer product intended for the treatment of an adult cancer and is directed at a molecular target that the FDA has determined is substantially relevant to the growth or progression of a pediatric cancer.

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 AEs 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 (PDMA) and Drug Supply Chain Security Act (DSCSA)

The distribution of pharmaceutical products is subject to the 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 DSCSA, 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 (i.e., serialization) in order to establish an electronic interoperable prescription product system to identify and trace certain prescription drugs distributed in the United States, 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. These requirements are being phased in over a ten-year period. The DSCSA replaced the prior drug "pedigree" requirements under the PDMA and preempts existing state drug pedigree laws and regulations. The DSCSA also establishes new requirements for the licensing of wholesale distributors and third-party logistic providers. These licensing requirements preempt states from imposing licensing requirements that are inconsistent with, less stringent than, directly related to, or otherwise encompassed by standards established by the FDA pursuant to the DSCSA. Until the FDA promulgates regulations to address the DSCSA's new national licensing standard, current state licensing requirements typically remain in effect.

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 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, the 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 United States 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. 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 payors 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, the 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 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 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. This information is made publicly available on a searchable website. Effective January 2022, information on payments or transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives will also need to be reported.

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 payor. Some states require the posting of information relating to clinical trials. Other states require the reporting of expenses relating to the marketing and promotion of drug products and the reporting of gifts and payments to individual healthcare practitioners in these states. Other states prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals. Still other states require the reporting of certain pricing information, including information pertaining to and justification of price increases, or prohibit prescription drug price gouging. In addition, states such as California, Connecticut, Nevada, and Massachusetts require pharmaceutical companies to implement compliance programs and/or marketing codes. 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 payors. Third-party payors 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 payors 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 payors. These third-party payors 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 payors' drug formularies or lists of medications for which third-party payors 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 payors 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 payor 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 payor 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 payor-by-payor basis, obtaining acceptable coverage and reimbursement from one payor does not guarantee that we will obtain similar acceptable coverage or reimbursement from another payor. If we are unable to obtain coverage of, and adequate reimbursement and payment levels for, our product candidates from third-party payors, 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 EU and China, the pricing of prescription drugs is subject to government control. In some non- United States 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 EU 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 United States 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, limitations on rebate payments by drug manufacturers, 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, the PPACA was signed into law. Among other cost containment measures, the 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. The 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 Institute 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 United States 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. More recently, the 2017 Tax Act was signed into law, which eliminated certain requirements of the PPACA, including the individual mandate, and the current administration has further suggested that it may seek repeal of all or portions of the PPACA. 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 2027 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, payor, 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, the Food and Drug Administration Act of 2017 reauthorized and amended several drug provisions that were scheduled to sunset, such as the prescription drug user fee provisions, and made other changes to the FFDCA, including provisions related to development of pediatric drugs and access to generic drugs. 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 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 EU, 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.

Our clinical trial programs and research collaborations may implicate international data protection laws, including the General Data Protection Regulation (GDPR) in the EU. The GDPR became effective on May 25, 2018 and governs the collections and use of personal data in the EU. The GDPR, which is wide-ranging in scope, imposes several obligations and restrictions concerning the consent of the individuals to whom the personal data relates, the information provided to the individuals, the transfer of personal data out of the EU, data breach notifications, security and confidentiality of the personal data, the use of third-party processors in connection with the processing of the personal data, and imposition of substantial potential fines for breaches of the data protection obligations.

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 United States Patent and Trademark Office (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 FFDCA 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 NCE, never previously approved by FDA either alone or in combination with another active moiety. No 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 EU also provides opportunities for additional market exclusivity. For example, in the EU, 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 EU 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 Bard, Omav, RTA 901, and RTA 1701. 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. Two issued United States patents, more than five issued foreign patents, two pending United States patent applications, and a number of pending foreign patent applications contain composition of matter claims to RTA 901 and related compounds. RTA 1701 is covered by more than 20 granted United States and foreign patents and a number of pending applications.

Our later-expiring granted patents with claims to compositions of matter for Bard, including patents claiming the commercial form, have an expiration date of 2029 in the United States and 2028 elsewhere. The patent that covers specific formulations of Bard, including the commercial formulation, has an expiration date of 2030. Other granted patents and pending patent applications relating to specific uses of Bard, including the treatment of pulmonary hypertension (PH), PAH, and CKD, have expiration dates ranging from 2029 to 2034. Fundamental composition of matter patents and applications claiming Omav have an expiration date in 2033. These patents and applications also contain claims to therapeutic uses of Omav. The fundamental United States composition of matter patent claiming RTA 901, and its foreign equivalents, have an expiration date in 2033. Patents and pending applications covering RTA 1701, including composition of matter claims and method of use claims, have expiration dates ranging from 2031 to 2037.

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.

Bard Patent Portfolio

Our Bard patent portfolio includes six 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 Bard 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 CKD, using Bard or its analogs. These United States patents and applications, and their foreign equivalents, are described in more detail below.

There are two families of composition of matter patents containing claims that cover Bard. The original patent family containing claims to Bard and related compounds was filed in 1999 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 Bard has an expiration date in 2022. Corresponding patents granted in Canada, Europe (validated in multiple European Patent Convention (EPC) 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 Bard, including the commercial form, are due to expire in 2028 or 2029. Two corresponding regional patents have been granted in Europe and each is validated in multiple EPC member states. 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 Bard have a longer statutory term than the corresponding foreign patents. This results from the USPTO's practice of granting patent term adjustments for examination delays originating at the USPTO. Such adjustments are generally not available under foreign patent laws. If Bard 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 Bard. 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 Bard, including the planned commercial formulation, and methods of using Bard for the treatment of multiple diseases including PH, PAH, endothelial dysfunction (an essential component of many cardiovascular disorders including PAH), cardiovascular disease, CKD, Alport syndrome, metabolic disorders, and obesity.

The most relevant granted United States patents with composition of matter or method of use claims covering Bard 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
8,633,243	Forms of CDDO Methyl Ester	August 13, 2028
8,129,429	Synthetic triterpenoids and methods of use in the treatment of disease	February 22, 2030
8,747,901	Delayed Release, Oral Dosage Compositions that Contain Amorphous CDDO-Me	November 6, 2030

Omav Patent Portfolio

Omav is protected by three families of patents. The first, filed in April 2009, contains composition of matter claims that encompass Omav and many related compounds. This family includes five 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 Omav 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 Omav without regard to morphic form, claims to several distinct morphic forms of Omav, including the form used in oral dosing formulations, and claims to various methods of therapeutic use. A first continuation application has also issued, and a second continuation application is pending. Foreign equivalents of the original United States application have been filed in Europe, Canada, Mexico, Japan, China, and more than 20 other territories. The European application has granted and has been validated in multiple EPC member states. In addition, a divisional application has been filed in Europe. The Japanese and Chinese applications have also granted. 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 Omav.

The most relevant granted United States patents with claims covering Omav are listed below, along with their projected expiration dates. As discussed above for Bard, if Omav 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 Omav. 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
9,670,147	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
9,856,286	2,2-Difluoropropionamide Derivatives of Bardoxolone Methyl, Polymorphic Forms and Methods of Use Thereof	April 24, 2034

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, Australia, China, Eurasia, Japan, Mexico, and New Zealand. Applications are pending in Europe, Canada, Mexico, and several other countries. A first United States continuation application has also issued, and a second United States continuation application is pending. 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
10,030,041	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 (Dartmouth) and The University of Texas MD Anderson Cancer Center (MD Anderson), an exclusive, sublicenseable, worldwide license to compounds, including Bard, 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 United States 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 $26.7 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 Omav, 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 Bard 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 $10.8 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 (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 (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 United States 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, 2018, we had 123 full-time employees, 27 of whom held Ph.D. or M.D. degrees, 80 of whom were engaged in research and development, and 43 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.

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 2020. We believe that our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

Executive Officers and Directors

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

Name	Position
Dawn C. Bir	Executive 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 Executive Vice President, Product Development
Keith W. Ward, Ph.D.*	Executive Vice President, Chief Development Officer
Jason D. Wilson	Chief Financial Officer and Executive Vice President, Strategy
Michael D. Wortley	Executive Vice President, Chief Legal Officer
James E. Bass (1)(2)(3)	Director
William D. McClellan, Jr. (1)(2)(3)	Director
R. Kent McGaughy, Jr. (2)(3)	Director
Jack B. Nielsen (1)(2)(3)	Director
William E. Rose (1)(2)	Director

* Dr. Ward has informed us of his intention to retire and has submitted his resignation effective March 8, 2019.
(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 and has served as Executive Vice President since 2018.

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 United States 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 Chairman of the board of directors since our founding in 2002. Prior to founding Reata, Mr. Huff served as CEO in a number of biotech 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 and, since 2018, Executive Vice President. 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, serving as Executive Vice President since 2018, 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, serving as Executive Vice President since 2018, 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. He currently serves on the board of directors of CytoSen Therapeutics, a private company. Mr. Wilson holds a B.B.A. in Accounting from Henderson University and an M.B.A. from the University of Central Arkansas.

Michael D. Wortley joined Reata as Chief Legal Officer in April 2015 and has served as Executive Vice President since 2018. 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 since July 2004. For the past five years, Mr. Bass has been managing family assets and investments as his primary business activity. Mr. Bass is a member of the board of Snowbird Holdings, LLC and Trinity Summits, LLC. 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 a 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 believes that Mr. Bass is qualified to serve on our Board due to his extensive experience investing and extensive service on the boards of directors and boards of managers of other enterprises.

William D. McClellan, Jr. has served as a member of the Board since March 2017. Mr. McClellan, Jr. has served as the Chief Financial Officer of Aerin Medical Inc. since January 2018. Mr. McClellan, Jr. is a financial management consultant to healthcare and life sciences companies, serving as the managing member of Goodwater Consulting, LLC since March 2017. 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 PricewaterhouseCoopers 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 since December 2004. Mr. McGaughy, Jr. has been a partner in CPMG, Inc. since 2006. 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 believes that Mr. McGaughy, Jr. is qualified to serve on our Board 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 since June 2006. Mr. Nielsen is a managing director in 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 that provides certain consultancy services to Novo A/S. He currently serves on the board of directors of Crinetics Pharmaceuticals, Inc., a publicly-traded company. Mr. Nielsen in the past has served on the board of directors of Akebia Therapeutics, Inc., Merus, N.V. and Apollo Endosurgery, Inc., each of which is a publicly-traded company. 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 of Denmark, and a Masters in Management of Technology from Center for Technology, Economics and Management, Technical University of Denmark. Our Board 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 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 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 will require additional financings to fund our operations.

We are a biopharmaceutical company with our lead product candidates, Bard and Omav, in clinical development. 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 and 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, 2018, 2017, and 2016, our net loss was $80.5 million, $47.7 million, and $6.2 million, respectively. As of December 31, 2018, we had an accumulated deficit of $420.3 million and capital resources consisting of cash and cash equivalents of $337.8 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 development and expand our clinical development efforts of our product candidates, 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 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 product candidates;
- the costs of development efforts, including the conduct of clinical trials with respect to our lead 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;
- the costs to grow our organization and increase the size of our facilities to meet our anticipated growth; 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 $26.6 million, $45.1 million, and $48.2 million under the AbbVie license and collaboration agreements and $24.7 million, $1.5 million, and $1.5 million under the KHK agreement, constituting 96%, 97%, and 100% of our revenue, for each of the years ended December 31, 2018, 2017, and 2016, 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 Bard or Omav. If AbbVie continues not to jointly develop and commercialize Bard or Omav, 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 us or our collaborators or are 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 us or 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.

Payments under the instruments governing our indebtedness may reduce our working capital. In addition, a default under our Restated Loan Agreement could cause a material adverse effect on our financial position.

In June 2018, we entered into the Restated Loan Agreement, under which the Lenders agreed to lend us up to $125.0 million, issuable in two separate tranches of $80.0 million (Term A Loan) and $45.0 million (Term B Loan). In March 2017, we borrowed $20.0 million and, in June 2018, we borrowed the remaining $60.0 million from the Term A Loan. The Company may, at its sole discretion, borrow an additional $45.0 million under the Term B Loan, upon the achievement of one of two milestones by the earlier of 30 days after the achievement of a milestone or December 31, 2019.

Our obligations under the Restated Loan Agreement are secured by a first priority security interest in substantially all of our current and future assets, including our owned intellectual property. All outstanding Term Loans will mature on June 1, 2023. We will make interest-only payments for 24 months through June 1, 2020; however, if we draw the Term B Loan, we will make interest-only payments for 36 months through June 1, 2021. The interest-only payment period will be followed by 36 equal monthly payments, or 24 equal monthly payments if we draw the Term B Loan, of principal and interest payments. Payments under the Restated Loan Agreement could result in a significant reduction of our working capital.

The Restated Loan Agreement requires us, and any debt arrangements we may enter into in the future may require us, to comply with various covenants that limit our ability to, among other things:

- incur indebtedness;
- encumber assets;
- dispose of assets;
- complete mergers or acquisitions;
- pay dividends or make other distributions to holders of our capital stock;
- make specified investments; and
- engage in transactions with our affiliates.

These restrictions could inhibit our ability to pursue our business strategies. If we default under our obligations under the Restated Loan Agreement, the Lenders could proceed against the collateral granted to them to secure our indebtedness or declare all obligation under the Restated Loan Agreement to be due and payable. In certain circumstances, procedures by the Lenders could result in a loss by us of all of our equipment and inventory, which are included in the collateral granted to the Lenders. If any indebtedness under the Restated Loan Agreement were to be accelerated, there can be no assurance that our assets would be sufficient to repay in full that indebtedness. In addition, upon any distribution of assets pursuant to any liquidation, insolvency, dissolution, reorganization, or similar proceeding, the holders of secured indebtedness will be entitled to receive payment in full from the proceeds of the collateral securing our secured indebtedness before the holders of other indebtedness or our common stock will be entitled to receive any distribution with respect thereto.

Risks Related to the Development and Commercialization of Our Product Candidates

We are substantially dependent on the success of our lead product candidates, Bard and Omav.

To date, we have invested a substantial portion of our efforts and financial resources in the research and development of Bard and Omav, which are currently our lead product candidates. These are our lead product candidates that have advanced into registrational clinical development, and it may be years before the trials required for their approval are completed, if ever. Our other clinical and preclinical programs are less advanced in development and may never enter into registrational 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.

Our near-term prospects are dependent upon successful interactions with global regulatory authorities and on successful registrational development and commercialization of Bard and Omav. We may 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 these product candidates. In addition, although there may be many potentially promising indications beyond those we are currently investigating, we are still exploring indications for which further development of, and investment for, our lead product candidates may be appropriate. Accordingly, the costs and time to complete development and the related risks are currently unknown.

