REATA PHARMACEUTICALS

ANNUAL REPORT 2021

TO OUR STOCKHOLDERS

J. Warren Huff,
Chief Executive Officer

Since Reata's beginning, we have centered our work on a single guiding mission: changing patients' lives for the better, by developing therapies with novel mechanisms of action and the potential to have high clinical impact on deadly diseases with few or no available therapies. This is a challenging mission that involves many risks but is also very meaningful.

Omaveloxolone in Friedreich's Ataxia

In line with that mission, we are developing omaveloxolone, a novel investigational, oral, once-daily activator of Nrf2, a transcription factor that induces molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signaling for the treatment of patients with Friedreich's ataxia. Friedreich's ataxia is a rare, genetic, debilitating, and degenerative neuromuscular disorder. Patients with Friedreich's ataxia experience progressive loss of coordination, muscle weakness, and fatigue that commonly results in motor incapacitation, with patients requiring a wheelchair in their teens or early twenties with an average survival in their mid-thirties. Friedreich's ataxia profoundly affects patients' motor function and, in almost all cases, shortens their lives. Currently, there are no approved therapies for these patients.

We recently completed the rolling submission of a New Drug Application (NDA) for omaveloxolone for the treatment of patients with Friedreich's ataxia in the United States. We are looking forward to working with the U.S. Food and Drug Administration (FDA) on its review of our NDA throughout this year. If approved, we are preparing to be in a position to launch this important drug by early 2023.

RTA 901 in Diabetic Peripheral Neuropathic Pain

Additionally, we are continuing to advance RTA 901, a highly potent and selective, oral, small-molecule C-terminal modulator of Hsp90 that has demonstrated activity in multiple preclinical models of both painful and insensate diabetic neuropathy with a novel and differentiated profile from other agents that have targeted diabetic neuropathy. RTA 901 increases transcription of Hsp70, another molecular chaperone that promotes cell survival in response to stress and affects mitochondrial function. We have completed a Phase 1 study of RTA 901 in healthy volunteers that demonstrated an acceptable safety profile with no safety signals. There were no drug discontinuations or serious adverse events (SAEs).

We initiated additional Phase 1 clinical pharmacology studies of RTA 901, including a drug-drug interaction study, in the first half of 2022. Following completion of these Phase 1 studies, we plan to initiate a randomized, double-blind placebo-controlled Phase 2 study of RTA 901 in diabetic patients with peripheral neuropathic pain in the second half of 2022.

Bardoxolone in Multiple Forms in CKD

Beyond our programs in neurological diseases, we have pursued the development of bardoxolone methyl (bardoxolone) for the treatment of patients with severe forms of chronic kidney disease (CKD). Bardoxolone is an investigational, once-daily, orally administered activator of Nrf2. In 2021, we submitted an NDA to the FDA for bardoxolone for the treatment of CKD caused by Alport syndrome. Following a negative vote by the FDA Cardiovascular and Renal Drugs Advisory Committee, the FDA issued a Complete Response Letter in February 2022. While this outcome is a significant disappointment for our company, as well as the many patients, families, and investigators who have participated in our development program for bardoxolone in patients with Alport syndrome, we will continue to work with the FDA to confirm our next steps on our Alport syndrome program.

We are additionally developing bardoxolone for the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD), a rare genetic form of CKD caused by mutations in PKD1 and PKD2 genes leading to the formation of fluid-filled cysts in the kidneys and other organs. ADPKD affects both men and women of all racial and ethnic groups and is the leading inheritable cause of kidney failure with an estimated diagnosed population of 140,000 patients in the United States. We are currently enrolling patients in FALCON, a Phase 3, international, multi-center, randomized, double-blind, placebo-controlled Phase 3 trial of bardoxolone in patients with ADPKD. We recently filed a protocol amendment for FALCON with the FDA. This is just one of the ways we are working with the FDA to continue the development of bardoxolone for patients with ADPKD.

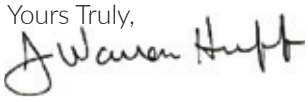
An important event for the bardoxolone development program will be the results of AYAME, a large Phase 3 clinical trial in patients with diabetic kidney disease being conducted by our strategic collaborator in Japan, Kyowa Kirin Co., Ltd. (Kyowa Kirin). Kyowa Kirin expects to complete the last study visit in the second half of this year. If the results of this trial are positive, it could provide clinical evidence that improvements in kidney function observed in bardoxolone-treated patients do in fact delay progression to kidney failure. Further, since it is such a large and long-term study, it is expected to provide important information on the safety profile of bardoxolone.

Closing Thoughts

As we continue to pursue these efforts, we are doing so with a strong cash position. As of December 31, 2021, we had $590 million in cash and cash equivalents and we recently extended our cash guidance through the end of 2024, providing us with the necessary financial flexibility in this environment.

Above all, we remain committed to our goal of developing and commercializing novel therapeutics for the treatment of patients with severe, life-threatening diseases and are looking forward to what 2022 has in store for Reata. We are grateful to you, our stockholders, for the crucial role you play in making this work possible.

Yours Truly,



J. Warren Huff
Chief Executive Officer

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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2021

OR

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

For the transition period from to

Commission File Number 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.)**
5320 Legacy Drive Plano, Texas	**75024**
(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:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Class A Common Stock, Par Value $0.001 Per Share	RETA	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 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C.7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the 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, 2021, was $3,870,110,507.

The number of shares of Registrant's Common Stock outstanding as of February 23, 2022 was 31,484,670 shares of Class A Common Stock and 4,919,249 shares of Class B Common Stock.

Portions of the Registrant's Definitive Proxy Statement relating to the Annual Meeting of Stockholders, scheduled to be held on June 8, 2022, are incorporated by reference into Part III of this Report.

Table of Contents

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 the 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;
- whether regulatory authorities determine that additional trials or data are necessary in order to accept a new drug application for review and/or approval;
- 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 manufacturing, supply, and 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, contract manufacturing 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 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;
- developments and projections relating to our competitors and our industry; and
- the impact of the coronavirus disease (COVID-19) on our clinical trials, our supply chain, and our operations.

These forward-looking statements 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. The following section summarizes the risk factors listed under Part I, Item 1A, “Risk Factors”. 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.

RISK FACTOR SUMMARY

Below is a summary of the material risk factors that make an investment in our Class A common stock speculative or risky. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found in Item 1A "Risk Factors" and should be carefully considered, together with other information in this Annual Report on Form 10-K before making investment decisions regarding our Class A common stock.

- 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, but the terms of certain of our agreements may restrict our ability to pursue our business strategies or obtain such financing.
- We are substantially dependent on the success of our lead product candidates, omaveloxolone and bardoxolone methyl (bardoxolone).
- The clinical and commercial success of omaveloxolone and bardoxolone will depend on a number of factors, many of which are beyond our control.
- The recent receipt of a complete response letter (CRL) from the United States Food and Drug Administration (FDA) with respect to the New Drug Application (NDA) for bardoxolone in patients with chronic kidney disease (CKD) caused by Alport syndrome puts our entire bardoxolone platform at risk; there is a high degree of risk that bardoxolone will not be approved for any indication in the United States or elsewhere.
- 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.
- Success in earlier Phase 1 and 2 clinical trials may not be indicative of the results that may be obtained in larger registrational clinical trials, which may delay or prevent obtaining regulatory approval.
- We may face delays in completing our ongoing or planned clinical trials due to a number of factors, including failure to enroll a sufficient number of patients in our clinical trials in a timely manner, or these studies may not be completed at all.
- 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.
- Clinical trials of our product candidates may not uncover all possible adverse events (AEs) that patients may experience.
- If we, our collaborators, or our third-party manufacturers cannot manufacture our product candidates or products at sufficient yields or quantities, we may experience delays in development, regulatory approval, and commercialization.
- 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.
- We have limited experience in submitting an NDA, a marketing authorization application (MAA), or other marketing applications and may be unable to do so efficiently or at all, for any product candidate we are developing or may develop in the future.
- If we or our collaborators 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.
- 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.
- We face substantial competition. There is a possibility that our competitors may discover, develop, obtain regulatory approval of, and commercialize drugs before we do or develop drugs that are safer, more effective, or less costly.
- Our 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, which we may not be able to achieve.
- We may not be successful in our efforts to identify, license, discover, develop, or commercialize additional product candidates.