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

The clinical and commercial success of Bard and Omav 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 Bard and Omav, which will depend substantially upon requirements for such trials imposed by the 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 provide approved product with a convenient and patient-friendly capsule configuration;

- 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, EMA, MHRA, Japanese PMDA, and Australian TGA requirements and the requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to 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, PMDA, TGA, 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 AEs 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, Bard and Omav, 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 Bard for the treatment of T2D CKD. While Bard 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, known as BEACON, that resulted in the termination of the T2D CKD program. Heart failure appeared to occur at a very low rate in only a particular type of patient studied during BEACON, which was not observed during Phase 2. Our other clinical programs with Bard and Omav 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 may 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 Bard and Omav 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 that any potential advantages that we believe Bard may have for our current clinical programs will be substantiated by our registrational clinical trials or that we will be able to include a discussion of any advantages in our labeling should we obtain approval. We cannot assure you that our previous data in our Phase 2 trial and our trials in T2D CKD may predict effects in our registrational trial in patients with CKD caused by Alport syndrome, ADPKD, or other forms of CKD. In addition, based on the data from our ongoing Phase 2 clinical trial in PAH, we believe that Bard, combined with current standard of care, may have benefits compared to treatment with current standard of care. However, our belief that Bard 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 Bard, and such data may not be replicated in our Phase 3 trial. Additionally, we have discussed the PAH and CKD caused by Alport syndrome trial data with the FDA, EMA and the PMDA and ADPKD trial data with the FDA. Preliminary discussions with the EMA have indicated that additional discussion will be needed and additional nonclinical and clinical studies may be required in advance of a MAA for CKD caused by Alport syndrome in that territory. We have had limited or no discussions of these trial data with other global regulatory health authorities, and these regulatory bodies may not concur that these studies would be adequate to support a marketing application or that the benefits would translate to approvable trial endpoints or be reflected on our product label.

In addition, we cannot assure that the potential advantages that we believe Omav may have will be substantiated by our registrational 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 discussed FA and melanoma trial data with the FDA and FA with the EMA. Preliminary discussions with the EMA have indicated that additional discussion will be needed and additional nonclinical or clinical studies may be required in advance of a MAA for FA in that territory. We have had limited or no discussions of these data with other global regulatory health authorities, and these regulatory bodies may not concur that these studies would be adequate to support a marketing application or that the 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 Bard and Omav have many co-morbidities that may cause severe illness or death, which may be attributed to Bard and Omav in a manner that negatively affects the safety profile of our product candidate. If the results of our ongoing or future clinical trials for Bard and Omav 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 AEs 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 Bard and Omav 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 CROs and clinical trial sites;
- manufacture sufficient quantities of product candidate with acceptable quality attributes for use in clinical trials;
- obtain required regulatory or IRB approval or guidance;
- maintain clinical sites in compliance with clinical trial protocols and 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 an SAE 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. AEs and 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 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 Bard or Omav beyond those seen in BEACON, patients treated with our products, if approved, may experience previously unreported 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 CROs' 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 Bard due to the SAEs or AEs we previously detected in a subset of patients with advanced T2D CKD, 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 Bard and Omav due to unforeseen factors beyond our control. Some of the conditions that we are studying 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. We, our collaborators, or our experienced third-party manufacturers may encounter difficulties in production, which may include but are not limited to:

- 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 and the lack of redundant and backup suppliers;
- quality control and assurance;
- shortages of qualified personnel and capital required to manufacture large quantities of product;
- competing capacity needs at CMOs supporting product development as quantities for supply increase;
- establishment of commercial supply capacity through binding supply agreements;
- 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, cyberattacks, 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.

Although we are conducting three registrational trials, specific labeling language has not yet been discussed with regulatory authorities. For both Bard and Omav, 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 an NDA, MAA, or other marketing applications and may be unable to do so efficiently or at all for Bard, Omav, or any product candidate we are developing or may develop in the future.

We have conducted, or are currently conducting, Phase 2 and Phase 3 or other registrational trials for Bard and Omav, and we may need to conduct additional Phase 2 trials before initiating additional Phase 3 or other registrational clinical trials with Bard and Omav. The conduct of Phase 3 trials and the submission of an NDA, MAA, or other marketing application 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, MAA, or other marketing application. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials and other requirements in a way that leads to the submission of an NDA, MAA, or other marketing application 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. Risks related to the successful execution of our trials or successful filing of the NDA exist not only because of the complexity of the process, but also because of our lack of previous experience as an organization.

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 fully-developed 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 increase 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 Bard and Omav, 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 Bard is approved and launched commercially for 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 clinical development with a Phase 2 injectable product candidate, lademirsen (RG-012), from Sanofi S.A. and Regulus Therapeutics Inc. Additionally, several inhibitors of the sodium-glucose cotransporter-2 protein, such as empagliflozin and dapagliflozin by Boehringer Ingelheim and Johnson and Johnson, are in development for inflammatory and inherited forms of CKD, and TRC101 is in development for the treatment of CKD patients with metabolic acidosis, a complication which may occur in patients with various forms of CKD, including some of the diseases for which we are developing Bard.

If Bard is approved and launched commercially for patients with ADPKD, it would launch into a landscape with one approved product and multiple products in commercial development. Otsuka Pharmaceutical Co. Ltd. received marketing authorization for tolvaptan (Jynarque) from the FDA in April 2018 for adults at risk of rapidly progressing ADPKD. Multiple other therapies are reported to be in clinical development for ADPKD, such as tesevatinib, venglustat, and lixivaptan by Kadmon Holdings, Inc., Sanofi Genzyme, and Palladio Biosciences, respectively.

If Bard is approved and launched commercially for patients with IgAN, T1D CKD, or FSGS, it could face competition. Other programs that are in clinical development for the treatment of IgAN include OMS-721, nefecon, sparsentan, LNP023, atacicept, APL-2, PBF-677, and cemdisiran by Omeros Corporation, Calliditas Therapeutics AB, Retrophin, Inc., Novartis AG, Merck KgaA, Apellis Pharmaceuticals Inc., Palobiofarma, and Alnylam Pharmaceuticals Inc., respectively. In T1D CKD, we are aware of three ongoing, clinical-stage, development programs including GKT831, BI685509, and empagliflozin by GenKyoTex SA, Eli Lilly and Company, and Boehringer Ingelheim. Sparsentan, CCX140, CXA-10, DMX-200, voclosporin, PF-06730512, and abatacept are reported to be in clinical development for the treatment of FSGS by Retrophin, Inc., ChemoCentryx, Inc., Complexa, Inc., Dimerix Bioscience Ltd., Aurinia Pharmaceuticals Inc., Pfizer Inc., and Bristol-Myers Squibb Company, respectively. These product candidates may be in competition with Bard for patient recruitment and enrollment for clinical trials and may be in competition with Bard if it is approved and launched commercially. Some of these product candidates may enter the market prior to Bard, and some of these product candidates could limit the market or level of reimbursement available for Bard if it is commercialized.

If Bard is approved and launched commercially for patients with CTD-PAH, it would launch into a product landscape of numerous approved therapeutics for PAH, 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, and KAR5585 are purported to be in development by such companies as Arena Pharmaceuticals, Inc., Gilead Sciences, Inc., Bial-Portela & Ca., SA, and Karos Pharmaceuticals, Inc., respectively. These product candidates may be in competition with Bard for patient recruitment and enrollment for clinical trials and may be in competition with Bard if it is approved and launched commercially. Some of these product candidates may enter the market prior to Bard, and some of these product candidates could limit the market or level of reimbursement available for Bard if it is commercialized.

Omav may face similar competitive risks as Bard. For our development program in FA, if Omav 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 TAK-831, RT001, epicatechin, JOT101, and vatiquinone. These candidates are being developed by such companies as Takeda Pharmaceutical Company Limited, Retrotope Inc., Cardero Therapeutics Inc., Jupiter Orphan Therapeutics, Inc., and BioElectron Technology Corporation, respectively. These product candidates may be in competition with Omav for patient recruitment and enrollment for clinical trials and may be in competition with Omav if it is approved and launched commercially. Some of these product candidates may enter the market prior to Omav, and some of these product candidates could limit the market or level of reimbursement available for Omav if it is commercialized.

RTA 901 may face similar competitive risks as Bard and Omav. Other HSP90 inhibitors are being developed for neurological indications, including arimoclomol and PUH-AD by such companies as Orphazyme AS and Samus Therapeutics Inc.

RTA 1701 may face similar competitive risks as Bard, Omav, and RTA 901. Other ROR gT modulators are in various stages of clinical development, including BOS172767, JTE451, AZD0284, JNJ3534, and others. These candidates are being developed by such companies as Boston Pharmaceuticals, Japan Tobacco Inc., AstraZeneca PLC, Phenex Pharmaceuticals AG, Bristol-Myers Squibb Company, Aurigene, Escalier Biosciences, BV, 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, testing, and other qualifying criteria for patient use, 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 completion of any genetic tests that are required by the product labeling or third party payors and formulary committees;
- 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, discover, or develop 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, including requiring genetic testing;
- 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. Payors may also add additional requirements, including genetic testing and requiring less expensive generic therapy first. New laws may be enacted or regulations may be promulgated in the United States that decrease the price at which products, if approved, are sold. For example, there are proposals to allow Medicare to negotiate drug prices, allow drugs approved for sale in the United States to be purchased in Canada, and price certain drugs based on the average price of the drug in certain European countries.

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 EU 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 have product liability and clinical trial insurance in amounts that we believe are adequate to cover this risk. 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 Bard 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 Bard for renal, metabolic, and cardiovascular indications with AbbVie in certain territories outside the United States that are not covered by the KHK agreement. However, AbbVie is not currently participating in the development of Bard in CKD caused by Alport syndrome, ADPKD, CTD-PAH, or other rare kidney diseases, and KHK is not currently participating in the development of Bard in CTD-PAH, ADPKD, or other rare kidney diseases but is reimbursing us the majority of the costs for our registrational trial in CKD caused by Alport syndrome in Japan. Additionally, we have entered into a collaboration agreement with AbbVie with respect to the development and commercialization of Omav and other Nrf2 activator product candidates globally, and currently AbbVie is not participating in the development of Omav. 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. AbbVie and KHK have allowed us to make regulatory filings and conduct clinical trials in its exclusive territory in order to generate clinical trial data that we may use in connection with seeking approval of our product candidates in the United States. There can be no assurance that one or more of these authorizations will not be withdrawn.

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 Omav as a product candidate for one indication and two related indications, and pursue further development of Omav in such indications, without AbbVie's consent. However, we are required to obtain AbbVie's consent to pursue the development of additional indications for Omav, once it is designated as a product candidate, which may not be obtainable. Even if Omav 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 the agreement permits and AbbVie did opt back in to development of Omav, we and AbbVie must reach a consensus on our registrational 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 Omav globally. Similarly, our collaboration with KHK for Bard 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 participating, or they should be permitted to participate, in 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, or we may terminate the engagements, 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 or if we terminate the engagement, we may be required to enter into alternative arrangements, or perform various functions ourselves, which could 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 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 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 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 suppliers of drug substance, a drug product intermediate, or final drug product candidates. Additionally, we do not have agreements with 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, 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 purpose(s) or indication(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. Bard, Omav, and RTA 901 are protected by granted United States and foreign patents claiming compositions of matter and methods of use. RTA 1701 is protected by granted United States and foreign patents claiming compositions of matter. Each compound is the subject of pending United States and foreign patent applications claiming compositions of matter or methods of use. 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 United States 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 inventor to file" system under the Leahy-Smith America Invents Act (AIA), effective March 16, 2013. Effects of this change and other elements of the AIA are evolving, as the 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. Creating further uncertainty, provisions under the AIA also include procedures for challenging issued patents and pending patent applications. We may become involved in opposition, *inter partes* review, 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. 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 under United States law, the approved product would likely be considered a NCE 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 initiating 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. Non-compliance 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 Hatch-Waxman Act, a pharmaceutical manufacturer may submit an 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 FFDCA 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.

Innovator pharmaceutical patents are particularly vulnerable in the complex milieu of administrative, regulatory, and legal challenge. Specifically, a patent that might become or already is the subject of litigation related to Paragraph IV certification can be challenged by any party, such as a generic competitor, at the United States PTO in an *inter partes* review (IPR). If an IPR is instituted by the Patent Trial and Appeal Board (PTAB) at the United States PTO, a court could stay the litigation pending a decision by the United States PTO in the IPR because the decision could affect substantive and procedural aspects at trial. Under these circumstances, however, and some litigation to date indicates, a court may decline to toll the 30-month stay for ANDA approval when staying the litigation. Thus, for instance, a decision by the PTAB not reversed on any appeal and invalidating all relevant claims of a patent-in-suit, could prompt a generic competitor to motion for lifting of the litigation stay, and thereafter motion for summary judgement in the litigation before expiration of the 30-month stay.

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 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, and similar health authorities outside the United States, 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 United States patents may be eligible for limited patent term extension under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent term extension of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. Patent term extension, however, is 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. In addition, only one patent applicable to an approved product is eligible for the extension.

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, M.D. Anderson, 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 our current or 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 be delayed in receiving or 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. In addition, future shutdowns of the United States federal government may result in delays in the review or approval, if any, of our NDAs. 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. Certain of our Phase 3 clinical trials are designed to permit us to file an application for accelerated approval based on positive interim data. Even if we believe the interim data will support an application for accelerated approval, the regulatory authorities may not agree, which could delay approval. 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 submit for regulatory approvals, and even if we submit, the applications may not be filed by the FDA or comparable regulatory agency, and 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.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. 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. In the EU, the EMA's Committee for Orphan Medicinal Products may grant orphan drug designation to promote the development of products that are intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union Community. Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating, or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the drug or biological product. In the EU, orphan drug designation provides a range of potential incentives for medicines that have been granted an orphan designation by the European Commission, including protocol assistance, access to the centralized authorization procedure, 10 years of market exclusivity, and fee reductions.

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 initial 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 by the FDA for Bard for the treatment of CKD caused by Alport syndrome and for the treatment of PAH. We have also received orphan drug designation in Europe for Bard for the treatment of Alport syndrome. We have also received orphan drug designation by the FDA and in Europe for Omav for the treatment of FA. We may seek orphan drug designation in the United States and Europe 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 other rare kidney diseases. 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 from the FDA or comparable accelerated development pathways from foreign regulatory authorities for some or all of our product candidates.

In 2012, the United States 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.

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;
- 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 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 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 (information on payments or transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives will also need to be reported);
- 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 relating to drug price increases; 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.

Our clinical trial programs and research collaborations may implicate international data protection laws, including the GDPR in the EU. The GDPR became effective on May 25, 2018 and governs the collections and use of personal data in the EU. The GDPR, which is wide-ranging in scope, imposes several obligations and restrictions concerning the consent of the individuals to whom the personal data relates, the information provided to the individuals, the transfer of personal data out of the EU, data breach notifications, security and confidentiality of the personal data, the use of third-party processors in connection with the processing of the personal data, and imposition of substantial potential fines or penalties for breaches or noncompliance of the data protection obligations. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU. Guidance on implementation and compliance practices are often updated or otherwise revised. Complying with varying jurisdictional requirements could increase the costs and complexity of compliance, including the new risk of substantial financial penalties for data breach or improper processing of personal data under the GDPR. Failure by our collaborators to comply with the GDPR on the transfer of personal data outside of the EU into the United States may result in the imposition of criminal and administrative sanctions on such collaborators, which could adversely affect our business and could create liability for us.

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 United States healthcare reform and other changes in the healthcare industry, laws, and regulations 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 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, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program, extended the rebate program to individuals enrolled in Medicaid managed care organizations, and established annual fees and taxes on manufacturers of certain branded prescription drugs. The PPACA also created 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. The Bipartisan Budget Act of 2018 increased the manufacturer's subsidy under this program from 50% to 70% of the negotiated price, beginning in 2019. The 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 2027 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.

In addition, the Trump Administration has indicated an intent to address prescription drug pricing and recent Congressional hearings have brought increased public attention to the costs of prescription drugs. The Trump Administration has proposed a regulation intended to eliminate the rebate-oriented model used for pricing pharmaceutical products under Medicare Part D and Medicaid Managed Care, with the policy objective of lower costs to consumers. If this proposal is finalized, a similar approach might be adopted by commercial insurance plans as well. In addition, the Trump Administration has proposed to base drug payment under Medicare Part B on an index of prices for the drug in certain specified foreign countries, which are typically lower than priced in the United States. Numerous bills have been introduced in Congress by members of both parties seeking to reduce drug prices using a variety of approaches. These actions and the uncertainty about the future of the PPACA and healthcare laws are likely to continue the downward pressure on pharmaceutical pricing and increase our regulatory burdens and operating costs.

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, the 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. More recently, the 2017 Tax Act was signed into law, which eliminated certain requirements of the PPACA, including the individual mandate, and the current administration has further suggested that it may seek repeal of all or portions of the PPACA. 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. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the United States government, including the FDA. For example, a prolonged shutdown may significantly delay the FDA's ability to timely review and process any submissions we have filed or may file or cause other regulatory delays, which could materially and adversely affect our business. 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 United States 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 United States Export Administration Regulations, United States Customs regulations, various economic and trade sanctions regulations administered by the United States Treasury Department's Office of Foreign Assets Controls, the United States Foreign Corrupt Practices Act of 1977, as amended (FCPA), the United States domestic bribery statute contained in 18 U.S.C. § 201, the United States 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 (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;
- price controls on our drug products;
- 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;
- business interruptions resulting from natural disasters or geopolitical actions, including war and terrorism, or systems failure including cybersecurity breaches; and
- compliance with evolving and expansive international data privacy laws, such as the EU GDPR.

For example, in June 2016, the U.K. electorate voted in a referendum to voluntarily depart from the EU, commonly referred to as "Brexit", which is expected to occur in March 2019. As a result of the referendum, the British government has been negotiating the terms of the U.K.'s future relationship with the EU. We do not know to what extent Brexit will impact the business and regulatory environment in the U.K., the EU, or other countries. Changes impacting our ability to conduct business in the U.K., or other EU countries, or changes to the regulatory regime in those countries, may impact certain portions of our research and general business operations in the U.K. and the EU. However, we do not expect Brexit to have a material impact on our consolidated results of operations.

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, compliance, and administration capabilities or contract with third parties to provide these capabilities for us. As our operations expand, 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 and Chief Medical 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, and our Chief Medical Officer, Colin Meyer. The loss of the services of Mr. Huff or Dr. Meyer 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, the further development of our drug candidates could be delayed, and we may be subject to regulatory actions, including fines or other penalties. 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. Further, these cybersecurity breaches may inflict reputational harm upon us that may result in decreased market value and erode public trust.

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 offices 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 offices or other facilities, 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 IPO 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 be sustained, and you may not be able to sell your shares quickly. Shares of our Class A common stock were sold in our IPO at $11.00 per share.

In August 2017, we closed a follow-on underwritten public offering of 3,737,500 shares of our Class A common stock at $31.00 per share. In November 2017, we entered into an at-the-market equity offering sales agreement with Stifel, Nicolaus & Company, Incorporated, that established a program pursuant to which we may offer and sell up to $50.0 million of our Class A common stock from time to time in at-the-market transactions. No shares have been sold under this program. In July 2018, we closed on a follow-on underwritten public offering of 3,450,000 shares of our Class A common stock at $72.00 per share. Since our IPO in May 2016, our closing stock price has reached a high of $99.50 and a low of $11.03 through February 22, 2019.

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;
- 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 the 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 and directors, together with their respective affiliates, 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 22, 2019, our executive officers and directors, together with their respective affiliates, collectively owned shares representing approximately 95.5% of our total Class B common stock, including shares subject to outstanding options that are exercisable within 60 days of such date, and approximately 18.7% 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 and directors, together with their respective affiliates, collectively beneficially own shares representing approximately 53.9% of the voting power of our outstanding capital 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 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 PCAOB;
- 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 $700.0 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 22, 2019, we have 5,702,052 shares of Class B common stock outstanding representing 19.9% 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, entered into with certain of our investors in connection with our Series A through H preferred stock financings, provides certain registration rights for 4,744,362 shares of Class B common stock and 2,091,585 shares of Class A common stock as of February 22, 2019. Once we register these shares, they can be freely sold in the public market.

In addition, as of February 22, 2019, there are approximately 4,224,053 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. 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, and particularly after we cease to be an emerging growth company, we incur significant legal, insurance, accounting, and other expenses. 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 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 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 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.

The Sarbanes-Oxley Act requires, among other things, that we assess the effectiveness of our internal control over financial reporting annually and disclosure controls and procedures quarterly. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. 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. If material weaknesses are identified in the future or we are not able to comply with the requirements of Section 404 in a timely manner, our reported financial results could be materially misstated, we could receive an adverse opinion regarding our internal controls over financial reporting from our accounting firm, if and when required, and we could be subject to investigations or sanctions by regulatory authorities, which would require additional financial and management resources, which 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. For so long as we remain as an emerging growth company, our accounting firm will not be required to provide an opinion regarding our internal controls over financial reporting.

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.

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, who also own a substantial number of shares of Class A common stock, 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 our Restated Loan Agreement preclude, and 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 (the Code), a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change 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 United States 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 United States 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 2020. 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 material 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 under the symbol "RETA".

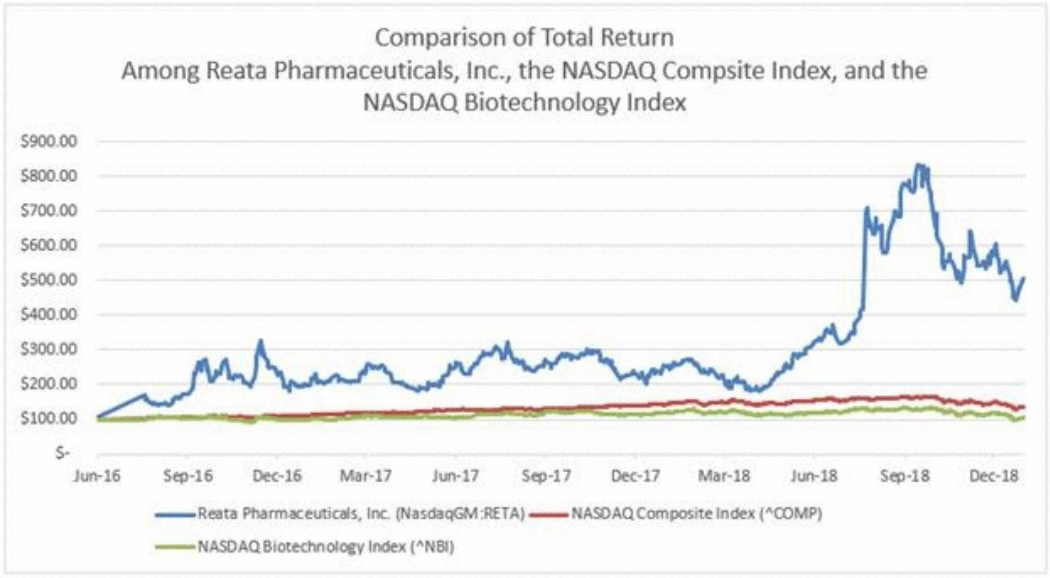
Our Class B common stock is not publicly traded. Our Class B common stock is convertible into Class A common stock on a one-for-one basis at the holder's election at any time. The conversion right of the Class B common stock has no expiration date.

Stockholders

As of February 22, 2019, there were 368 and 135 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, 2018, 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 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 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	2017	2018
Reata Pharmaceuticals, Inc.	RETA	$ 100.00	$ 197.38	$ 256.06	$ 507.23
NASDAQ Composite Index	^IXIC	$ 100.00	$ 109.97	$ 141.03	$ 135.56
NASDAQ Biotechnology Index	^NBI	$ 100.00	$ 96.37	$ 116.67	$ 105.79

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

The table below discloses information as of December 31, 2018, with respect to our equity compensation plans and outstanding stock options granted pursuant to individual compensation arrangements.

Plan Category	Number of shares of Class B common stock to be Issued on Exercise of Outstanding Options, Warrants and Rights(1)	Weighted Exercise Price of Outstanding Options, Warrants and Rights	Number of securities remaining available for future issuance under Equity Compensation Plans (excluding securities reflected in the first column)(2)
Equity compensation plans approved by security holders:	—	—	—
Equity compensation plans not approved by security holders(3):	3,320,571	$ 21.20	685,340
Total	3,320,571	$ 21.20	685,340

(1) Represents 3,294,225 stock options outstanding under our 2007 LTIP and 26,346 stock options granted pursuant to individual compensation arrangements. All outstanding stock options were granted with respect to shares of our Class B common stock.

(2) Represents the number of securities remaining available under our 2007 LTIP as of December 31, 2018. Beginning January 1, 2017, on January 1 of each calendar year prior to expiration of the 2007 LTIP, the total number of shares of stock reserved and available for issuance shall automatically increase by an amount equal to 3% of the number of shares of common stock (of all classes) outstanding on the immediately preceding December 31, including as outstanding all securities convertible into shares of common stock on an as converted basis. The compensation committee retains the authority to determine that there will be no increase or a lesser increase in reversed shares for any year.

(3) For purposes of this chart, the 2007 LTIP, which was approved by security holders prior to our initial public offering in May 2016, is categorized as a plan not approved by security holders.

Issuer's Purchases of Equity Securities

None.

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				
	2018	2017	2016	2015	2014
	(in thousands, except share and per share data)				
Collaboration revenue					
License and milestone	$ 52,351	$ 47,103	$ 49,730	$ 50,295	$ 51,368
Other revenue	1,238	955	126	24	586
Total collaboration revenue	53,589	48,058	49,856	50,319	51,954
Expenses					
Research and development (1)	97,288	71,273	39,453	35,141	34,305
General and administrative (1)	32,748	23,260	16,603	13,693	11,512
Depreciation	431	437	682	1,819	2,512
Total expenses	130,467	94,970	56,738	50,653	48,329
Other income (expense)					
Investment income	3,541	701	214	32	43
Interest expense	(6,176)	(1,454)	—	—	—
Loss on extinguishment of debt	(1,007)	—	—	—	—
Other income (expense)	—	(3)	—	—	—
Total other income (expense)	(3,642)	(756)	214	32	43
(Loss) income before taxes on income	(80,520)	(47,668)	(6,668)	(302)	3,668
Provision (benefit) for taxes	26	3	(441)	1,148	2,979
Net (loss) income	$ (80,546)	$ (47,671)	$ (6,227)	$ (1,450)	$ 689
Net (loss) income per share—basic and diluted(2)	$ (2.91)	$ (1.99)	$ (0.31)	$ (0.09)	$ 0.04
Net (loss) income per share—diluted (2)	$ (2.91)	$ (1.99)	$ (0.31)	$ (0.09)	$ 0.04
Weighted-average number of common shares used in net (loss) income per share basic (2)	27,701,783	23,933,309	19,816,635	15,974,974	15,950,023
Weighted-average number of common shares used in net (loss) income per share diluted (2)	27,701,783	23,933,309	19,816,635	15,974,974	15,979,768

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

	Years Ended December 31				
	2018	2017	2016	2015	2014
	(in thousands)				
Research and development	$ 3,943	$ 2,409	$ 1,121	$ 671	$ 787
General and administrative	6,607	4,121	1,246	1,404	736
	$ 10,550	$ 6,530	$ 2,367	$ 2,075	$ 1,523

(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,				
	2018	2017	2016	2015	2014
	(in thousands)				
Condensed Consolidated Balance Sheet Data					
Cash and cash equivalents	$ 337,790	$ 129,780	$ 84,732	$ 42,008	$ 87,758
Federal income tax receivable	—	—	—	31,926	15,243
Working capital	286,353	85,492	27,652	16,439	48,603
Total assets	345,208	135,337	89,093	78,954	125,604
Term loan	79,219	19,614	—	—	—
Deferred revenue (including current portion)	225,721	244,438	291,041	340,771	390,366
Accumulated deficit	(420,323)	(337,143)	(289,354)	(283,127)	(281,677)
Total stockholders' equity (deficit)	$ 15,159	$ (146,973)	$ (215,048)	$ (273,156)	$ (274,246)

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

Reata's mission is to develop innovative therapies that change patients' lives for the better. We focus on developing small-molecule therapeutics with novel mechanisms of action for the treatment of severe, life-threatening diseases with few or no approved therapies. Our lead product candidates, bardoxolone methyl (Bard) and omaveloxolone (Omav), activate the transcription factor Nrf2, which plays an important role in regulating the cellular response to injury. By activating Nrf2, Bard and Omav normalize mitochondrial function, restore redox balance, and resolve inflammation. We have fully enrolled two registrational clinical trials: CARDINAL, studying Bard in chronic kidney disease (CKD) caused by Alport syndrome, and MOXIe, studying Omav in Friedreich's ataxia (FA). CKD caused by Alport syndrome and FA are rare, serious diseases with no approved therapy. We designed CARDINAL and MOXIe based on the results of earlier clinical studies and guidance from the FDA on a potential path to approval. We expect to have top-line data from both of these clinical trials in the second half of 2019. In each of these trials, FDA approval may provide expansion opportunities into other related indications. We are also conducting a third registrational trial, CATALYST, studying Bard in patients with a rare and serious form of pulmonary arterial hypertension caused by connective tissue disease (CTD-PAH), and we expect to have top-line data from this trial during the first half of 2020. We expect our current cash to fund our operations through data readouts for these three ongoing registrational clinical trials.