- 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.
- If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.
- If we fail to maintain and establish collaborators with development, regulatory, and commercial expertise, it may disrupt our business, or we may not be able to capitalize on the development and commercialization of our current and future product candidates.
- If our third-party contractors, which conduct many aspects of our preclinical and clinical studies and our manufacturing activities for our product candidates, do not properly and successfully perform their obligations under our agreements with them, our ability to successfully obtain approval and provide sufficient quantities of product for our product candidates could suffer.
- Our product candidates and certain of the components of our product candidates are currently acquired from single-source suppliers and in most cases 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 rely on, but may not have, adequate protection of our proprietary technologies to compete effectively in our market.
- Confidentiality agreements with third-party contractors and collaborators may not prevent a competitor from discovering, misappropriating, or disclosing our trade secrets.
- We may not be able to effectively maintain our intellectual property position throughout the global market.
- 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.
- 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.
- The regulatory approval process is highly uncertain, and we may not obtain regulatory approval for the commercialization of our product candidates. Even if we believe our completed, current, or planned clinical trials are successful, regulatory authorities may not agree that they provide adequate data on safety or efficacy or may require that we conduct confirmatory clinical trials either prior to approval or after market approval.
- If our product candidates obtain marketing approval, we will be subject to more extensive healthcare laws, regulation, and enforcement, including recent U.S. healthcare reform and other changes, and our failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.
- We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, privacy, and anti-money laundering laws and regulations. We can face criminal liability, fines, penalties, or other serious consequences for violations, which can harm our business.
- 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 may encounter difficulties in managing our growth and expanding our operations successfully.
- If we fail to attract and retain certain senior management and key personnel, we may be unable to successfully develop our product candidates, conduct our clinical trials, and commercialize our product candidates.
- Our business and operations may be materially adversely affected in the event of computer system failures or security breaches.
- The COVID-19 outbreak has caused and could continue to cause disruptions in our business and operating results, including our clinical development and supply chain activities.

DEFINED TERMS

Unless the context requires otherwise, references to "Reata," "the Company," "we," "us," or "our" in this 2021 Form 10-K refer to Reata Pharmaceuticals, Inc. and its subsidiaries. We also have used several other terms in this 2021 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
3PLs	Third-party logistics providers
AbbVie	AbbVie Inc.
ACE	Angiotensin converting enzyme
ADL	Activities of Daily Living
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AIA	Leahy-Smith America Invents Act
ALS	Amyotrophic lateral sclerosis
ALT	Alanine
ANDA	Abbreviated new drug application
ARB	Angiotensin receptor blockers
ASC	Accounting Standards Codification
AST	aspartate aminotransferases
ASU	Accounting Standards Update
ATP	Adenosine triphosphate
bardoxolone	Bardoxolone methyl
BNP	Brain natriuretic peptide
BXLS	Blackstone Life Sciences, LLC
CARES Act	Coronavirus Aid, Relief, and Economic Security Act
CGIC	Clinical global impression of change
CGMP	Current good manufacturing practice
CKD	Chronic kidney disease
CMC	Chemistry manufacturing controls
CMO	Contract manufacturing organization
CMS	Center for Medicare and Medicaid Services
the Code	Internal Revenue Code of 1986, as amended

Abbreviated Term	Defined Term
COSO framework	Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission
CRL	Complete response letter
COVID-19	Coronavirus disease
CPA	Certified Public Accountant
Credits	Tax credits
CRO	Contract research organization
CTA	clinical trial application
CTD-PAH	Pulmonary arterial hypertension associated with connective tissue disease
CVD	Cardiovascular disease
Dartmouth	The Trustees of Dartmouth College
DOJ	United States Department of Justice
DPN	Diabetic peripheral neuropathy
DPNP	Diabetic peripheral neuropathic pain
DSCSA	Drug Supply Chain Security Act
DSMB	Data safety monitoring board
EC	European Commission
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPC	European Patent Convention
ESKD	End-stage kidney disease
EU	European Union
Exchange Act	Securities Exchange Act of 1934
FA	Friedreich's ataxia
FARA	Friedreich's Ataxia Research Alliance
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
FFS	Fee-for-service
FSA	Flexible spending account
FSGS	Focal segmental glomerulosclerosis
GBM	Glomerular basement membrane
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
HDL	High-density lipoprotein
HHS	United States Department of Health and Human Services
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
IPO	Initial public offering
IPR	*Inter partes* review
IRB	Institutional review board
ITT	Intent to treat
Kyowa Kirin	Kyowa Kirin Co., Ltd. (formerly KHK or Kyowa Hakko Kirin Co., Ltd.)
LDL	Low-density lipoprotein

Abbreviated Term	Defined Term
LOQ	List of Questions from the EMA
LTIP Plan	Second Amended and Restated Long Term Incentive Plan
MAA	Marketing Authorization Application
MAD	Multiple ascending dose
MD Anderson	The University of Texas MD Anderson Cancer Center
mFARS	Modified Friedreich's Ataxia Rating Scale
MHLW	Ministry of Health, Labour and Welfare of Japan
MHRA	United Kingdom Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed-model Repeated Measures
NCE	New chemical entity
NDA	New Drug Application
NIH	National Institute of Health
NOL	Net operating loss
PAH	Pulmonary arterial hypertension
PCAOB	Public Company Accounting Oversight Board
PD	Pharmacodynamic
PDMA	Prescription Drug Marketing Act
PDUFA	Prescription Drug User Fee Act
PGIC	Patient global impression of change
PK	Pharmacokinetic
PMDA	Pharmaceutical and Medical Devices Agency of Japan
PPACA	Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act of 2010
PREA	Pediatric Research Equity Act
PTAB	Patent Trial and Appeal Board
Registrational or pivotal trial	An adequate and well-controlled trial designed to be sufficient to apply for regulatory approval of a drug candidate, although notwithstanding the Company's design a regulatory agency may determine that further clinical studies or data are required
REMS	Risk evaluation and mitigation strategy
ROS	Reactive oxygen species
RSU	Restricted stock units
SaaS	Software as a service
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
Sarbanes-Oxley Act	The Sarbanes-Oxley Act of 2002
SCA	Spinocerebellar ataxia
SEC	United States Securities and Exchange Commission
Securities Act	Securities Act of 1933
T2D	Type 2 diabetic
TGA	Australian Therapeutic Goods Administration
TEAE	Treatment-emergent adverse effect
T1D CKD	Type 1 diabetic CKD
T2D CKD	Type 2 diabetic CKD
UACR	Urinary albumin-to-creatinine ratio
ULN	Upper limit of normal
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

We are a clinical-stage biopharmaceutical company focused on identifying, developing, and commercializing innovative therapies that change patients' lives for the better. We concentrate on small-molecule therapeutics with novel mechanisms of action for the treatment of severe, life-threatening diseases with few or no approved therapies. Our lead programs are omaveloxolone in a rare neurological disease called Friedreich's ataxia (FA) and bardoxolone in rare forms of CKD. Both of our lead product candidates activate the transcription factor Nrf2 to normalize mitochondrial function, restore redox balance, and resolve inflammation. Because mitochondrial dysfunction, oxidative stress, and inflammation are features of many diseases, we believe omaveloxolone, bardoxolone, and our next-generation Nrf2 activators have many potential clinical applications. We possess exclusive, worldwide rights to develop, manufacture, and commercialize omaveloxolone, bardoxolone, and our next-generation Nrf2 activators, excluding certain Asian markets for bardoxolone in certain indications, which are licensed to Kyowa Kirin Co., Ltd. (Kyowa Kirin). In addition, we are developing RTA 901, the lead product candidate from our Hsp90 modulator program, in neurological indications. We are the exclusive licensee of RTA 901 and have worldwide commercial rights.

Programs in Neurological Diseases

Omaveloxolone for Friedreich's Ataxia

FA is an inherited, debilitating, and degenerative neuromuscular disorder that is typically diagnosed during adolescence and can ultimately lead to premature death. Patients with FA experience progressive loss of coordination, muscle weakness, and fatigue, which commonly progresses to motor incapacitation, wheelchair reliance, and eventually death. Symptoms generally first occur in children, with patients requiring a wheelchair by their teens or early-20s and generally dying in their mid-30s. FA affects approximately 5,000 children and adults in the United States and 22,000 individuals globally. There are currently no approved therapies to treat FA. The FDA and the European Commission (EC) have granted orphan drug designation to omaveloxolone for the treatment of FA.

In the third quarter of 2021, we completed our pre-NDA meeting with the FDA. The purpose of the pre-NDA meeting was to discuss the content of Reata's planned NDA submission for approval for omaveloxolone for the treatment of patients with FA. On November 18, 2021, the FDA granted omaveloxolone Fast Track Designation for the treatment of FA, providing eligibility for FDA programs such as Priority Review and rolling submission of the NDA, if relevant criteria are met. The FDA granted our request for a rolling submission and in January 2022, we initiated rolling submission of our NDA which is expected to be completed by the end of the first quarter of 2022. This NDA is supported by the efficacy and safety data from MOXIe Part 1, Part 2, and MOXIe Extension studies discussed below, which we believe provide sufficient evidence of safety and efficacy to support a standard (full) approval of the NDA.

Omaveloxolone for Other Neurological Indications

Based on our understanding of the pathophysiology of neurological diseases, characterized by mitochondrial dysfunction, inflammation, and oxidative stress, we believe omaveloxolone may be applicable to diseases such as progressive supranuclear palsy, Parkinson's disease, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and epilepsy. Consistent with this, we have observed promising activity of omaveloxolone and our other Nrf2 activators in preclinical models of many of these diseases. We plan to pursue the development of omaveloxolone and our other Nrf2 activators for one or more of these diseases.