We are developing Bard for the treatment of patients with CKD caused by Alport syndrome, autosomal dominant polycystic kidney disease (ADPKD), and other rare forms of CKD that, in the aggregate, affect more than 700,000 patients in the United States. CKD is characterized by a progressive worsening in the rate at which the kidney filters waste products from the blood, called the glomerular filtration rate (GFR). When GFR gets too low, patients typically develop end-stage kidney disease (ESKD) and require dialysis or a kidney transplant to survive. In 10 separate CKD clinical trials, Bard has been shown to consistently improve estimated GFR (eGFR) in patients with diverse etiologies of CKD. We believe that Bard treatment has the potential to delay or prevent GFR declines that cause the need for dialysis or a transplant in patients with Alport syndrome, ADPKD, and other rare forms of CKD.

We are conducting a Phase 2/3 clinical trial studying Bard in patients with CKD caused by Alport syndrome called CARDINAL. Alport syndrome affects both children and adults and, in patients with the most severe forms of the disease, approximately 50% progress to dialysis by age of 25, 90% by age 40, and nearly 100% by age 60. In the Phase 2 portion of CARDINAL, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 48 weeks of treatment in 25 patients. Available historical data for 22 of these patients showed an average annual decline in eGFR of 4.2 mL/min/1.73 m^2 in the three-year period prior to study entry. Bard also demonstrated a statistically significant increase from baseline in mean eGFR at Week 52 after withdrawal of drug for four weeks. This retained eGFR benefit is important because it provides compelling evidence that drug treatment will delay or prevent the need for dialysis or transplant. The FDA has provided us with written guidance that, in patients with CKD caused by Alport syndrome, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval, and an improvement versus placebo after two years of treatment may support full approval. The Phase 3 portion of CARDINAL is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in 157 Alport syndrome patients randomized one-to-one to active drug or placebo. We have fully enrolled the Phase 3 portion of CARDINAL, and we expect to have one year top-line results available in the second half of 2019. If the trial results are positive, we believe the results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of CKD caused by Alport syndrome.

We are currently initiating a Phase 3 trial studying Bard in patients with ADPKD called FALCON. ADPKD is a rare and serious hereditary form of CKD caused by a genetic defect in genes called PKD1 or PKD2 and is characterized by the formation of fluid-filled cysts in the kidneys. ADPKD is the most common single-gene disorder of the kidneys, and there are an estimated 400,000 patients in the United States, with approximately 140,000 patients diagnosed with the disease. During 2018, we completed a Phase 2 clinical trial studying Bard in patients with ADPKD. In the Phase 2 study, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 12 weeks of treatment in 31 patients. Available historical data for 29 of these patients showed an average annual decline in eGFR of 4.8 mL/min/1.73 m^2 in the three-year period prior to study entry. The FDA has provided us with written guidance that, in patients with ADPKD, an analysis of retained eGFR demonstrating an improvement versus placebo after one year of Bard treatment may support accelerated approval, and an improvement versus placebo after two years of treatment may support full approval. FALCON is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in approximately 300 ADPKD patients randomized one-to-one to active drug or placebo. We plan to enroll the first ADPKD patient in FALCON in mid-2019.

We collected Phase 2 data studying Bard in each of IgA nephropathy (IgAN), type 1 diabetic CKD (T1D CKD), and focal segmental glomerulosclerosis (FSGS). In each of these Phase 2 studies, Bard demonstrated a statistically significant increase from baseline in mean eGFR after 12 weeks of treatment in patients whose available historical data showed annual declines in eGFR in the three-year period prior to study entry. We plan to pursue each of these rare and serious forms of CKD as commercial indications.

In addition to our CKD development programs, we are conducting a registrational Phase 2 clinical trial, part 2 of MOXIe, studying our second Nrf2 activator, Omav, in patients with FA. FA is a rare, inherited, debilitating, and degenerative neuromuscular disorder caused by mutations in the gene for frataxin, a mitochondrial protein. Patients with FA are typically dependent on wheelchair use 10 to 15 years after disease onset, and their median age of death is in the mid-30s. There are no currently approved therapies for the treatment of FA. In part 1 of MOXIe, at the optimal dose level, Omav demonstrated a statistically significant improvement in modified Friedreich's Ataxia Rating Scale (mFARS) scores of 3.8 points ($p=0.0001$) versus baseline and a placebo-corrected improvement in mFARS scores of 2.3 points ($p=0.06$). Part 2 of MOXIe is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Omav in 103 FA patients randomized one-to-one to active drug or placebo. The FDA has provided us with written guidance that the mFARS score is acceptable as the primary endpoint for part 2 of MOXIe and that it may consider either accelerated or full approval based on the overall results of the trial and strength of the data. We have fully enrolled the trial, and we expect to have top-line data from the trial in the second half of 2019. If the trial results are positive, we believe the trial results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Omav for the treatment of FA.

We are also conducting a Phase 3 trial studying Bard in patients with CTD-PAH called CATALYST. CTD-PAH is a rare, serious and progressive disease that leads to heart failure and death. CTD-PAH patients are less responsive to existing vasodilator therapies than patients with the idiopathic form of PAH (I-PAH) and have a worse prognosis. We have completed a Phase 2 clinical trial called LARIAT in patients with PAH. In LARIAT, Bard demonstrated a statistically significant time-averaged increase in mean 6-minute walk distance (6MWD) at 16 weeks in CTD-PAH patients compared to baseline. Based on discussions with the FDA, the primary endpoint of the study is the change from baseline in 6MWD compared to placebo after 24 weeks of treatment. CATALYST is an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of Bard in approximately 200 CTD-PAH patients randomized one-to-one to active drug or placebo. We expect to have top-line data from the CATALYST trial in the first half of 2020. If the trial results are positive, we believe the results, together with other data from our development program, will be sufficient to form the basis of an NDA submission to the FDA seeking approval of Bard for the treatment of CTD-PAH.

In addition to our lead programs, we are currently exploring a battery of additional clinical and preclinical programs in diseases that may include meaningful expansion opportunities for Bard and Omav. We also have completed or have ongoing Phase 1 clinical trials with RTA 901, our lead product candidate from our Hsp90 modulator program, which includes highly potent and selective C-terminal modulators of Hsp90, and RTA 1701, our lead product candidate from our proprietary series of RORγt inhibitors.

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 and KHK, from sales of our securities, and secured loans. 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, 2018, we had $337.8 million of cash and cash equivalents and an accumulated deficit of $420.3 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 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.

On July 27, 2018, we closed a follow-on underwritten public offering of 3,450,000 shares of our Class A common stock for gross proceeds of $248.4 million. The Company received net proceeds from the offering of $232.9 million, after deducting underwriting discounts and commissions and offering expenses. We intend to use the net proceeds for working capital and general corporate purposes, which include, but are not limited to, advancing the development of Bard and Omav through clinical trials, preparing to file one or more NDAs, and planning for commercialization of our potential products.

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 license agreement with KHK, our license agreement with AbbVie, and our collaboration agreement with AbbVie and consists of upfront payments and milestone payments. License revenue recorded with respect to the KHK license agreement, the AbbVie license agreement, and the AbbVie collaboration agreement consists solely of the recognition of deferred revenue. Under our revenue recognition policy, license revenue associated with upfront, non-refundable license payments received under the license and collaboration agreements with AbbVie and KHK are deferred and recognized ratably over the expected term of the performance obligations under the agreements. The AbbVie collaboration agreement and the KHK license agreement extend through 2021, and 2026, respectively. As of November 2017, the deferred revenue related to the AbbVie license agreement has been fully recognized, which resulted in a decrease in license revenue recognized in 2018.

The Company achieved and received a milestone payment of $30.0 million related to the KHK license agreement in 2018. The Company included this variable consideration to the transaction price and recognized $22.5 million in collaboration revenue, including a cumulative catch-up for the portion of this milestone that was satisfied in prior periods. The remaining balance was recorded in deferred revenue on the balance sheet and is being recognized over the remaining performance obligation period. Additionally, we recognized approximately $3.6 million in related license fees and other expenses related to the achievement of this regulatory milestone.

We also have other license revenue, which consists of milestone payments from a disease advocacy organization in 2018 and 2017, 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, 2018, we have incurred a total of $646.8 million in research and development expense, a majority of which relates to the development of Bard and Omav. 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 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 Bard for the treatment of CKD caused by Alport syndrome, ADPKD, CTD-PAH, or other rare kidney diseases, and we are therefore incurring all costs for this program. AbbVie has the right to opt-in to these programs 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 would be split equally.

With respect to our Omav 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 Omav. Therefore, AbbVie no longer co-funds the exploratory development costs of this program, but retains the right to opt back in. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the United States, 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.

Currently, KHK is not participating in the development of Bard in CTD-PAH, ADPKD, or other rare kidney diseases but is reimbursing us the majority of the costs for our registrational trial in CKD caused by Alport syndrome in Japan. The Company's expenses were reduced by $2.0 million for KHK's share of the study costs for the year ended December 31, 2018.

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

	2018	2017	2016
		(in thousands)	
Bard	$ 43,566	$ 35,999	$ 17,188
Omav	19,277	10,123	5,011
RTA 901	350	1,927	2,187
RTA 1701	2,263	2,942	87
Other research and development expenses	31,832	20,282	14,980
Total research and development expenses	$ 97,288	$ 71,273	$ 39,453

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 SEC requirements, director and officer insurance premium, legal, audit and tax fees, compliance with the Sarbanes-Oxley Act, 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, 2018, 2017, and 2016

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

	2018	Change	2017	Change	2016
	(in thousands, except percentage data)				
Consolidated Statements of Operations Data					
Collaboration revenue					
License and milestone	$ 52,351	11%	$ 47,103	(5)%	$ 49,730
Other revenue	1,238	30%	955	658%	126
Total collaboration revenue	53,589	12%	48,058	(4)%	49,856
Expenses					
Research and development	97,288	37%	71,273	81%	39,453
General and administrative	32,748	41%	23,260	40%	16,603
Depreciation	431	(1)%	437	(36)%	682
Total expenses	130,467	37%	94,970	67%	56,738
Other income (expense)					
Investment income	3,541	405%	701	228%	214
Interest expense	(6,176)	(325)%	(1,454)	(100)%	—
Loss on extinguishment of debt	(1,007)	(100)%	—	—	—
Other income (expense)	—	100%	(3)	(100)%	—
Total other income (expense)	(3,642)	(382)%	(756)	(453)%	214
Loss before taxes on income	(80,520)	(69)%	(47,668)	(615)%	(6,668)
Provision (benefit) for taxes	26	767%	3	101%	(441)
Net loss	$ (80,546)	(69)%	$ (47,671)	(666)%	$ (6,227)

Revenue

License and milestone revenue represented approximately 98%, 98%, and 100% of total revenue for the years ended December 31, 2018, 2017, and 2016, respectively, and consisted primarily of the recognition of deferred revenue. License and milestone revenue increased by 11% during 2018 compared to 2017. The increase was primarily due to additional revenue of $22.5 million related to the KHK agreement, offset by the full recognition of deferred revenue for the AbbVie license agreement in November 2017.

License and milestone revenue decreased by 5% during 2017 compared to 2016. The decrease was primarily due to full recognition of deferred revenue for the AbbVie license agreement in November 2017, compared to a full year of recognition in 2016.

Other revenue increased by 30% during 2018 compared to 2017 and by 658% during 2017 compared to 2016, primarily due to revenue 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:

	2018	2017	2016
	(in thousands)		
License and milestone			
AbbVie license agreement	$ —	$ 18,420	$ 21,470
AbbVie collaboration agreement	26,647	26,647	26,720
KHK agreement	24,704	1,536	1,540
Other	1,000	500	—
Total license and milestone	$ 52,351	$ 47,103	$ 49,730
Other revenue	1,238	955	126
Total collaboration revenue	$ 53,589	$ 48,058	$ 49,856

Research and Development Expenses

Research and development expenses increased by 37% during 2018 compared to 2017. The increase was primarily due to an increase in clinical and manufacturing activities, primarily from increases totaling $24.9 million for CARDINAL, PHOENIX, and part 2 of MOXIe, offset by decreases totaling $10.3 million in clinical and manufacturing activities related to REVEAL, MOTOR, and RTA 901, which were completed in 2017. Additionally research and development expenses increased by $4.8 million in medical affairs activities in our Bard clinical programs, $4.6 million in personnel and equity compensation expenses to support growth in our development activities, and $1.8 million in additional discovery activities.

Research and development expenses increased by 81% during 2017 compared to 2016. The increase was primarily due to $23.9 million in expanded clinical and manufacturing activities, primarily for CARDINAL, CATALYST, the extension trial for CATALYST and LARIAT patients, part 2 of MOXIe, part 1 of MOTOR, REVEAL, and PHOENIX, $2.9 million in increased preclinical and manufacturing activities in our RTA 1701, $4.0 million in personnel and equity compensation expenses to support growth in our development activities, and $0.8 million in increased medical affairs activities.

Research and development expenses, as a percentage of total expenses, was 75%, 75%, and 70%, for 2018, 2017, and 2016, respectively. The increase of 5% during 2017 compared to 2016 was primarily due to increased clinical and manufacturing activity related to our registrational trials.

General and Administrative Expenses

General and administrative expenses increased by 41% during 2018 compared to 2017. The increase was primarily due to $4.3 million in personnel, consulting, and equity compensation expenses to support growth in our development activities, $3.6 million sublicense fees and other expenses from the achievement of the KHK milestone, and $2.2 million in commercial research activities.

General and administrative expenses increased by 40% during 2017 compared to 2016. The increase was primarily due to $4.7 million in personnel, consulting, and equity compensation expenses to support growth in our development activities, $0.9 million in commercial research activities, and $0.6 million in intellectual property costs due to additional validation of patents, new applications, national stage filings, and license fees.

General and administrative expenses, as a percentage of total expenses, was 25%, 24%, and 29%, for 2018, 2017, and 2016, respectively. The decrease of 5% during 2017 compared to 2016 was primarily due to the increase in research and development expenses for clinical and manufacturing activity related to our registrational trials.