RTA 901 for Neurological Indications, Including Diabetic Peripheral Neuropathic Pain

We are developing RTA 901, the lead product candidate from our Hsp90 modulator program, in neurological indications. We have observed favorable activity of RTA 901 in a range of preclinical models of neurological disease, including models of diabetic neuropathy, neuroinflammation, and neuropathic pain. We have completed a Phase 1 trial to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of RTA 901 administered orally, once-daily in healthy adult volunteers. RTA 901 was well tolerated in both single and multiple ascending dose (SAD and MAD) studies across all dose groups with no safety signals, drug discontinuations, or serious adverse events (SAEs). Additionally, we observed an acceptable PK profile with exposures greater than required for efficacy in preclinical animal models. We plan to initiate additional Phase 1 studies to evaluate the PK and drug-drug interaction potential of RTA 901 in the first half of 2022 and a randomized, placebo-controlled Phase 2 study in diabetic peripheral neuropathic pain (DPNP) in the second half of 2022. We are the exclusive licensee of RTA 901 and have worldwide commercial rights.

Programs in Chronic Kidney Disease

We and our strategic collaborator are developing bardoxolone for the treatment of CKD in multiple indications, including CKD caused by Alport syndrome, autosomal dominant polycystic kidney disease (ADPKD), and type 1 and 2 diabetic CKD. CKD is characterized by a progressive worsening in the rate at which the kidney filters waste products from the blood. Declining kidney function leads to the buildup of high levels of waste products in the blood that cause the patient to suffer symptoms, such as nausea and fatigue, and develop complications including high blood pressure, anemia, weak bones, poor nutritional health, and nerve damage.

We received a CRL from the FDA in February 2022 with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome. The CRL indicated that the FDA cannot approve the NDA in its present form. Based on its review, the FDA concluded that it does not believe the submitted data demonstrates that bardoxolone is effective in slowing the loss of kidney function in patients with Alport syndrome and reducing the risk of progression to kidney failure and has requested additional data to support the efficacy and safety of bardoxolone. Their conclusion was based on efficacy and safety concerns primarily set forth in the FDA's briefing book and discussed at the Cardiovascular and Renal Drugs Advisory Committee meeting held on December 8, 2021.

The FDA stated that the issues could be resolved by providing evidence of effectiveness that includes evidence from an adequate and well-controlled study showing a clinically relevant effect on the rate of loss of kidney function in patients with Alport syndrome or, alternatively, an effect on a clinical outcome (i.e., an endpoint that captures how patients with Alport syndrome feel, function, or survive). In addition, the FDA stated that we would need to address whether bardoxolone has a clinically relevant effect on the QT interval and show that the demonstrated clinical benefits of bardoxolone outweigh its risks. The FDA welcomed continued discussion on the details of a path forward. We plan to work closely with the FDA to bring this important medicine to patients in the US.

Bardoxolone for CKD Caused by Alport Syndrome

Alport syndrome is a rare, genetic form of CKD caused by mutations in the genes encoding type IV collagen, which is a major structural component of the glomerular basement membrane (GBM) in the kidney. Patients with CKD caused by Alport syndrome experience a progressive worsening of the kidney's capacity to filter waste products out of the blood, which can lead to end-stage kidney disease (ESKD) and the need for chronic dialysis treatment or a kidney transplant. Alport syndrome affects both children and adults. In patients with the most severe forms of the disease, approximately 50% progress to dialysis by age 25, 90% by age 40, and nearly 100% by age 60. According to the Alport Syndrome Foundation, Alport syndrome affects approximately 30,000 to 60,000 people in the United States. There are currently no approved therapies to treat CKD caused by Alport syndrome.

We completed the Phase 3 CARDINAL study in November 2020. The study met its primary and key secondary endpoints at the end of Year 1, and on November 9, 2020, we announced that the Phase 3 CARDINAL study met its primary and key secondary endpoints at the end of Year 2. Bardoxolone was generally reported to be well tolerated in this study, and the safety profile was similar to that observed in prior trials.

On March 1, 2021, we submitted our NDA for bardoxolone for the treatment of CKD caused by Alport syndrome to the FDA. On April 26, 2021, the FDA accepted for filing our NDA, set the Prescription Drug User Fee Act (PDUFA) date for February 25, 2022, and stated that the FDA also planned to hold an advisory committee meeting to discuss the application. On December 8, 2021, the Cardiovascular and Renal Drugs Advisory Committee voted no on the question of whether the provided evidence demonstrated that bardoxolone is effective in slowing the progression of CKD in patients with Alport syndrome and that its benefits outweigh its risks.

On February 25, 2022, we received a CRL from the FDA with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome. We will continue to work with the FDA to confirm our next steps on our Alport syndrome program.

Regarding non-U.S. regulatory applications for bardoxolone in the treatment of patients with CKD caused by Alport syndrome, on October 28, 2021, we submitted an MAA to the European Medicines Agency (EMA), and on July 27, 2021, our strategic collaborator in CKD in Japan, Kyowa Kirin, submitted an NDA in Japan to the Ministry of Health, Labour and Welfare (MHLW). Both applications are currently under review. The FDA and the EC have granted orphan drug designation to bardoxolone for the treatment of Alport syndrome.

We recently received the 120-day List of Questions (LOQ) from the EMA. We are in the process of reviewing the questions and preparing our responses.

Bardoxolone for Autosomal Dominant Polycystic Kidney Disease

ADPKD is a rare and serious hereditary form of CKD caused by a genetic defect in *PKD1* or *PKD2* genes leading to the formation of fluid-filled cysts in the kidneys and other organs. Cyst growth can cause the kidneys to expand up to five to seven times their normal volume, leading to pain and progressive loss of kidney function. ADPKD affects both men and women of all racial and ethnic groups and is the leading inheritable cause of kidney failure with an estimated diagnosed population of 140,000 patients in the United States. Despite current standard of care treatment, an estimated 50% of ADPKD patients progress to ESKD and require dialysis or a kidney transplant by 60 years of age. The FDA and the EC have granted orphan drug designation to bardoxolone for the treatment of ADPKD.

We are currently enrolling patients in FALCON, an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of bardoxolone in patients with ADPKD randomized one-to-one to active drug or placebo. FALCON is enrolling patients in a broad range of ages, 18 to 70 years old, with an estimated glomerular filtration rate (eGFR) between 30 to 90 mL/min/1.73 m^2. We recently filed a protocol amendment with the FDA and requested a Type A meeting to discuss the overall ADPKD development program including the recently submitted major protocol amendment. The major protocol amendment changes include increases in the sample size from 550 to 850 patients, addition of adolescent (12 to 17 years) patients with ADPKD, removal of the off-treatment period (Week 48 – Week 52) during Year 1, change of the primary endpoint of off-treatment eGFR change from baseline at Week 52 (or 4 weeks after drug discontinuation in Year 1) to eGFR change from baseline at Week 108 (8 weeks after planned drug discontinuation at Week 100), addition of an exploratory endpoint of eGFR change from baseline at Week 112 (12 weeks after planned drug discontinuation at Week 100), and addition of a sub study with ambulatory blood pressure monitoring.

Pursuant to the protocol amendment, patients will be treated with bardoxolone or placebo for 100 weeks followed by a twelve-week withdrawal period. The trial will remain blinded until study completion. All patients

will be asked to return at Week 108 independent of the time of study drug discontinuation. In November 2021 we announced a plan to increase the FALCON sample size from 550 to 700 patients. In order to maintain statistical power, with changes being made to the primary endpoint, the sample size has been increased from 550 to 850 patients in our recently submitted protocol amendment. The secondary endpoint is the eGFR change from baseline at Week 100. The statistical analysis plan (SAP), detailing the proposed analyses, has also been submitted. More than 500 patients are currently enrolled in the study.

Bardoxolone in Patients with CKD at Risk of Rapid Progression

MERLIN was a proof of concept, multi-center, double-blind, placebo-controlled, Phase 2 trial to evaluate the safety and efficacy of bardoxolone in patient populations with CKD secondary to varying etiologies at risk of rapid progression. MERLIN enrolled patients from ages 18 to 75 years old, with eGFR ≥ 20 to < 60 mL/min/1.73 m^2, and other risk factors for rapid progression of kidney disease. Eighty-one patients were enrolled and randomized 1:1 to either bardoxolone or placebo. The primary endpoint was the change in eGFR from baseline after 12 weeks of treatment, and the secondary endpoint was the change in eGFR from baseline after 12 weeks of treatment by CKD etiology. MERLIN also incorporated an exploratory efficacy endpoint of change in eGFR from baseline at off-treatment Days 3, 7, 14, 21, 28, and 35 to examine the time period for resolution of the acute pharmacodynamic (PD) effects of bardoxolone.