Investment Income

The year-over-year increases in investment income during 2018, 2017, and 2016 were due to investment and interest income earned on cash equivalents.

Interest Expense

The year-over-year increases in interest expense during 2018, 2017, and 2016 were attributable to borrowing activities under our Restated Loan Agreement entered in June 2018 and our Loan Agreement entered in March 2017.

Provision (Benefit) for Taxes

The year-over-year changes in provision (benefit) for taxes during 2018, 2017, and 2016 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, the sale of preferred and common stock, and secured loans. To date, we have raised gross cash proceeds of $476.6 million through the sale of convertible preferred stock and $780.0 million from payments under license and collaboration agreements. We also obtained $402.3 million in net proceeds from our IPO and follow-on offerings of our Class A common stock and $77.2 million in net proceeds from our Restated Loan Agreement. We have not generated any revenue from the sale of any products. As of December 31, 2018, we had available cash and cash equivalents of approximately $337.8 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:

	2018	2017	2016
		(in thousands)	
Net cash (used in) provided by:			
Operating activities	$ (83,783)	$ (83,256)	$ (19,259)
Investing activities	(679)	(343)	(339)
Financing activities	292,472	128,647	62,322
Net change in cash and cash equivalents	$ 208,010	$ 45,048	$ 42,724

Operating Activities

Net cash used in operating activities was $83.8 million for the year ended December 31, 2018, consisting primarily of net loss of $80.5 million adjusted for non-cash items including stock-based compensation expense of $10.6 million, depreciation and amortization expense of $1.2 million, loss on extinguishment of debt of $1.0 million, and a net decrease in operating assets and liabilities of $16.1 million. The significant items in the change in operating assets and liabilities include an increase of prepaid expenses and other current assets of $1.1 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 $4.4 million due to clinical and manufacturing activities, an increase in accounts payable of $2.0 million due to timing of vendor payment, and a decrease in deferred revenue of $21.4 million. The decrease in deferred revenue relates to the ratable recognition of revenue over the expected term of the performance obligations under our collaboration agreements with AbbVie and KHK, which resulted in recognition of $51.4 million of license and milestone revenue, offset by the achievement of regulatory milestone of $30.0 million related to the KHK agreement, which was recognized as deferred revenue.

Net cash used in operating activities was $83.3 million for the year ended December 31, 2017, consisting primarily of net loss of $47.7 million adjusted for non-cash items including stock-based compensation expense of $6.5 million, depreciation and amortization expense of $0.6 million, and a net decrease in operating assets and liabilities of $42.7 million. The significant items in the change in operating assets and liabilities include an increase of prepaid expenses and other current assets of $1.3 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 $7.0 million due to clinical trial activities, a decrease in accounts payable of $1.8 million due to timing of vendor payment, and a decrease in deferred revenue of $46.6 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 $46.6 million of license and milestone revenue.

Investing Activities

Net cash used in investing activities consisted of purchases and sales of property and equipment. Net cash used in investing activities were not significant for the years ended December 31, 2018, 2017, and 2016 totaling $0.7 million, $0.3 million and $0.3 million, respectively.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2018 was $292.5 million, primarily due to net proceeds of $232.9 million from our follow-on public offering and $57.7 million from our Restated Loan Agreement.

Net cash provided by financing activities for the year ended December 31, 2017 was $128.6 million, primarily due to net proceeds of $108.5 million from our follow-on public offering and $19.5 million from our Amended Loan Agreement.

Net cash provided by financing activities for the year ended December 31, 2016 was $62.3 million, primarily due to net proceeds of $62.1 million from our IPO.

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 continue 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.

On June 14, 2018, we amended and restated our Loan Agreement. Under our Restated Loan Agreement, the Term A Loan was increased from $20.0 million to $80.0 million, of which Reata borrowed an additional $60.0 million on June 14, 2018, which resulted in an outstanding principal balance of $80.0 million under the Term A Loan at June 14, 2018. We may, at our sole discretion, borrow an additional $45.0 million under the Term B Loan, upon the achievement of one of two milestones by the earlier of 30 days after the achievement of a milestone or December 31, 2019. If we borrow under the Term B Loan, we expect to incur additional related interest expense.

In November 2017, the Company entered into an at-the-market equity offering sales agreement with Stifel, Nicolaus & Company, Incorporated, that established a program pursuant to which it may offer and sell up to $50.0 million of its Class A common stock from time to time in at-the-market transactions as stated in the prospectus supplement filed with the SEC pursuant to Rule 424(b)(5), dated as of November 9, 2017. To date, no sales have been made under the Company's at-the-market offering program.

On July 27, 2018, the Company closed a follow-on underwritten public offering of 3,450,000 shares of its Class A common stock for gross proceeds of $248.4 million. Net proceeds to the Company from the offering were approximately $232.9 million, after deducting underwriting discounts and commissions and offering expenses.

Our longer term liquidity requirements will 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. We believe our existing cash and cash equivalents, combined with available future debt, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into 2021. However, we anticipate opportunistically raising additional capital before that time through equity offerings, collaboration or license agreements, or additional debt in order to maintain adequate capital reserves. 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 be based 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. We may explore strategic collaborations or license arrangements for certain of our earlier stage assets, including RTA 901 and RTA 1701. If we do explore any arrangements, there can be no assurance that any agreement will be reached, and we may determine to cease exploring a potential transaction for any or all of the assets at any time. If an agreement is reached, there can be no assurance that any such transaction would provide us with a material amount of additional capital resources.

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, commercial loans, and collaboration or license transactions. 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 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, 2018, our contractual obligations were as follows:

	Payments due by period			
	Less than 1 year	1 to 3 years	4 to 5 years	Total
	(unaudited) (in thousands)			
Operating lease obligations	$ 577	$ 592	$ —	$ 1,169
Outstanding term loan	—	42,222	37,778	80,000
Total contractual obligations	$ 577	$ 42,814	$ 37,778	$ 81,169

Clinical Trials

As of December 31, 2018, 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 United States 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 primarily from licensing fees received under our collaborative licensing agreements with AbbVie and KHK and reimbursements for expenses from KHK. The terms of the agreements include non-refundable upfront fees, funding of research and development activities, payments based upon achievement of milestones, and royalties on net product sales.

Under Accounting Standards Update (ASU) No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the promised goods or services in the contract with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including the constraint on variable consideration; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when or as the entity satisfies a performance obligation.

At contract inception, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when or as the performance obligation is satisfied.

Licenses of intellectual property: If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from non-refundable, up-front fees allocated to the license when the license is transferred to the customer, and the customer can use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement that includes milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the value of the associated milestone (such as a regulatory submission by the Company) is included in the transaction price, which is then allocated to each performance obligation. Milestone payments that are not within the control of the Company, such as approvals from regulators, are not considered probable of being achieved until those approvals are received. At the end of each subsequent reporting period, the Company re-evaluates the probability of achievement of such development milestones and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license, collaboration, and other revenues and earnings in the period of adjustment and in future periods through the end of the performance obligation period.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and where the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (a) when the related sales occur, or (b) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

Manufacturing Supply Services: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the customer's discretion are generally considered options. The Company assesses if these options provide a material right to the licensee and, if so, they are accounted for as separate performance obligations. If the Company is entitled to additional payments when the customer exercises these options, any additional payments are recorded when the customer obtains control of the goods, which is upon delivery.

For a complete discussion of accounting for collaborative licensing agreements, see Note 3, *Collaboration Agreements*. The Company's revenue to date has been generated primarily from licensing fees received under its collaborative licensing agreements with AbbVie and KHK and reimbursements for expenses from KHK. The terms of the agreements include non-refundable upfront fees, funding of research and development activities, payments based upon achievement of milestones, and royalties on net product sales.

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 us and through CROs, 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 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 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.

Realization of deferred tax assets is generally dependent upon future earnings, if any, the timing and amount of which are uncertain. As of December 31, 2018, based on known factors, we cannot conclude that it is more likely than not that the remaining deferred tax assets will be utilized, and we have recorded a valuation allowance to fully offset its deferred tax assets.

We 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

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, 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 do not have sufficient trading history to estimate the volatility of our common stock, the expected volatility was estimated based on our own historical volatility since our IPO and 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 United States 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.

We will continue to use judgment in evaluating the expected volatility and expected terms utilized for our stock-based compensation calculations on a prospective basis. We account for forfeitures of share-based awards when they occur.

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

	Years Ended December 31		
	2018	2017	2016
Dividend yield	—%	—%	—%
Volatility	72.77%	75.14%	72.77%
Risk-free interest rate	2.79%	2.19%	1.76%
Expected term of options (in years)	6.35	6.37	6.74

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 $337.8 million at December 31, 2018, 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 increase of 100 basis points 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 United States dollars. However, we may be subject to fluctuations in foreign currency rates in connection with agreements not denominated in United States 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, 2018. 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 SEC'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 financial 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, 2018, 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

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rule 13a-15(f) under the Exchange Act, as amended. Our management conducted an evaluation of the effectiveness of our internal control over financial reporting based on the 2013 framework in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on its evaluation under the framework in Internal Control—Integrated Framework, our management concluded that the Company maintained effective internal control over financial reporting at a reasonable assurance level as of December 31, 2018, based on those criteria.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to a transition period established by the JOBS Act for emerging growth companies.

Changes in Internal Control Over Financial Reporting

There have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Exchange Act, during the year ended December 31, 2018, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

Dr. Ward, Executive Vice President and Chief Development Officer, has informed us of his intention to retire and has submitted his resignation effective March 8, 2019. Dr. Ward will provide consulting services to us for 90 days for a fee of approximately $102,000.

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 is contained in Part I, Item 1 of this Form 10-K and that will be contained in our proxy statement related to the 2019 Annual Meeting of Stockholders, which we intend to file with the SEC 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 2019 Annual Meeting of Stockholders, which we intend to file with the SEC 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 2019 Annual Meeting of Stockholders, which we intend to file with the SEC 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 2019 Annual Meeting of Stockholders, which we intend to file with the SEC 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 2019 Annual Meeting of Stockholders, which we intend to file with the SEC 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.

Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
1.1	At-the-Market Equity Offering Sales Agreement, dated November 9, 2017, between Reata Pharmaceuticals, Inc., and Stifel, Nicolaus & Company, Incorporated.	10-Q	001-37785	1.1	11/13/2017	
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	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 Dawn C. Bir dated September 6, 2016.	10-Q	001-37785	10.1	11/14/2016	
10.2+	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	
10.3+	Indemnification Agreement by and between the Registrant and William D. McClellan dated March 1, 2017.	8-K	001-37785	10.1	03/02/2017	
10.4+	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	
10.5+	Amended and Restated Employment Agreement, by and between the Registrant and J. Warren Huff, dated as of June 14, 2017.	S-3	333-218915	10.2	06/23/2017	
10.6+	Amended and Restated Employment Agreement, by and between the Registrant and Dawn C. Bir, dated as of June 14, 2017, 2017.	S-3	333-218915	10.3	06/23/2017	
10.7+	Amended and Restated Employment Agreement, by and between the Registrant and Colin Meyer, dated as of June 14, 2017, 2017.	S-3	333-218915	10.4	06/23/2017	
10.8+	Amended and Restated Employment Agreement, by and between the Registrant and Keith Ward, dated as of June 14, 2017, 2017.	S-3	333-218915	10.5	06/23/2017	
10.9+	Amended and Restated Employment Agreement, by and between the Registrant and Jason Wilson, dated as of June 14, 2017, 2017.	S-3	333-218915	10.6	06/23/2017	

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.10+	Amended and Restated Employment Agreement, by and between the Registrant and Michael D. Wortley, dated as of June 14, 2017, 2017.	S-3	333-218915	10.7	06/23/2017	
10.11	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	
10.12	Lease Amendment No. 11, effective as of November 9, 2017, between Reata Pharmaceuticals, Inc. and SDCO Gateway Commerce I & II, Inc.	10-Q	001-37785	10.1	11/13/2017	
10.13#	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	
10.14#	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	
10.15#	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	
10.16#	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	
10.17#	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	
10.18	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	Second Supplement to Exclusive License and Supply Agreement, by and between the Registrant and Kyowa Hakko Kirin Co., Ltd., dated as of March 21, 2017.	S-3	333-218915	10.1	06/23/2017	
10.20#	Third Supplement to Exclusive License and Supply Agreement, dated as of December 6, 2017, between Reata Pharmaceuticals, Inc. and Kyowa Hakko Kirin Co., Ltd.	8-K	001-37785	10.1	12/07/2017	
10.21#	Fourth Supplement to Exclusive License and Supply Agreement, dated as of December 6, 2017, between Reata Pharmaceuticals, Inc. and Kyowa Hakko Kirin Co., Ltd.	8-K	001-37785	10.2	12/07/2017	
10.22#	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	

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.23#	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	
10.24+	Non-Employee Director Compensation Policy.	10-K	001-37785	10.19	03/03/2017	
10.25+	Amended and Restated Non-Employee Director Compensation Policy dated as of December 6, 2017.	10-K	001-37785	10.25	03/02/2018	
10.26	Loan and Security Agreement, dated as of March 31, 2017, by and among Reata Pharmaceuticals, Inc., as borrower, Oxford Finance LLC, as the collateral agent and a lender, and Silicon Valley Bank, as a lender.	8-K	001-37785	10.1	04/03/2017	
10.27	First Amendment to Loan and Security Agreement, dated as of November 3, 2017, by and among Reata Pharmaceuticals, Inc., as borrower, Oxford Finance LLC, as the collateral agent and a lender, and Silicon Valley Bank, as a lender.	8-K	001-37785	10.1	11/07/2017	
10.28	Amended and Restated Loan and Security Agreement, dated as of June 14, 2018, by and among Reata Pharmaceuticals, Inc., as borrower, Oxford Finance LLC, as the collateral agent and a lender, and Silicon Valley Bank, as a lender.	8-K	001-37785	10.1	06/14/2018	
10.29	Second Amended and Restated Non-Employee Director Compensation Policy dated as of December 11, 2018.					X
10.30	Notice of Stock Option Grant forms for employees and director/consultants.					X
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 Extension 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.