MERLIN met the primary endpoint at Week 12. Treatment with bardoxolone resulted in a higher mean eGFR change from baseline compared to placebo, with a placebo-corrected statistically significant mean difference of 7.71 mL/min/1.73 m^2 (n=81, $p < 0.0001$, CI: 5.18, 10.24) at Week 12. When eGFR data were broken down by different etiologies of CKD (secondary endpoint), mixed-model repeated measures (MMRM) analysis showed results favor bardoxolone over placebo in all subgroups.

The change in eGFR in patients treated with bardoxolone was maximal in MERLIN at Week 8, two weeks after the last planned dose titration at Week 6. Mean eGFR change from baseline began to decrease within three days after the planned cessation of treatment at Week 12. A statistically significant difference in mean eGFR change from baseline was observed for the bardoxolone group compared to the placebo group through Day 14 off-treatment, with a placebo-corrected mean difference of 3.70 mL/min/1.73 m^2 ($p = 0.0040$, CI: 1.22, 6.18). At Day 21 off-treatment and beyond, there was no significant placebo-corrected difference between the placebo and bardoxolone groups, suggesting the acute effects of bardoxolone had resolved by Day 21 off-treatment. Consistent with previous studies, treatment with bardoxolone at doses up to 30 mg and for up to 12 weeks was generally safe and well tolerated.

The MERLIN data were submitted as an amendment to our NDA. However, the FDA did not accept this amendment as a major amendment.

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 components:

Programs in Neurological Diseases

- Complete the rolling submission of our NDA for omaveloxolone for the treatment of patients with FA by the end of the first quarter of 2022 and prepare for commercial launch in the United States;
- Continue the regulatory procedures and submissions required for filing an MAA with the EMA for approval of omaveloxolone for the treatment of patients with FA; and
- Initiate a phase 2 study of RTA 901 for the treatment of diabetic peripheral neuropathic pain in the second half of 2022.

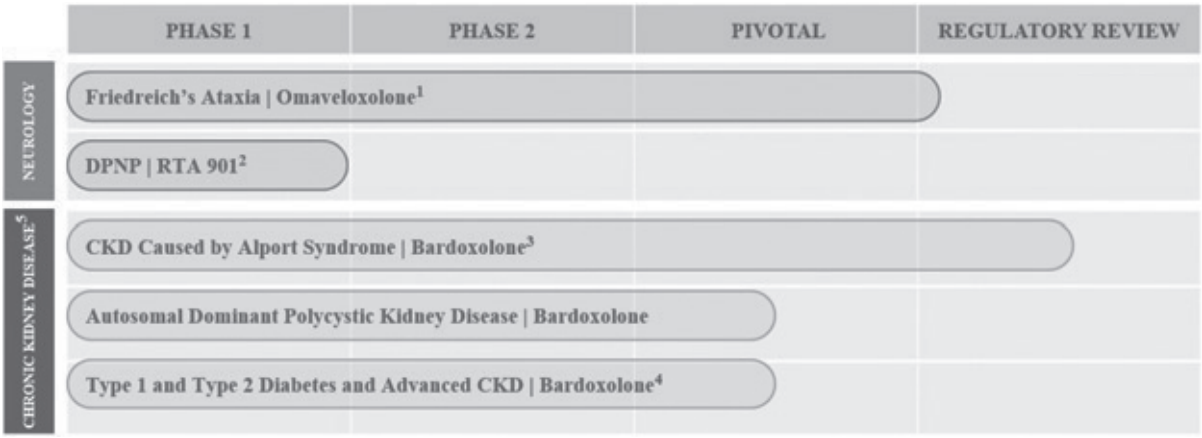
Programs in Chronic Kidney Disease

- Continue our efforts with regulatory agencies around the world, seeking approval of bardoxolone for patients with Alport syndrome, specifically:
  - We will continue to work with the FDA to confirm our next steps on our Alport syndrome program;
  - We will continue to work with the EMA in their review of our MAA in the European Union (EU); and
  - We will continue to support Kyowa Kirin with their discussions with the Pharmaceuticals and Medical Devices Agency of Japan (PMDA);
- Pursue development of bardoxolone for patients with ADPKD including:
  - Meet with FDA to discuss the overall ADPKD development program including the recently submitted major protocol amendment; and
  - Complete enrollment of the Phase 3 FALCON study;
- Continue to develop long-term safety data from patients in EAGLE, our open-label, extended access trial in patients with CKD caused by Alport syndrome who participated in the CARDINAL trial and patients with ADPKD who participated in the FALCON trial; and
- Based on the outcome of the AYAME and FALCON trials, and our discussions with the FDA regarding the bardoxolone program, we will decide future development plans for bardoxolone in additional forms of CKD. AYAME is a Phase 3 study for the treatment of diabetic kidney disease that is being conducted by our strategic collaborator, Kyowa Kirin, in Japan.

Other Clinical Programs

- Continue to advance next generation Nrf2 activators through preclinical studies into clinical development;
- Leverage our multiple technologies and relationships to discover new molecules and explore preclinical proof of concept; and
- Pursue business development opportunities to further expand our robust pipeline of drug candidates.

Our Pipeline



[1]Rolling NDA submission initiated in the first quarter of 2022. We expect to complete submission of the NDA by the end of the first quarter of 2022.
[2]DPNP: Diabetic peripheral neuropathic pain.
[3]On February 25, 2022, we received a CRL from the FDA. We will continue to work with the FDA to confirm our next steps on our Alport syndrome program. MAA in EU is under review.
[4]AYAME study conducted in Japan by our strategic collaborator in CKD, Kyowa Kirin. Kyowa Kirin expects the last patient out in the second half of 2022.
[5]Based on the outcome of AYAME and FALCON trials, and our discussions with the FDA regarding the bardoxolone program, we will decide future development plans for bardoxolone in additional forms of CKD.

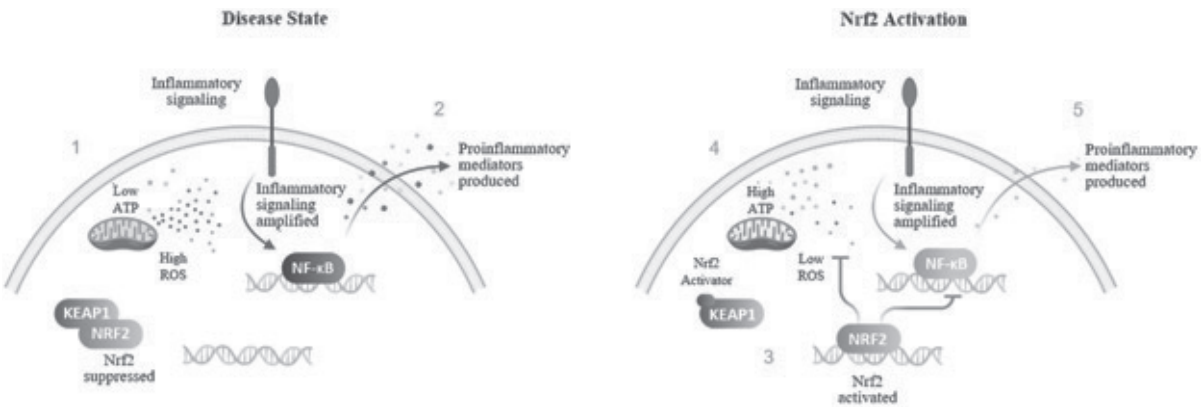
An In-Depth Review of Our Programs

Foundational Biology of Our Nrf2 Activators

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 pro-inflammatory mediators. During this reprogramming, the mitochondria release 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 restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signaling. 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.



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 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, omaveloxolone and bardoxolone 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 pro-inflammatory signaling. In addition, Nrf2 directly suppresses the expression of pro-inflammatory cytokine genes by inhibiting their transcription.

Omaveloxolone and bardoxolone 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, omaveloxolone and bardoxolone stabilize Nrf2 and increase its activity. Since mitochondrial dysfunction, oxidative stress, and inflammation are features of many diseases, Nrf2 activators, such as omaveloxolone, bardoxolone, and our next-generation Nrf2 activators, may have many potential clinical applications. Omaveloxolone and bardoxolone 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.

Programs in Neurological Diseases

We are developing omaveloxolone for the treatment of patients with FA, an inherited, debilitating, and degenerative neuromuscular disorder that is usually diagnosed during adolescence and can ultimately lead to premature death. Because mitochondrial dysfunction is a key feature of many neuromuscular diseases, we believe omaveloxolone may be broadly applicable to treat neurological diseases by activating Nrf2 to normalize and improve mitochondrial function and ATP production. In January 2022, we initiated rolling submission of our NDA for omaveloxolone for the treatment of patients with FA. We expect to complete the submission of the NDA by the end of the first quarter of 2022. We plan to pursue the development of omaveloxolone and our other Nrf2 activators for one or more additional neurological diseases.

We are also developing RTA 901 for the treatment of neurological diseases. RTA 901 is a highly potent and selective C-terminal modulator of Hsp90, which has a critical role in mitochondrial function, protein folding, and inflammation. RTA 901 has demonstrated profound efficacy in a wide range of animal models of neurological disease, including diabetic neuropathy, neuroinflammation, and neuropathic pain. We plan to initiate a randomized, placebo-controlled Phase 2 study in DPNP in the second half of 2022.

Omaveloxolone in Patients with Friedreich's Ataxia

We are developing omaveloxolone for the treatment of patients with FA. Patients with FA experience progressive loss of coordination, muscle weakness, and fatigue, which commonly progresses to motor incapacitation and wheelchair reliance. Based on literature and proprietary research, we believe FA affects approximately 5,000 children and adults in the United States and 22,000 individuals globally. According to data provided by IQVIA in 2020, there are approximately 4,000 projected patients diagnosed with FA in the United States. The FDA has granted Orphan Drug and Fast Track Designations to omaveloxolone for the treatment of FA. The EC has granted Orphan Drug Designation in Europe to omaveloxolone for the treatment of FA.

Diagnosis of FA typically occurs by genetic testing, and approximately 75% of people in the United States with FA are 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.

Initially we plan to concentrate our commercial efforts in the United States primarily in specialty clinics comprising eight FA Collaborative Clinical Research Network Sites in FA as disclosed by the Friedreich's Ataxia Research Alliance (FARA), 22 ataxia clinics as disclosed by the National Ataxia Foundation, 225 Muscular Dystrophy Association centers as disclosed by the Muscular Dystrophy Association, and key neurology practices based on claims data. If approved by regulatory authorities, omaveloxolone has the potential to be the first therapy for the treatment of FA.

Rationale for Development of Omaveloxolone in Friedreich's Ataxia

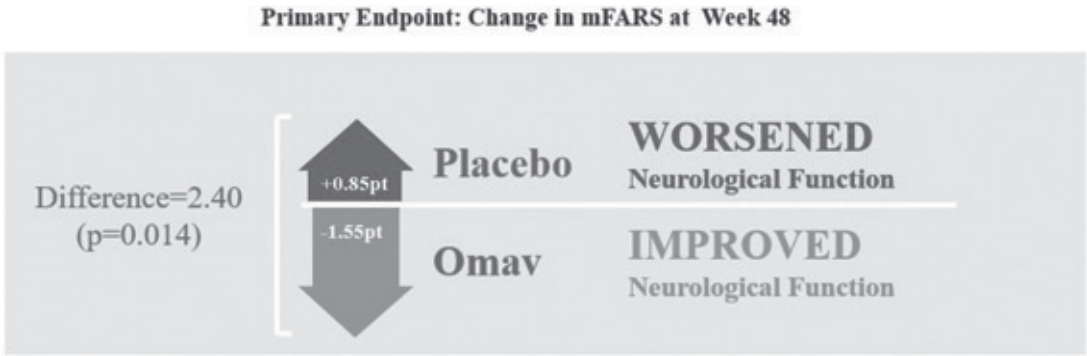
FA is typically caused by a trinucleotide repeat expansion in the first intron of the frataxin gene, which encodes the mitochondrial protein frataxin. Pathogenic repeat expansions can lead to impaired transcription and reduced frataxin expression, which can lead to mitochondrial iron overload and poor cellular iron regulation, increased sensitivity to oxidative stress, and impaired mitochondrial ATP production. Because impaired ATP production in FA patients likely contributes to the progressive muscle weakness, decreased coordination, exercise intolerance, and fatigue observed in these patients, as well as other disease manifestations, we believe that omaveloxolone 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, omaveloxolone has been shown *in vitro* to restore mitochondrial activity in fibroblasts isolated from FA patients. Accordingly, we believe that Nrf2 activation by omaveloxolone may result in a clinical benefit to FA patients.

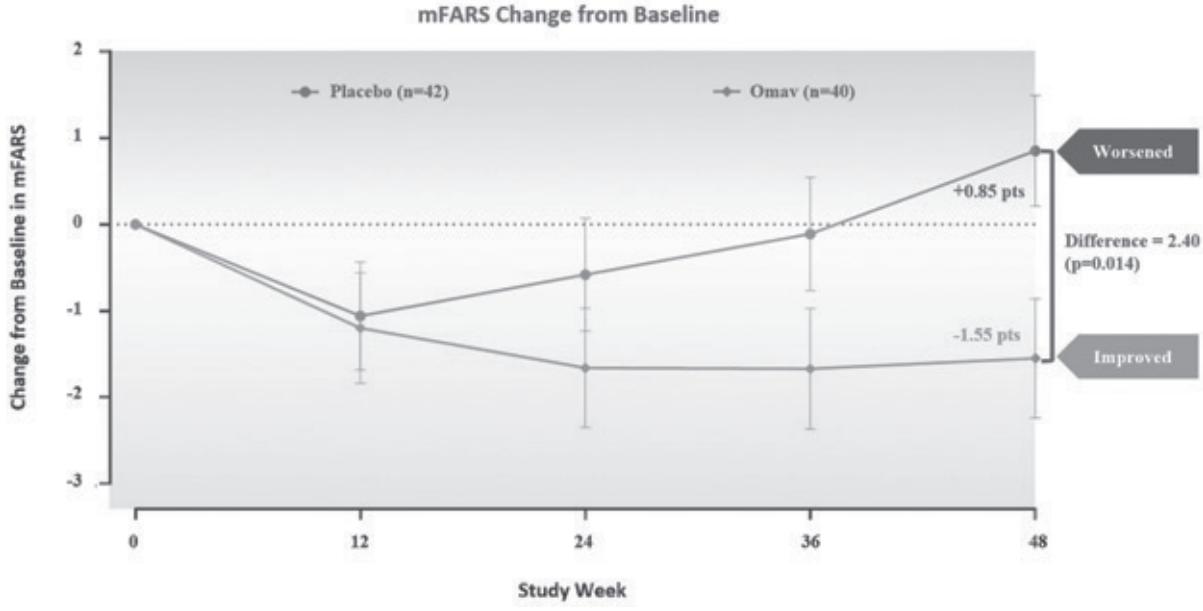
MOXIe Part 2 Study Results

Part 2 of our Phase 2 trial, called MOXIe (MOXIe Part 2), was an international, multi-center, double-blind, placebo-controlled, randomized registrational study, that enrolled 103 patients with FA at 11 trial sites in the United States, Europe, and Australia. MOXIe Part 2 is one of the largest global, interventional trials ever completed in FA. Patients were randomized one-to-one to omaveloxolone or placebo. MOXIe Part 2 was completed in October 2019. The primary analysis population included patients without pes cavus (n=82), a musculoskeletal foot deformity that may interfere with the patient's ability to perform some components of the neurological exam used to score the primary endpoint of the study. Safety analyses were evaluated in the all-randomized population (n=103).

The primary endpoint for the trial was the change in the Modified Friedreich's Ataxia Rating Scale (mFARS) score for omaveloxolone relative to placebo after 48 weeks of treatment. The mFARS is a physician-assessed neurological rating scale used to measure FA disease progression. The FDA agreed that mFARS was an acceptable primary endpoint to evaluate the effect of omaveloxolone for the treatment of patients with FA. Omaveloxolone treatment demonstrated statistically significant evidence of efficacy for the primary endpoint of the trial, producing a placebo-corrected -2.40 point mean improvement in mFARS (n=82; p=0.014). Patients treated with omaveloxolone experienced a mean improvement in mFARS of -1.55 points from baseline, while patients treated with placebo experienced a mean worsening in mFARS of +0.85 points from baseline.