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: February 28, 2019

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*)	February 28, 2019
/s/ Jason D. Wilson Jason D. Wilson	Chief Financial Officer (*Principal Financial Officer*)	February 28, 2019
/s/ Elaine Castellanos Elaine Castellanos	Vice President, Finance and Accounting (*Principal Accounting Officer*)	February 28, 2019
/s/ James E. Bass James E. Bass	Member of the Board of Directors	February 28, 2019
/s/ William D. McClellan, Jr. William D. McClellan, Jr.	Member of the Board of Directors	February 28, 2019
/s/ R. Kent McGaughy, Jr. R. Kent McGaughy, Jr.	Member of the Board of Directors	February 28, 2019
/s/ Jack B. Nielsen Jack B. Nielsen	Member of the Board of Directors	February 28, 2019
/s/ William E. Rose William E. Rose	Member of the Board of Directors	February 28, 2019

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Reata Pharmaceuticals, Inc. (the Company) as of December 31, 2018 and 2017, and the related consolidated statements of operations, stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with U.S. generally accepted accounting principles.

Adoption of New Accounting Standards

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2018 due to the adoption of Accounting Standards Update (ASU) No. 2014-09, Revenue from Contracts with Customers (Topic 606), and the related amendments.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting 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.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2002.

Dallas, Texas

February 28, 2019

Reata Pharmaceuticals, Inc.

Consolidated Balance Sheets
(in thousands, except share data)

	December 31,	
	2018	**2017**
Assets		
Cash and cash equivalents	$ 337,790	$ 129,780
Prepaid expenses and other current assets	4,483	3,329
Total current assets	342,273	133,109
Property and equipment, net	1,445	718
Other assets	1,490	1,510
Total assets	$ 345,208	$ 135,337
Liabilities and stockholders' equity (deficit)		
Accounts payable	$ 4,473	$ 2,067
Accrued direct research liabilities	15,416	12,627
Other current liabilities	4,696	3,511
Current portion of term loan	—	1,229
Current portion of deferred revenue	31,335	28,183
Total current liabilities	55,920	47,617
Other long-term liabilities	524	53
Term loan, net of current portion and debt issuance costs	79,219	18,385
Deferred revenue, net of current portion	194,386	216,255
Total noncurrent liabilities	274,129	234,693
Commitments and contingencies		
Stockholders' equity (deficit):		
Common stock A, $0.001 par value: 500,000,000 shares authorized; issued and outstanding – 24,000,683 and 19,975,340 at December 31, 2018 and December 31, 2017, respectively	24	20
Common stock B, $0.001 par value: 150,000,000 shares authorized; issued and outstanding – 5,728,175 and 6,166,166 shares at December 31, 2018 and December 31, 2017, respectively	6	7
Additional paid-in capital	435,452	190,145
Shareholder notes receivable	—	(2)
Accumulated deficit	(420,323)	(337,143)
Total stockholders' equity (deficit)	15,159	(146,973)
Total liabilities and stockholders' equity (deficit)	$ 345,208	$ 135,337

See accompanying notes.

Reata Pharmaceuticals, Inc.

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

	Years Ended December 31		
	2018	2017	2016
Collaboration revenue			
License and milestone	$ 52,351	$ 47,103	$ 49,730
Other revenue	1,238	955	126
Total collaboration revenue	53,589	48,058	49,856
Expenses			
Research and development	97,288	71,273	39,453
General and administrative	32,748	23,260	16,603
Depreciation	431	437	682
Total expenses	130,467	94,970	56,738
Other income (expense)			
Investment income	3,541	701	214
Interest expense	(6,176)	(1,454)	—
Loss on extinguishment of debt	(1,007)	—	—
Other income (expense)	—	(3)	—
Total other income (expense)	$ (3,642)	(756)	214
Loss before taxes on income	(80,520)	(47,668)	(6,668)
Provision (benefit) for taxes	26	3	(441)
Net loss	$ (80,546)	$ (47,671)	$ (6,227)
Net loss per share—basic and diluted	$ (2.91)	$ (1.99)	$ (0.31)
Weighted-average number of common shares used in net loss per share basic and diluted	27,701,783	23,933,309	19,816,635

See accompanying notes.

Reata Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity (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, 2016	—	$ —	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)
Compensation expense related to stock option and restricted stock	—	—	—	—	6,648	—	(118)	6,530
Exercise of options	—	—	59,112	1	659	—	—	660
Proceeds from payments of shareholder promissory notes	—	—		—	37	13	—	50
Public offering of common stock, net of offering costs	3,737,500	3	—	—	108,503	—	—	108,506
Conversion of common stock Class B to Class A	4,549,866	5	(4,549,866)	(5)	—	—	—	—
Net loss	—	—	—	—	—	—	(47,671)	(47,671)
Balance at December 31, 2017	19,975,340	20	6,166,166	7	190,145	(2)	(337,143)	(146,973)
Compensation expense related to stock option and restricted stock	—	—	—	—	10,550	—	—	10,550
Exercise of options	—	—	137,352	—	1,885	—	—	1,885
Proceeds from payments of shareholder promissory notes	—	—		—	6	2	—	8
Public offering of common stock, net of offering costs	3,450,000	3	—	—	232,866	—	—	232,869
Conversion of common stock Class B to Class A	575,343	1	(575,343)	(1)	—	—		—
Adoption of new accounting guidance							(2,634)	(2,634)
Net loss	—	—	—	—	—	—	(80,546)	(80,546)
Balance at December 31, 2018	24,000,683	$ 24	5,728,175	$ 6	$ 435,452	$ —	$ (420,323)	$ 15,159

See accompanying notes.

Reata Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Years Ended December 31		
	2018	**2017**	**2016**
Operating activities			
Net loss	$ (80,546)	$ (47,671)	$ (6,227)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	431	437	682
Amortization of debt issuance costs	888	138	—
Stock-based compensation expense	10,550	6,530	2,367
Loss on extinguishment of debt	1,007	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(1,154)	(778)	(1,218)
Other assets	20	(519)	(438)
Accounts payable	1,955	(1,763)	299
Accrued direct research and other current and long-term liabilities	4,417	6,973	3,080
Federal income tax receivable/payable	—	—	31,926
Deferred revenue	(21,351)	(46,603)	(49,730)
Net cash used in operating activities	(83,783)	(83,256)	(19,259)
Investing activities			
Sales/disposals of fixed assets	—	1	1
Purchases of property and equipment	(679)	(344)	(340)
Net cash used in investing activities	(679)	(343)	(339)
Financing activities			
Proceeds from issuance of common stock	233,496	108,910	64,705
Payments on deferred offering costs	(627)	(404)	(2,607)
Proceeds from long-term debt	60,000	20,000	—
Payments on deferred issuance costs	(2,290)	(524)	—
Exercise of options	1,885	660	4
Proceeds from payments of shareholder promissory notes	8	50	265
Payment of capital lease obligation	—	(45)	(45)
Net cash provided by financing activities	292,472	128,647	62,322
Net increase in cash and cash equivalents	208,010	45,048	42,724
Cash and cash equivalents at beginning of year	129,780	84,732	42,008
Cash and cash equivalents at end of period	$ 337,790	$ 129,780	$ 84,732
Supplemental disclosures			
Cash paid for interest	$ 4,741	$ 1,164	$ —
Purchases of equipment in accounts payable and other current liabilities	$ 492	$ 13	$ 20

See accompanying notes.

1. Description of Business

The Company's mission is to develop innovative therapies that change patients' lives for the better. The Company focuses on developing small-molecule therapeutics with novel mechanisms of action for the treatment of severe, life-threatening diseases with few or no approved therapies. The Company's lead product candidates, bardoxolone methyl (Bard) and omaveloxolone (Omav), activate the transcription factor Nrf2, which plays an important role in regulating the cellular response to injury. By activating Nrf2, Bard and Omav normalize mitochondrial function, restore redox balance, and resolve inflammation. The Company has fully enrolled two registrational clinical trials: CARDINAL, studying Bard in chronic kidney disease (CKD) caused by Alport syndrome, and MOXIe, studying Omav in Friedreich's ataxia (FA). CKD caused by Alport syndrome and FA are rare, serious diseases with no approved therapy. The Company designed CARDINAL and MOXIe based on the results of earlier clinical studies and guidance from the FDA on a potential path to approval. The Company expects to have top-line data from both of these clinical trials in the second half of 2019. In each of these trials, FDA approval may provide expansion opportunities into other related indications. The Company is also conducting a third registrational trial, CATALYST, studying Bard in patients with a rare and serious form of pulmonary arterial hypertension caused by connective tissue disease (CTD-PAH), and the Company expects to have top-line data from this trial during the first half of 2020. The Company expects its current cash to fund its operations through data readouts for these three ongoing registrational clinical trials. In addition to its lead programs, the Company is currently exploring a battery of additional clinical and preclinical programs in diseases that may include meaningful expansion opportunities for Bard and Omav. The Company also has completed or has ongoing Phase 1 clinical trials with RTA 901, its lead product candidate from our Hsp90 modulator program, which includes highly potent and selective C-terminal modulators of Hsp90, and RTA 1701, its lead product candidate from its proprietary series of RORγt inhibitors.

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

On May 25, 2016, the Company's registration statement on Form S-1 (File No. 333-208843) relating to its IPO, of its common stock was declared effective by the United States 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 $60,940,000, net of underwriting discounts and commissions and offering expenses.

On August 1, 2017, the Company closed a follow-on underwritten public offering of 3,737,500 shares of its Class A common stock, which included 487,500 shares of its Class A common stock issued pursuant to an option granted to the underwriters, for gross proceeds of $115,900,000. The Company received total proceeds from the offering of $108,525,000, after deducting underwriting discounts and commissions and offering expenses.

On November 9, 2017, the Company entered into an at-the-market equity offering sales agreement with Stifel, Nicolaus & Company, Incorporated, that established a program pursuant to which it may offer and sell up to $50,000,000 of its Class A common stock from time to time in at-the-market transactions. As of the filing date of this Form 10-K, no shares have been sold under this program.

On July 27, 2018, the Company closed a follow-on underwritten public offering of 3,450,000 shares of its Class A common stock for gross proceeds of $248,400,000. The Company received net proceeds from the offering of $232,869,000, after deducting underwriting discounts and commissions and offering expenses.

2. Summary of Significant Accounting Policies

Revenue Recognition

The Company's revenue to date has been generated primarily from licensing fees received under its collaborative licensing agreements with AbbVie Inc. (AbbVie) and Kyowa Hakko Kirin Co., Ltd. (KHK) and reimbursements for expenses from KHK. The terms of the agreements include non-refundable upfront fees, funding of research and development activities, payments based upon achievement of milestones, and royalties on net product sales.

Under Accounting Standards Update (ASU) No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to- receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the promised goods or services in the contract with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including the constraint on variable consideration; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when or as the entity satisfies a performance obligation.

At contract inception, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when or as the performance obligation is satisfied.

Licenses of intellectual property: If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from non-refundable, up-front fees allocated to the license when the license is transferred to the customer, and the customer can use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement that includes milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the value of the associated milestone (such as a regulatory submission by the Company) is included in the transaction price, which is then allocated to each performance obligation. Milestone payments that are not within the control of the Company, such as approvals from regulators, are not considered probable of being achieved until those approvals are received. At the end of each subsequent reporting period, the Company re-evaluates the probability of achievement of such development milestones and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license, collaboration, and other revenues and earnings in the period of adjustment and in future periods through the end of the performance obligation period.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and where the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (a) when the related sales occur, or (b) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

Manufacturing Supply Services: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the customer's discretion are generally considered options. The Company assesses if these options provide a material right to the licensee and, if so, they are accounted for as separate performance obligations. If the Company is entitled to additional payments when the customer exercises these options, any additional payments are recorded when the customer obtains control of the goods, which is upon delivery.

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. The Company recorded collaboration revenue totaling $1,000,000, $500,000, and $0 related to milestone payments during the years ended December 31, 2018, 2017, and 2016, respectively.

For a complete discussion of accounting for collaborative licensing agreements, see Note 3, *Collaboration Agreements*.

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 (CROs), 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 Bard for the treatment of CKD caused by Alport syndrome, CTD-PAH, or other rare kidney diseases, and the Company is therefore incurring all costs for this program. AbbVie has the right to opt-in to these programs at any time. 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 would be split equally.

With respect to its Omav 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 Omav. Therefore, AbbVie no longer co-funds the exploratory development costs of this program, but retains the right to opt back in. Depending upon what point, if any, AbbVie opts back into development, AbbVie may retain its right to commercialize a product outside the United States 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.

In December 2017, the Company and KHK entered into the Third Supplement to the KHK Agreement, which allows the Company to begin a portion of the CARDINAL registrational trial in Japan, for which KHK will reimburse costs incurred up to $3,000,000. The Company deemed that this was not a material modification to the KHK Agreement because no payment terms or deliverables were changed. The Company's expenses were reduced by $1,973,000 for KHK's share of the study costs for twelve months ended December 31, 2018.

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 CROs 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 Accounting Standards Codification (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 2018, 2017, and 2016.

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.

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, 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 does not have sufficient trading history to estimate the volatility of its common stock, the expected volatility was estimated based on its own historical volatility since its IPO and 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 United States 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 will continue to use judgment in evaluating the expected volatility and expected terms utilized for its stock-based compensation calculations on a prospective basis. The Company accounts for forfeitures of share-based awards when they occur.

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.

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.

Debt Issuance Costs

The Company defers costs related to debt issuance and amortizes these costs to interest expense over the term of the debt, using the effective interest method. Debt issuance costs are presented in the balance sheet as a deduction from the carrying amount of the debt liability.

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.

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 other comprehensive income (loss) for the years ended December 31, 2018, 2017, and 2016 were immaterial.

Recent Accounting Pronouncements

The Company is an "emerging growth company," as defined in 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 Financial Accounting Standards Board (FASB) issued Topic 606, which supersedes the revenue recognition requirements in ASC 605, *Revenue Recognition* (Topic 605). The FASB has subsequently issued a number of amendments to Topic 606. The Company adopted this new standard on January 1, 2018 using the modified retrospective transition method. As of January 1, 2018, upon adoption of Topic 606, the Company recorded a cumulative adjustment of $2,634,000 to increase accumulated deficit and increase deferred revenue. This adjustment was the remainder of the transaction price related to the $15,000,000 received milestones that were recognized under the prior milestone recognition methodology when the milestones were achieved in 2010 and 2012. For a complete discussion of accounting for collaborative licensing agreements, see Note 3, *Collaboration Agreements*.

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. Operating leases will result in straight-line expense while finance leases will result in a front-loaded expense pattern. 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. In July 2018, the FASB issued Accounting Standards Update (ASU) No. 2018-11, *Leases* (ASU 2018-11), which offers a transition option to entities adopting the new lease standard. Under the transition option, entities can elect to apply the new guidance using a modified retrospective approach at the beginning of the year in which the new lease standard is adopted, rather than to the earliest comparative period presented in their financial statements. The

Company will adopt the standard using the modified retrospective method and elect a package of practical expedients for leases that commenced prior to January 1, 2019 and will not reassess: (i) whether any expired or existing contracts are or contain leases; (ii) lease classification for any expired or existing leases; and (iii) initial direct costs capitalization for any existing leases. The Company is finalizing its assessment of the impact of this guidance and anticipates establishing liabilities and corresponding right-of-use assets on its consolidated balance sheets with no material impact to its consolidated statements of income.