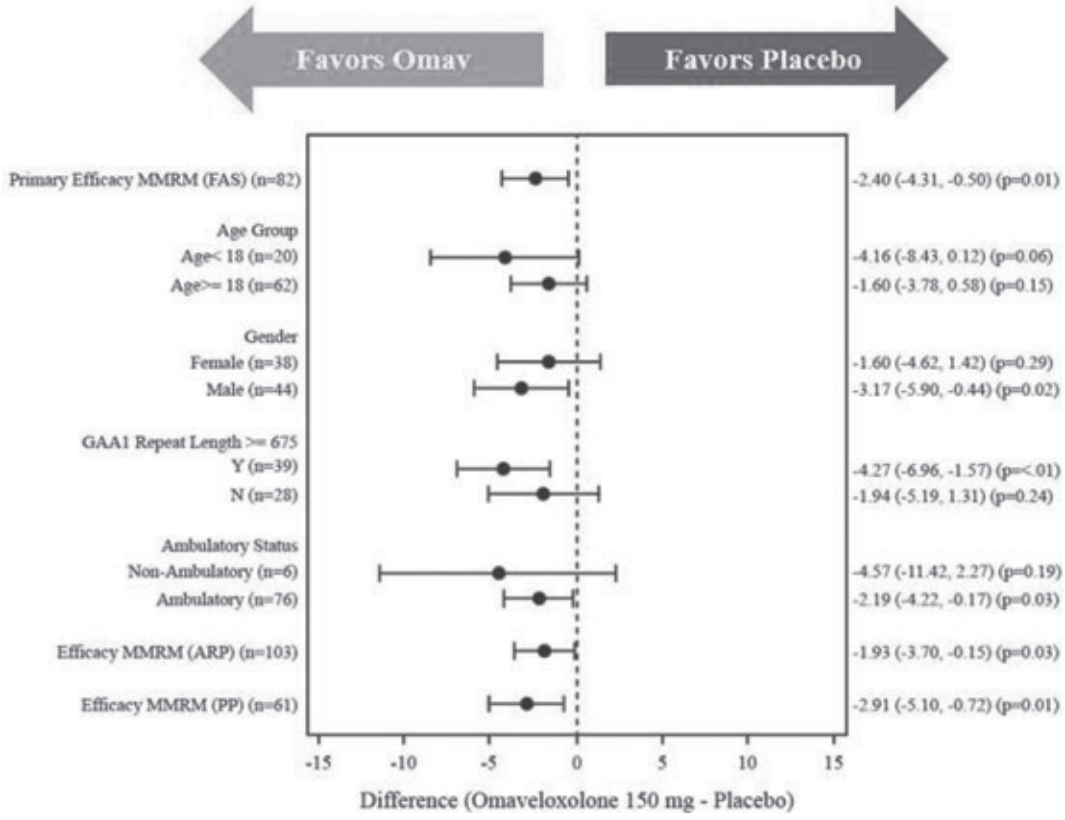


Further, the observed placebo-corrected improvements in mFARS were time-dependent, increasing over the course of treatment with the largest improvement observed after 48 weeks of treatment.



Omaveloxolone treatment also demonstrated statistically significant evidence of efficacy in mFARS at Week 48 when the pes cavus patients were included in the analysis (the all-randomized population). In the all-randomized population, omaveloxolone treatment produced a statistically significant, placebo-corrected -1.93 point mean improvement in mFARS (n=103; p=0.034). Omaveloxolone treatment also improved several secondary endpoints included in the trial.

An analysis of the change in mFARS from baseline demonstrated that patients in the omaveloxolone arm performed numerically better than placebo on all subsections of the mFARS exam. Furthermore, omaveloxolone patients in subgroups that typically have a worse prognosis and progress faster, including patients with longer GAA1 repeats, patients with cardiomyopathy, non-ambulatory patients, and younger patients, on average, experienced a larger placebo-corrected improvement in mFARS compared to the study population as a whole.



Additionally, all secondary endpoints either favored the omaveloxolone arm or were neutral. Patients on omaveloxolone experienced a nominal improvement in the Activities of Daily Living (ADL) questionnaire, with all nine questions favoring the omaveloxolone arm. On average, ADL scores for patients on omaveloxolone did not change from baseline, while placebo-treated patients worsened. Both patient global impression of change (PGIC) and clinical global impression of change (CGIC) numerically favored omaveloxolone, and improvement in PGIC correlated with the observed improvement in mFARS.

Endpoint	Omaveloxolone vs Baseline	Omaveloxolone vs Placebo
mFARS	**Improved (p=0.027)**	**Improved (p=0.014)**
PGIC	Improved	Improved
CGIC	Improved	Improved
FA-ADL	Improved	**Improved (p=0.042)**
Peak Work	Improved	No Difference
9-Hole Peg Test	No Difference	No Difference
Timed 25FT Walk Test	No Difference	Improved
Frequency of Falls	N/A	Improved

Omaveloxolone was reported to be generally well-tolerated. Four (8%) omaveloxolone patients and two (4%) placebo patients discontinued trial drug due to an AE. The reported AEs were generally mild to moderate in intensity, and the most common AEs (i.e., reported in > 10% of omaveloxolone-treated patients) observed more frequently (>5% difference) in omaveloxolone compared to placebo were headache, nausea, increased aminotransferases, fatigue, abdominal pain, diarrhea, oropharyngeal pain, muscle spasms, back pain, and decreased appetite. Increases in aminotransferases are a pharmacological effect of omaveloxolone, which increases production of aminotransferases in vitro, which we believe are related to restoration of mitochondrial function. In MOXIe Part 2, the aminotransferase increases were associated with improvements (reductions) in total bilirubin and were not associated with any evidence of liver injury.

In MOXIe Part 2, the overall rate of SAEs was low, with five patients in the omaveloxolone group and three patients in the placebo group reporting SAEs. No new safety signals were identified, and the reported SAEs were sporadic and generally expected in FA patients. In the patients who reported SAEs while receiving omaveloxolone, none led to discontinuation. Atrial fibrillation was balanced and reported in one omaveloxolone and one placebo patient. One omaveloxolone patient reported anemia which was considered unrelated to omaveloxolone. One omaveloxolone patient reported multiple SAEs, including viral upper respiratory tract infection and laryngitis, along with palpitations, non-cardiac chest pain, and sinus tachycardia. While several of this patient's SAEs were considered possibly related to omaveloxolone, no imbalances in infection or arrhythmia AEs were observed overall in the trial.

At a Type C meeting in August 2020, the FDA provided us guidance that, although it did not have concerns with the reliability of the mFARS primary endpoint results from MOXIe Part 2, it was not convinced that the results from MOXIe Part 2, as a single study, were sufficient to support approval. We proposed the Baseline-Controlled Study to supplement the MOXIe Part 2 findings.

MOXIe Extension Study

The open-label MOXIe Extension trial is ongoing, with a total of 149 patients enrolled (57 patients from MOXIe Part 1 and 92 patients from MOXIe Part 2). A total of 73 out of 75 (97%) patients without pes cavus who completed MOXIe Part 2 were enrolled in the MOXIe Extension, including 39 patients previously randomized to placebo (the placebo-to-omaveloxolone group) and 34 patients previously randomized to omaveloxolone (the omaveloxolone-to-omaveloxolone group). Due to the COVID-19 pandemic, not all patients had mFARS assessments performed at each time point.

Baseline-Controlled Study Results

The Baseline-Controlled Study evaluated the efficacy of omaveloxolone treatment using a baseline-controlled analysis design in which patients serve as their own controls, and changes in mFARS during the pre-treatment period in either MOXIe Part 1 or Part 2 are compared to changes in mFARS during the treatment period in the MOXIe Extension. Efficacy was assessed by comparing the annualized rate of change in mFARS during the pre-treatment period to the annualized rate of change in mFARS during the treatment period for patients who received approximately 48 weeks of omaveloxolone in the MOXIe Extension (the paired difference). The primary analysis population included MOXIe Part 1 patients and Part 2 patients randomized to placebo without pes cavus who had an mFARS assessment at Week 48 of the MOXIe Extension. The Baseline-Controlled Study demonstrated a statistically significant -3.76 point improvement (p=0.0022) for the primary endpoint of the paired difference in annualized mFARS slopes between the treatment and pre-treatment periods in the primary analysis population.

These results were provided to the FDA, and after an internal review, the FDA concluded that it did not believe the results strengthened the results of MOXIe Part 2. The FDA suggested an additional exploratory analysis to evaluate whether omaveloxolone treatment has an effect on disease course using patients randomized to placebo during MOXIe Part 2 who then went on study drug in the MOXIe Extension. We refer to the additional analysis as the Delayed-Start Analysis.

Delayed-Start Analysis Results

The intent of the post-hoc Delayed-Start Analysis is to evaluate whether omaveloxolone has a persistent effect on FA disease course. Conceptually, this analysis evaluates whether the treatment effect that was observed in the placebo-controlled MOXIe Part 2 study is maintained in the MOXIe Extension study when all patients are receiving omaveloxolone. If the treatment effect is maintained between those originally randomized to placebo (the placebo-to-omaveloxolone group) versus those originally randomized to omaveloxolone (the omaveloxolone-to-omaveloxolone group), then it demonstrates evidence of a persistent effect on the course of the disease. If the treatment effect is not maintained, and the patients originally randomized to placebo are able to achieve the same absolute response and "catch up" to the patients initially randomized to omaveloxolone, the results are consistent with a symptomatic treatment that does not affect the underlying course of the disease.

Two timepoints were used in the analysis. The first timepoint was at Week 48, the final week of treatment in the placebo-controlled MOXIe Part 2 study. The second timepoint was at Week 72 of the open-label MOXIe Extension in which all patients received omaveloxolone. A non-inferiority test was used to evaluate if the difference in mFARS between groups observed at the first timepoint was maintained or non-inferior at the second timepoint. The analysis methods, including the specified non-inferiority margin, were based on literature (Liu-Seifert, 2015a, 2015b). A decrease in mFARS (i.e., negative change from baseline) shows improvement. When comparing treatment groups using this methodology, maintaining a negative difference between treatment groups in mFARS is evidence of a persistent treatment effect.

February 2021 Data Cut-Off (Used in Pre-NDA Briefing Documents)

The Delayed-Start Analysis used in Pre-NDA briefing documents submitted to the FDA was performed using data as of February 2021. In this analysis, 50 out of 73 patients from MOXIe Part 2 without pes cavus who enrolled into MOXIe Extension had at least 72 weeks of exposure in MOXIe Extension.

The analysis demonstrated that the between-group difference in mFARS observed at the end of the placebo-controlled MOXIe Part 2 period (LS mean difference = -2.26 ± 1.03) was preserved at MOXIe Extension Week 72 in the delayed-start period (LS mean difference = -3.37 ± 1.51). Consistent with a persistent treatment effect on disease, the upper limit of the 90% CI for the difference estimate was less than zero (-0.362), meeting the threshold for demonstrating significant evidence of non-inferiority.

Delayed-Start Analysis Primary Endpoint (Non-Inferiority Test)[1]

	Placebo-Controlled Week 48 (Δ_1)	**Delayed-Start Week Ex. 72 (Δ_2)**
Difference (LS Mean ± SE)	-2.26 ± 1.03 p=0.029	-3.37 ± 1.51 p=0.026
Estimate = $\Delta_2 - 0.5\times \Delta_1$	-2.24 ± 1.47	
Upper Limit of 1-sided 90% CI for Estimate	-0.362	

[1]Non-Inferiorty test performed using a MMRM center analysis with a Toeplitz covariance structure.

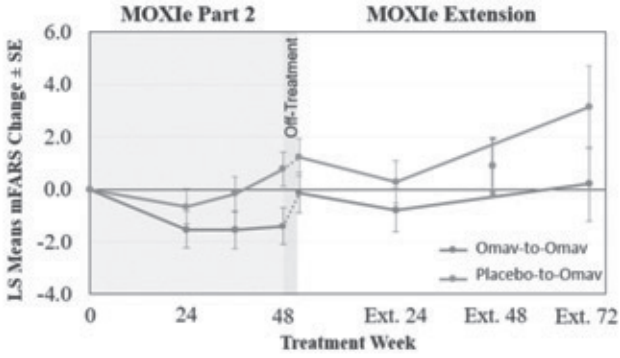
A longitudinal analysis used to calculate annualized slopes incorporating all available data from the MOXIe Extension showed similar slopes in mFARS for the placebo-to-omaveloxolone group (0.29 points per year) when compared to the omaveloxolone-to-omaveloxolone group (0.17 points per year) with no significant difference between slopes (p=0.85). In MOXIe Extension, omaveloxolone-treated patients have been progressing at a rate that is >75% less than the approximately two points per year that patients progressed in a recent large natural history study (Patel, 2016).

MOXIe Extension Annualized mFARS Slope (± SE)

Omav-Omav (n=34)	Placebo-Omav (n=39)	Difference
0.17 ± 0.61	0.29 ± 0.68	-0.12 ± 0.62 p=0.85

The graphical representation of changes from baseline in mFARS for omaveloxolone and placebo groups shows the separation at the end of the placebo-controlled period is maintained in the open-label period at Extension Week 72.

Change from Baseline in mFARS (Patients without Pes Cavus)



[1]*Figure Notes: Data plotted are LS means mFARS change from baseline ± standard error estimated from an MMRM analysis using an unstructured covariance structure.*

Many of the visits at Week 48 and Week 72 of the MOXIe extension were scheduled during the initial peak of COVID-19 cases during Spring to Fall 2020. The mFARS assessment must be conducted in the clinic, and many in-clinic visits did not occur due to COVID-19 related travel restrictions and site closures during this period. Apart from the data at MOXIe Extension Week 48, parallel trajectories were seen in LS Mean mFARS change from baseline between the placebo-to-omaveloxolone group and the omaveloxolone-to-omaveloxolone group in MOXIe Extension.

August 2021 Data Cut-Off (Used in Clinical Modules of NDA Submission)

The Delayed-Start Analysis used in clinical modules in our initial NDA rolling submission for omaveloxolone was updated as of August 2021. In this updated analysis 58 of 73 patients from MOXIe Part 2 without pes cavus who enrolled into MOXIe Extension had at least 72 weeks of exposure in MOXIe Extension, and 28 of these patients had at least 120 weeks of exposure in the Moxie Extension.

Results of this analysis demonstrated that the between-group difference in mFARS observed at the end of the placebo-controlled MOXIe Part 2 period (least squares mean difference = -2.25 ± 1.07) was preserved at MOXIe Extension Week 72 in the delayed-start period (LS mean difference = -3.51 ± 1.45). Consistent with a persistent treatment effect on disease, the upper limit of the 90% CI for the difference estimate was less than zero (-0.615), meeting the threshold for demonstrating significant evidence of non-inferiority.

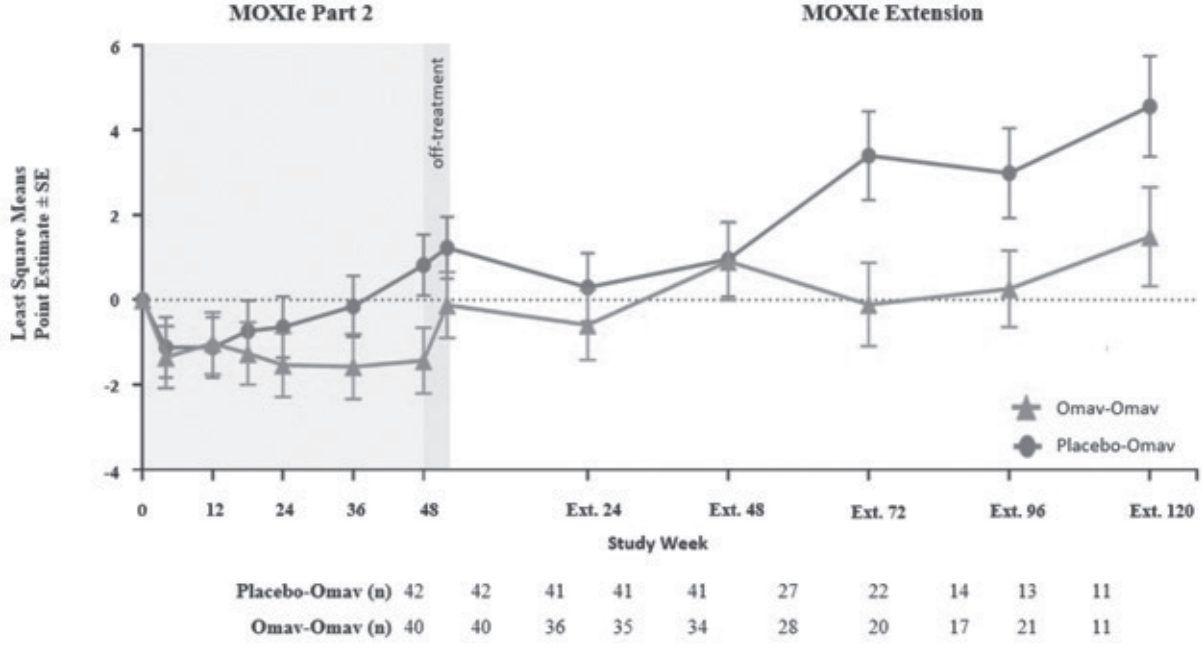
Delayed-Start Analysis Primary Endpoint (Non-Inferiority Test)[1]

	Placebo-Controlled Week 48 (Δ_1)	Delayed-Start Week Ex. 72 (Δ_2)
Difference (LS Mean ± SE)	-2.25 ± 1.07 p=0.037	-3.51 ± 1.45 p=0.016
Estimate = $\Delta_2 - 0.5\times \Delta_1$	-2.39 ± 1.38	
Upper Limit of 1-sided 90% CI for Estimate	-0.615	

[1]Non-Inferiorty test performed using a MMRM analysis with a Toeplitz covariance structure.

The graphical representation of changes from baseline in mFARS for omaveloxolone and placebo groups shows the separation at the end of the placebo-controlled period is maintained in the open-label period at Extension Week 72 and beyond.

Change from Baseline in mFARS (Patients without Pes Cavus)



Many of the visits at Week 48 and Week 72 of the MOXIe Extension were scheduled during the initial peak of COVID-19 cases during Spring to Fall 2020. The mFARS assessment must be conducted in the clinic, and many in-clinic visits did not occur due to COVID-19 related travel restrictions and site closures during this period. Apart from the data at MOXIe Extension Week 48, parallel trajectories were seen in LS Mean mFARS change from baseline between the placebo-to-omaveloxolone group and the omaveloxolone-to-omaveloxolone group in MOXIe Extension.