In July 2018, the FASB issued ASU No. 2018-09, *Codification Improvements* (ASU 2018-09). This ASU provided various minor codification updates and improvements to address comments that the FASB had received regarding unclear or vague accounting guidance. The guidance is effective for fiscal years beginning after December 15, 2018, including interim reporting periods within that fiscal year. The Company is currently evaluating the impact of the guidance on its consolidated financial statements and does not anticipate that this guidance will have a material impact.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement: Disclosure Framework* (Topic 820) (ASU 2018-13). This ASU eliminates, modifies, and adds certain disclosure requirements for fair value measurements. This update is effective in fiscal years, including interim periods, beginning after December 15, 2019, and early adoption is permitted. The added disclosure requirements and the modified disclosure on the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented. All other changes to disclosure requirements in this update should be applied retrospectively to all periods presented upon their effective date. The Company is currently evaluating the impact on its financial statements of adopting this guidance.

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements* (Topic 808) (ASU 2018-18). This update provides clarification on the interaction between *Revenue Recognition* (Topic 606) and *Collaborative Arrangements* (Topic 808) including the alignment of unit of account guidance between the two topics. This update is effective in fiscal years, including interim periods, beginning after December 15, 2020, and early adoption is permitted. The Company is currently evaluating the impact on its financial statements of adopting this guidance.

3. Collaboration Agreements

On January 1, 2018, the Company adopted Topic 606 using the modified retrospective transition method applied to those contracts which were not completed as of January 1, 2018. Results for reporting periods beginning after January 1, 2018 are presented under Topic 606, while prior period amounts are not adjusted and continue to be reported in accordance with the Company's historical accounting under Topic 605.

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 $26,647,000, $26,647,000, and $26,720,000 as collaboration revenue during the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018 and 2017, the Company recorded deferred revenue totaling approximately $211,643,000 and $238,292,000, respectively, of which approximately $26,647,000 and $26,647,000, 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 Bard 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, 2018, the Company has received $150,000,000 related to regulatory 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 Bard 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 up-front license fee and the Company's participation on joint steering committees were accounted for as a single unit of accounting, and accordingly, revenue was recognized ratably through November 2017, which was 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 Bard to AbbVie, which occurred in November 2010 and, accordingly, recognized approximately $0, $18,420,000, and $21,470,000 in collaboration revenue during the years ended December 31, 2018, 2017, and 2016, respectively. As of November 2017, the deferred revenue has been fully recognized.

KHK

In December 2009, the Company entered into the KHK Agreement for an exclusive license to develop and commercialize Bard 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, 2018, the Company received $45,000,000 related to regulatory development milestone payments from KHK and has the potential in the future to achieve another $52,000,000 from six 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 Bard. 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 Company evaluated the KHK agreement under Topic 606 and identified three performance obligations at contract inception: (1) the exclusive license rights to develop and commercialize Bard in Japan and licensed territory, (2) the obligation to participate in JSCs, and (3) the obligation to supply Bard for KHK's clinical trial and commercial needs. The transaction price was allocated to the exclusive license rights and the obligation to participate on JSCs, which are accounted for as a single performance obligation and is recognized as revenue ratably through December 2021, which is the estimated minimum period to complete the performance obligation under the KHK agreement. Any consideration related to the Company's obligation to supply KHK with drug product is recognized upon delivery.

Upon adoption of Topic 606, the Company determined that the transaction price for this agreement at contract inception includes the upfront fee of $35,000,000 and regulatory development milestones of $15,000,000 received prior to 2013. In May 2018, the Company achieved its regulatory development milestone of $30,000,000. The Company believes the remaining additional regulatory development milestones of $52,000,000 and commercial milestones of $140,000,000 are fully constrained as they are not within the control of the Company or KHK and did not include these remaining milestones in the transaction price. Any consideration related to royalties will be recognized when the related sales occur.

As of December 31, 2018, the Company included the regulatory development milestone of $30,000,000 as variable consideration to the transaction price. During the year ended December 31, 2018, the Company received $30,000,000 and recognized $22,510,000 in collaboration revenue, including a cumulative catch-up for the portion of this milestone that was satisfied in prior periods. The remainder of $7,490,000 was recorded in deferred revenue on the balance sheet as of December 31, 2018 and will be recognized over the remaining performance obligation period ending December 2021. The Company also recognized related license fees and other expenses of approximately $3,600,000 related to achievement of this milestone.

The Company began recognizing revenue related to the up-front payment upon transfer of the license and technical knowledge of Bard to KHK, which occurred in December 2009, and, accordingly, recognized approximately $24,704,000, $1,536,000, and $1,540,000 as collaboration revenue during the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018 and 2017, the Company recorded deferred revenue totaling approximately $14,078,000 and $6,146,000, respectively, of which approximately $4,688,000 and $1,536,000 respectively, is reflected as the current portion of deferred revenue.

Due to the adoption of Topic 606, collaboration revenue was decreased and net loss was increased by $6,835,000 for the year ended December 31, 2018. Basic and diluted net loss per share increased by $0.25 for the year ended December 31, 2018.

4. ***Term Loan***

On March 31, 2017, the Company entered into a loan and security agreement (Loan Agreement) with Oxford Finance LLC and Silicon Valley Bank (collectively, the Lenders), under which the Lenders agreed to lend the Company up to $35,000,000, issuable in two separate term loans of $20,000,000 (Term A Loan) and $15,000,000 (Term B Loan, and together with the Term A Loan, the Term Loans). On March 31, 2017, the Company borrowed $20,000,000 from the Term A Loan.

On November 3, 2017, the Company amended the Loan Agreement (Amended Loan Agreement) and increased the Term B Loan amount to either $20,000,000 or $25,000,000, which extends the interest only period from six to twelve months if the Term B Loan is drawn. The Company paid an amendment fee of $ 250,000 on November 8, 2017, upon the execution of the Amended Loan Agreement.

On June 14, 2018, the Company entered into an Amended and Restated Loan and Security Agreement (the Restated Loan Agreement). Under the Restated Loan Agreement, the Term A Loan was increased from $20,000,000 to $80,000,000 and the Term B Loan availability was increased to $45,000,000, upon the achievement of one of two milestones by the earlier of 30 days after the achievement of a milestone or December 31, 2019. If the Company is entitled to draw the Term B Loan but does not draw the Term B Loan by December 31, 2019, the Company is obligated to pay a non-utilization fee of $450,000. On June 14, 2018, the Company borrowed the remaining $60,000,000 available under the Term A Loan and recorded a loss on extinguishment as a result of the debt modification of $1,007,000, which consisted primarily of lender fees and unamortized debt issuance costs.

All outstanding Term Loans will mature on June 1, 2023. Under the Term A Loan, the Company will make interest-only payments for 24 months through June 1, 2020; however, if the Company draws the Term B Loan, the Company will make interest-only payments for 36 months through June 1, 2021. The interest-only payment period will be followed by 36 equal monthly payments, or 24 equal monthly payments if the Company draws the Term B Loan, of principal and interest payments. The Term Loans will bear interest at a floating per annum rate calculated as 7.79% plus the greater of the 30-day United States Dollar LIBOR rate reported in The Wall Street Journal on the last business day of the month that immediately precedes the month in which the interest will accrue or 1.91%, with a minimum rate of 9.7% and maximum rate of 12.29%.

The Company has the option to prepay all, but not less than all, of the borrowed amounts, provided that the Company will be obligated to pay a prepayment fee equal to (a) the aggregate amount of interest that the Company would have paid through the maturity date if prepayment is made on or before the first anniversary of the applicable funding date of the Term Loan, (b) 4.0% of the outstanding principal balance of the applicable Term Loan if prepayment is made after the first anniversary date and on or before the second anniversary of the applicable funding date, (c) 3.0% of the outstanding principal balance of the applicable Term Loan if prepayment is made after second anniversary date and on or before the third anniversary of the applicable funding date, or (d) 1.5% of the outstanding principal balance of the applicable Term Loan if prepayment is made after the third anniversary date and on or before the fourth anniversary of the applicable funding date. The Company will also be required to make a final exit fee payment of 6.5% of the principal balance of the Term A Loan and 4.0% of the Term B Loan, payable on the earliest of the prepayment of the Term Loans, acceleration of any Term Loan, or at maturity of the Term Loans.

The Company may use the proceeds from the Term Loans for working capital and to fund its general business requirements. The Company's obligations under the Restated Loan Agreement are secured by substantially all of its current and future assets, including its owned intellectual property.

As of December 31, 2018, the Company had $80,000,000 outstanding under the Term A Loan, which was recorded at its initial carrying value of $80,000,000, less unamortized discount and debt issuance costs of approximately $5,981,000. In connection with the Term A Loan, the discount and debt issuance costs were recorded as a reduction to debt on its balance sheet and are being accreted to interest expense over the life of the Term A Loan. Additionally, the final exit fee of approximately $5,200,000 is being accrued over the life of the Term A Loan through interest expense. The Term A Loan has a current effective interest rate of 10.88% before debt issuance costs and final exit fee and 13.43% including debt issuance costs and final exit fee. The Company is in compliance with all covenants under the Restated Loan Agreement as of December 31, 2018.

The future principal payments for the Company's Term A Loan as of December 31, 2018 are as follows (in thousands):

2019	$ —
2020	15,555
2021	26,667
2022	26,667
2023	11,111
	$ 80,000

5. Property and Equipment

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

	2018	2017
Computer equipment and software	$ 2,414	$ 1,831
Laboratory equipment	5,025	4,654
Office furniture	1,331	1,282
Office and other equipment	286	286
Leasehold improvements	5,103	4,959
	14,159	13,012
Less accumulated depreciation and amortization	(12,714)	(12,294)
Property and equipment, net	$ 1,445	$ 718

6. Income Taxes

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

	2018	2017	2016
Current	$ 26	$ 3	$ (441)
Deferred	—	—	—
Total provision (benefit) for taxes on income	$ 26	$ 3	$ (441)

The following table reconciles the Company's effective income tax rate from continuing operations to the federal statutory tax rate of 21%:

	2018	2017	2016
U.S. federal income taxes	21%	35%	35%
Stock-based compensation	1	—	(2)
Change in valuation allowance	(34)	48	(25)
2017 Tax Act	—	(111)	—
Federal and state tax credits	12	28	—
Other	—	—	(1)
Recorded federal income tax benefit (provision)	0%	0%	7%

The Tax Cuts and Jobs Act of 2017 (the 2017 Tax Act), which was signed into law on December 22, 2017, has resulted in significant changes to the United States corporate income tax system. These changes included a federal statutory rate reduction from 35% to 21% and the elimination or reduction in the deductibility of certain credits and limitations, such as Credits related to designated orphan drugs, net operating losses, interest expense, and executive compensation. The federal statutory rate reduction took effect on January 1, 2018. As a result of the reduction of federal corporate income tax rates, the Company recorded a reduction of $53,113,000 at December 31, 2017 to its deferred tax assets. Consistent with 2017, its deferred tax assets continue to be fully offset by a valuation allowance in 2018 as the Company cannot currently conclude that it is more likely than not that the remaining deferred tax assets will be utilized. Consequently, although the future potential benefit from its deferred tax assets was materially reduced by the reduction of federal corporate income tax rates, there was no effect on its 2017 and 2018 Consolidated Statement of Operations.

On December 22, 2017, Staff Accounting Bulletin No. 118 (SAB 118) was issued to address the application of U.S. GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the 2017 Tax Act. At December 31, 2018, we have now completed our accounting for all of the enactment-date income tax effects of the 2017 Tax Act.

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):

	2018	2017
Deferred tax assets:		
Deferred revenue	$ 47,432	$ 51,332
Net operating loss	45,011	25,601
Federal and state tax credits	30,739	20,928
Stock-based compensation	4,072	2,118
Depreciation	119	318
Other	379	301
Subtotal	127,752	100,598
Less: Valuation allowance	(127,752)	(100,598)
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 2018. 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. The valuation allowance increased by $27,154,000 in 2018 and decreased by $22,788,000 in 2017.

As of December 31, 2018, the Company had accumulated net operating losses of approximately $214,340,000 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 $120,390,000 of the net operating loss carryforwards expire between fiscal years 2023 and 2037. Under the 2017 Tax Act, the remaining $93,950,000 will be carried forward indefinitely but is limited to 80% of our taxable income.

As of December 31, 2018, the Company has federal orphan drug tax credit and federal and state research and development tax credit carryforwards of $29,236,000 and $1,503,000, respectively. These Credits expire beginning in 2024.

As of December 31, 2018, 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 IRS completed an examination of the Company's United States income tax returns for 2013, 2014, and 2015 in June 2018 and proposed adjustments with respect to certain items that were reported by the Company for the 2013 tax year. The Company believes that it has accurately reported all amounts in its tax returns and intends to vigorously defend its reported positions and believes the ultimate resolution of the adjustments proposed by the IRS examination team will not have a material adverse effect on its consolidated financial statements. 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.

7. 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, 2018, 2017, or 2016.

8. 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.

Bard 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 August 2018, the Company paid a sublicensing fee of $1,500,000 related to the milestone payment received from KHK under the KHK agreement.

In January 2009, the Company filed a patent application claiming the use of Bard and related compounds in treating CKD, 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. In August 2018, the Company paid a sublicensing fee of $600,000 related to the milestone payment received from KHK under the KHK agreement.

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.

9. Common Stock

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

Reserved Shares

At December 31, 2018, common stock reserved for issuance is as follows:

Outstanding common stock options under the 2007 Long Term Incentive Plan	3,294,225
Outstanding common stock options under standalone option agreements	26,346
Common stock available for future grant under the 2007 Long Term Incentive Plan	685,340
Total common shares reserved for future issuance	4,005,911

10. Convertible Preferred Stock

As of December 31, 2018 and 2017, 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.

11. Stock-Based Compensation

The 2007 Long Term Incentive Plan (the 2007 LTIP) 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. A total of 685,340 shares of common stock are available for future grant under the 2007 LTIP.

As of December 31, 2018, no shares of restricted stock are outstanding under the 2007 LTIP, and options to purchase 3,320,571 shares have been granted and are outstanding under the 2007 LTIP and standalone option agreements. These options vest over the stated periods through 2022. 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 over the vesting period of the options using the straight-line attribution method. The Company accounts for forfeitures when they occur.

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

	Years Ended December 31		
	2018	2017	2016
Research and development	$ 3,943	$ 2,409	$ 1,121
General and administrative	6,607	4,121	1,246
	$ 10,550	$ 6,530	$ 2,367

The following table summarizes stock option activity as of December 31, 2018, and changes during the years ended December 31, 2018 under the 2007 LTIP and standalone option agreements:

	Number of Options	Weighted-Average Price
Outstanding at January 1, 2018	3,251,696	19.83
Granted	230,054	38.14
Exercised	(137,352)	13.72
Forfeited	(21,461)	25.84
Expired	(2,366)	30.30
Outstanding at December 31, 2018	3,320,571	21.20
Exercisable at December 31, 2018	1,532,522	18.95

At December 31, 2018, 3,320,571 stock options are fully vested or are expected to vest and have a weighted-average outstanding term of 7.80 years and a weighted-average exercise price of $21.20. Exercisable stock options have a weighted-average outstanding term of 7.12 years.

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		
	2018	2017	2016
Dividend yield	—%	—%	—%
Volatility	72.77%	75.14%	72.77%
Risk-free interest rate	2.79%	2.19%	1.76%
Expected term of options (in years)	6.35	6.37	6.74

Expected volatility is based on the Company's own historical volatility since its IPO and benchmarked public companies during fiscal years 2018, 2017 and 2016. The risk-free interest rate, ranging from 2.34% to 3.19% during the year ended December 31, 2018, is based on the United States 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, 2018, 2017, and 2016, was $115,849,000, $28,613,000, and $12,951,000, respectively. The total intrinsic value of exercisable options at December 31, 2018, 2017, and 2016, was $56,933,000, $11,469,000, and $3,841,000, respectively. In 2018, 2017, and 2016, 137,352, 59,112, and 35,207 options were exercised, respectively. As of December 31, 2018, total unrecognized compensation expense of $26,220,000 related to equity awards is expected to be recognized over a weighted average of 2.78 years.

12. Commitments and Contingencies

Lease Commitments

The Company leases certain office and laboratory space under a non-cancelable operating lease. On November 9, 2017, the Company amended the lease agreement to extend its lease term by 24 months for an expiration date of October 2020, with a one-year renewal option. Rent is expensed on a straight-line basis, and an accrued rent liability of approximately $62,000 and $72,000 is recorded in other accrued liabilities on the accompanying consolidated balance sheets at December 31, 2018 and 2017, respectively.

Future minimum lease payments under non-cancelable operating leases are as follows at December 31, 2018 (in thousands):

2019	631
2020	538
Thereafter	—
	$ 1,169

For the years ended December 31, 2018, 2017, and 2016, the Company recorded total rent expense of approximately $632,000, $512,000, and $463,000, respectively.

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, 2018.

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.

13. Net (Loss) Income per Share

The computation of basic and diluted net (loss) income per share attributable to common stockholders of the Company for the years ended December 31 is summarized in the following table:

	2018	2017	2016
Numerator			
Net loss (in thousands)	$ (80,546)	$ (47,671)	$ (6,227)
Denominator			
Weighted-average number of common shares used in net loss per share – basic	27,701,783	23,933,309	19,816,635
Dilutive potential common shares	—	—	—
Weighted-average number of common shares used in net loss per share – diluted	27,701,783	23,933,309	19,816,635
Net loss per share – basic	(2.91)	(1.99)	(0.31)
Net loss per share – diluted	(2.91)	(1.99)	(0.31)

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 3,320,571, 3,251,696, and 2,311,146 shares for the years ended 2018, 2017, and 2016, respectively.

14. Selected Quarterly Financial Data

The following table contains quarterly financial information for 2018 and 2017. 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).

	2018			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total collaboration revenue	$ 32,392	$ 7,571	$ 5,175	$ 8,451
Total expenses	28,136	34,223	34,735	33,373
Total other income (expense)	(174)	(1,553)	(1,266)	(649)
Provision for taxes on income	—	6	9	11
Net income (loss)	4,082	(28,211)	(30,835)	(25,582)
Net income (loss) per share – basic	0.16	(1.08)	(1.07)	(0.86)
Net income (loss) per share – diluted	0.15	(1.08)	(1.07)	(0.86)

	2017			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total collaboration revenue	$ 12,732	$ 12,806	$ 12,557	$ 9,963
Total expenses	19,906	24,000	24,575	26,489
Total other income (expense)	76	(395)	(289)	(148)
Provision for taxes on income	—	2	1	—
Net loss	(7,098)	(11,591)	(12,308)	(16,674)
Net loss per share – basic and diluted	(0.32)	(0.52)	(0.50)	(0.64)

15. Subsequent Events

On January 2, 2019, the Company granted an aggregate of 969,975 options to purchase shares of common stock to employees with a grant price of $55.73.

Exhibit 10.29

December 11, 2018

REATA PHARMACEUTICALS, INC.
SECOND AMENDED AND RESTATED 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 Second Amended and Restated 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 11, 2018 (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 held on September 12, 2018 (collectively, the "***Annual Cash Fees***"). All Annual Cash Fees are vested upon payment.

1. Annual Board Service Retainer:
    a. All Eligible Directors: $38,000
    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: $7,125
    c. Chairman of the Nominating and Corporate Governance Committee: $3,500

Beginning with the second regular Board meeting held after the 2019 annual stockholder meeting, the Annual Cash Fees shall be as follows:

1. Annual Board Service Retainer:
    a. All Eligible Directors: $40,000

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: $10,000
   b. Member of the Compensation Committee: $6,375
   c. Member of the Nominating and Corporate Governance Committee: $5,000
3. Annual Committee Chair Service Retainer (in addition to Annual Committee Member Service Retainer):
   d. Chairman of the Audit Committee: $25,000
   e. Chairman of the Compensation Committee: $7,125
   f. Chairman of the Nominating and Corporate Governance Committee: $5,000

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 18,000 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 9,000 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 9,000 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, 2019, then the Eligible Director would receive an Annual Grant of 4,500 shares on January 5, 2019, which Annual Grant would vest 50% on April 5, 2019, and 50% on July 5, 2019, subject to the Terms; the new Eligible Director and all other Eligible Directors would receive an Annual Grant of 9,000 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.

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.

Prior Policies

Cash payments and equity grants made pursuant to the terms and provisions of any prior version of this Policy shall be governed by the terms and provisions of such prior version of this Policy.

Date

Notice of Grant of Stock Option
(Employee)

Award Details

Name :
Address :

Employee ID :
Award Amount :
Grant ID :
Grant Date :
Award Type :
Vesting Schedule :
Vesting Start Date :
Vesting End Date :
Expiration Date :
Deadline to Accept : 30 days from grant notification

Award Vesting Summary

The Option Shares shall be deemed "Nonvested Shares" unless and until they have become "Vested Shares," as defined below. The Option Shares will become "Vested Shares" as detailed in the table above; provided, however, that, except as otherwise provided in the Stock Option Agreement (the "Agreement"), such Nonvested Shares will become Vested Shares on such dates only if you remain in the employ of or a service provider to the Company or its Subsidiaries continuously from the Date of Grant through the applicable vesting date.

Notwithstanding the foregoing, following a Change in Control, any Option Shares that are Nonvested Shares on the date of the Change in Control shall become Vested Shares with respect to one eighteenth of all such Nonvested Shares on the one month anniversary of the Change in Control and thereafter with respect to an additional one eighteenth of all such Nonvested Shares at the time of the Change in Control on each subsequent month anniversary of the Change in Control such that the Option Shares will be 100% Vested Shares on the eighteenth month anniversary of the Change in Control, in each case, so long as you remain in the employ of or a

service provider to the Company or its Subsidiaries continuously from the Date of Grant through the applicable vesting date; provided, however, that if 100% of the Option Shares would otherwise become Vested Shares pursuant to the vesting rules set forth in the preceding paragraph prior to the eighteenth month anniversary of the date of the Change in Control, then the Option Shares will become Vested Shares in accordance with such vesting rules.

Fractions of Option Shares shall not vest on a vesting date and the Option Shares that do vest on a vesting date shall be rounded down to the nearest whole Option Share; provided, however, that such fractions of Option Shares shall be added to the number of Option Shares that vest on the final vesting date or that otherwise vest due to terms of the Agreement (with any resulting fraction of an Option Share being rounded down to the nearest whole Option Share).

Online Grant Acceptance

By your acceptance of this Option, you hereby acknowledge your receipt of this Option granted on the Date of Grant indicated above, which has been issued to you under the terms and conditions of this Notice of Grant, the Amended and Restated 2007 Long Term Incentive Plan (the ”Plan”) and the Agreement, including the vesting and risk of forfeiture provisions set forth therein. Capitalized terms used but not defined in this Notice of Grant shall have the meanings set forth in the Plan.

By your acceptance of this Option, you agree to the following provisions of this paragraph. You understand and acknowledge that if the purchase price of the Stock under this Option is less than the Fair Market Value of such Stock on the date of grant of this Option, then you may incur adverse tax consequences under sections 409A and/or 422 of the Code. You acknowledge and agree that (a) you are not relying upon any determination by the Company, its affiliates, or any of their respective employees, directors, officers, attorneys or agents (collectively, the “Company Parties”) of the Fair Market Value of the Stock on the Date of Grant, (b) you are not relying upon any written or oral statement or representation of the Company Parties regarding the tax effects associated with your acceptance of this Option and your receipt, holding and exercise of this Option, and (c) in deciding to accept this Option, you are relying on your own judgment and the judgment of the professionals of your choice with whom you have consulted. You hereby release, acquit and forever discharge the Company Parties from all actions, causes of actions, suits, debts, obligations, liabilities, claims, damages, losses, costs and expenses of any nature whatsoever, known or unknown, on account of, arising out of, or in any way related to the tax effects associated with your acceptance of this Option and your receipt, holding and exercise of this Option. You consent to receive documents from the Company and any plan administrator by means of electronic delivery, provided that such delivery complies with applicable law, including, without limitation, documents pursuant or relating to any equity award granted to you under the Plan or any other current or future equity or other benefit plan of the Company (collectively, a “Company Plan”). This consent shall be effective for the entire time that you are a participant in a Company Plan.

Exhibit 10.30

Date

Notice of Grant of Stock Option

(Director/Consultant)

Award Details

Name : **Address :** **Employee ID :** **Award Amount :** **Grant ID :** **Grant Date :** **Award Type :** **Vesting Schedule :** **Vesting Start Date :** **Vesting End Date :** **Expiration Date :** **Deadline to Accept :** 30 days from grant notification

Award Vesting Summary

The Option Shares shall be deemed "Nonvested Shares" unless and until they have become "Vested Shares," as defined below. The Option Shares will become "Vested Shares" as detailed in the table above; provided, however, that, except as otherwise provided in the Stock Option Agreement (the "Agreement"), such Nonvested Shares will become Vested Shares on such dates only if you remain a director or employee of or a service provider to the Company or its Subsidiaries continuously from the Date of Grant through the applicable vesting date.

Notwithstanding the foregoing, in the event of (i) a Change of Control, (ii) a separation from service by reason of death, or (iii) a separation from service by reason of Disability (as defined in the Agreement), any Option Shares that are Nonvested Shares on the date of such event shall become Vested Shares on such date.

Fractions of Option Shares shall not vest on a vesting date and the Option Shares that do vest on a vesting date shall be rounded down to the nearest whole Option Share; provided, however, that

such fractions of Option Shares shall be added to the number of Option Shares that vest on the final vesting date or that otherwise vest due to terms of the Agreement (with any resulting fraction of an Option Share being rounded down to the nearest whole Option Share).

Online Grant Acceptance

By your acceptance of this Option, you hereby acknowledge your receipt of this Option granted on the Date of Grant indicated above, which has been issued to you under the terms and conditions of this Notice of Grant, the Amended and Restated 2007 Long Term Incentive Plan (the "Plan") and the Agreement, including the vesting and risk of forfeiture provisions set forth therein. Capitalized terms used but not defined in this Notice of Grant shall have the meanings set forth in the Plan.

By your acceptance of this Option, you agree to the following provisions of this paragraph. You understand and acknowledge that if the purchase price of the Stock under this Option is less than the Fair Market Value of such Stock on the date of grant of this Option, then you may incur adverse tax consequences under sections 409A and/or 422 of the Code. You acknowledge and agree that (a) you are not relying upon any determination by the Company, its affiliates, or any of their respective employees, directors, officers, attorneys or agents (collectively, the "Company Parties") of the Fair Market Value of the Stock on the Date of Grant, (b) you are not relying upon any written or oral statement or representation of the Company Parties regarding the tax effects associated with your acceptance of this option and your receipt, holding and exercise of this Option, and (c) in deciding to accept this Option, you are relying on your own judgment and the judgment of the professionals of your choice with whom you have consulted. You hereby release, acquit and forever discharge the Company Parties from all actions, causes of actions, suits, debts, obligations, liabilities, claims, damages, losses, costs and expenses of any nature whatsoever, known or unknown, on account of, arising out of, or in any way related to the tax effects associated with your acceptance of this Option and your receipt, holding and exercise of this Option. You consent to receive documents from the Company and any plan administrator by means of electronic delivery, provided that such delivery complies with applicable law, including, without limitation, documents pursuant or relating to any equity award granted to you under the Plan or any other current or future equity or other benefit plan of the Company (collectively, a "Company Plan"). This consent shall be effective for the entire time that you are a participant in a Company Plan.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-8 No. 333-211682) pertaining to the Reata Pharmaceuticals, Inc. Amended and Restated 2007 Long Term Incentive Plan,

(2) Registration Statement (Form S-8 No. 333-216412) pertaining to the Reata Pharmaceuticals, Inc. Amended and Restated 2007 Long Term Incentive Plan,

(3) Registration Statement (Form S-8 No. 333-223407) pertaining to the Reata Pharmaceuticals, Inc. Amended and Restated 2007 Long Term Incentive Plan,

(4) Registration Statement (Form S-3 No. 333-218915) and in the related Prospectus; and

(5) Registration Statement (Form S-3 No. 333-226289) and in the related Prospectus.

of our report dated February 28, 2019, 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, 2018.

/s/ Ernst & Young LLP

Dallas, Texas
February 28, 2019

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 registrant 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) 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

   (d) 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: February 28, 2019

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 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) 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

   (d) 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: February 28, 2019

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, 2018 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: February 28, 2019

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, 2018 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: February 28, 2019

By: /s/ Jason D. Wilson

Jason D. Wilson
Chief Financial Officer
(Principal Financial Officer)