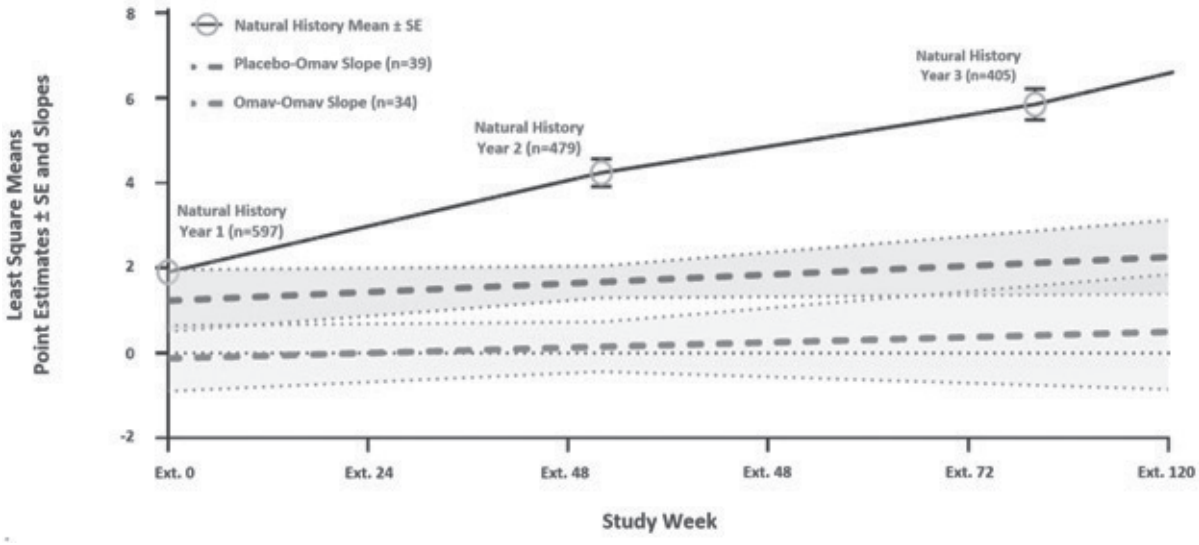
A longitudinal analysis was also performed to calculate annualized slopes incorporating all available data from the MOXIe Extension, which showed similar mean slopes in mFARS for the placebo-to-omaveloxolone group (0.45 ± 0.38 points per year) when compared to the omaveloxolone-to-omaveloxolone group (0.27 ± 0.59 points per year) with no significant difference between slopes (difference = -0.18 ± 0.67; p=0.79). In MOXIe

Extension, omaveloxolone-treated patients have been progressing at a rate that is >75% less than the approximately two points per year that patients progressed in a recent large natural history study (Patel, 2016).

MOXIe Extension Annualized mFARS Slope (± SE)

Omav-Omav (n=34)	Placebo-Omav (n=39)	Difference
0.27 ± 0.59	0.45 ± 0.38	-0.18 ± 0.67 p=0.79

Natural History mFARS and MOXIe Extension mFARS Slope[1]



[1]A MMRM was used to fit change from baseline mFARS using all available data from MOXIe Extension through Extension Week 120 to estimate annualized slopes based on MOXIe Part 2 randomized treatment group. The slopes were calculated using a linear model with time, treatment, and the interaction of treatment and time as fixed factors. Natural History mean change ± SE per year is based on Patel et. al. Ann. Clin. Transl. Neurol. 2016

Overall, these results from the Delayed-Start Analysis using two different data cut off dates indicate a persistent omaveloxolone treatment effect on the disease course of FA. Patients who received omaveloxolone during the double-blind MOXIe Part 2 had a benefit that could not be achieved by patients initially randomized to placebo who began omaveloxolone one year later in MOXIe Extension. Notably, patients previously randomized to omaveloxolone in MOXIe Part 2 continued to show mean mFARS values that were similar to their original baseline after over three years of treatment.

We believe that the results of the Delayed-Start Analysis provide evidence supporting the positive primary endpoint findings in MOXIe Part 2 and provide additional evidence of the effectiveness of omaveloxolone in FA.

Regulatory Interactions

A Delayed-Start Analysis using data from February 2021 was provided in the Type C briefing document submitted to the FDA in the second quarter of 2021. These results, together with a conceptual proposal for a confirmatory study to support an accelerated approval pathway, were reviewed by the FDA prior to the scheduled Type C meeting. The FDA stated that, after their preliminary review of the briefing materials, the most appropriate format for discussion was a pre-NDA meeting. They also requested that we focus the new briefing materials on applicable pre-NDA topics.

Based on the communication from the FDA, we requested a pre-NDA meeting. In the third quarter of 2021 we completed our pre-NDA meeting with the FDA. The purpose of the pre-NDA meeting was to discuss the content of Reata's planned NDA submission including the nonclinical data and chemistry manufacturing controls (CMC) packages, data standard plan, and the overall content plan.

In the meeting, we stated that we believed that the MOXIe data, along with the Delayed-Start Analysis, would provide sufficient clinical data to support a full approval. The FDA stated that the proposed primary and supportive efficacy data appear reasonable, though the Delayed-Start Analysis was viewed as exploratory. The FDA noted that the ability of the data to support full approval, and the adequacy of the data and the determination of which data may be supportive of efficacy, would be a matter of review. In response to our other questions about the contents of the NDA, the FDA exercised its discretion based on the seriousness of the indication and unmet medical need, subject to review, to permit us to submit the results of certain clinical pharmacology and nonclinical studies after approval. The additional studies include a thorough QT study with omaveloxolone, nonclinical metabolite toxicity studies, and six-month and two-year nonclinical carcinogenicity studies. The need for a drug-drug interaction study with a moderate CYP3A inducer will be established upon review of the adequacy of our submitted physiological based PK model.

On November 18, 2021, the FDA granted omaveloxolone Fast Track Designation for the treatment of FA, providing eligibility for FDA programs such as Priority Review and rolling submission of the NDA, if relevant criteria are met. The FDA granted our request for a rolling submission and in January 2022, we initiated rolling submission of our NDA, which included the MOXIe Extension data from the cut-off of August 2021 that had not previously been provided to the FDA. We expect to complete the submission of the NDA by the end of the first quarter of 2022. This NDA is supported by the efficacy and safety data from MOXIe Part 1, Part 2, and MOXIe Extension studies as noted above.

We are continuing to complete the regulatory procedures and submissions required prior to filing a marketing application in Europe for approval for omaveloxolone for the treatment of patients with FA. This includes securing agreement on our Pediatric Investigation Plan this year.

Potential Safety Review Topics

Below is a discussion of potential safety topics that may arise during NDA review and how we plan to respond. The safety topics of interest were closely monitored during the development program, and the findings are consistent with what would be expected based on the known pharmacological properties of omaveloxolone. This list is not comprehensive, and other matters may arise during the NDA review process.

Aminotransferases

Omaveloxolone treatment has been shown to increase alanine (ALT) and aspartate aminotransferases (AST) levels in the serum, and we have been able to characterize this profile in non-clinical and clinical studies to differentiate it from drug-induced hepatotoxicity.

In MOXIe Part 2, increases in ALT, AST, and gamma-glutamyl transferase (GGT) levels that exceeded the upper limit of normal (ULN) occurred in a greater percentage of omaveloxolone-treated patients than placebo-treated patients. The increases were transient, occurred shortly after initiation of treatment, peaked approximately two to four weeks after treatment initiation, and trended downward while patients remained on the study drug. At the post-treatment visit (four weeks after stopping the study drug), aminotransferase levels generally decreased further and returned to near baseline levels. Moreover, aminotransferase increases were generally mild or moderate, and for most omaveloxolone-treated patients (68.6%), ALT and AST levels remained less than three times ULN. Elevations in aminotransferases and GGT were not associated with elevations in total bilirubin and no cases meeting Hy's law criteria have been reported with omaveloxolone treatment.

We have demonstrated that omaveloxolone pharmacologically induces gene expression of aminotransferases, including ALT and AST, which reflects metabolic adaptations coordinated by Nrf2, rather

than liver toxicity (Lewis, 2021; Zhang, 2006). Genetic manipulation of Nrf2 in animal models affects the expression and serum activity of ALT and AST, and treatment with omaveloxolone analogs increases ALT and AST expression in cultured cells and in vivo without any liver toxicity. Additionally, omaveloxolone analogs are protective in multiple models of hepatotoxicity (e.g., acetaminophen, concanavalin A, aflatoxin, and carbon tetrachloride models).

Weight Changes

Omaveloxolone treatment has been shown to reduce body weight in some patients, and we and our collaborators have been able to characterize the weight changes in nonclinical studies.

In MOXIe Part 2, a mean decrease of -1.35 ± 3.585 (SD) kg in weight relative to baseline was observed with omaveloxolone treatment over 48 weeks. A similar trend of weight decrease has been observed in the patients during the Moxie Extension study. Adolescent patients treated with omaveloxolone had mean changes in weight that were comparable to adult patients treated with placebo. Overall, there were no meaningful differences in weight loss by age, sex, geographic region, or baseline pes cavus status. In MOXIe Part 2, decreases in weight of at least 5% were observed more frequently in omaveloxolone-treated patients (34% of patients, n=17) than placebo-treated patients (19.2% of patients, n=10). No patients discontinued treatment with omaveloxolone due to weight loss or appetite loss. Adverse events of weight loss associated with omaveloxolone treatment were uncommon. Weight loss can be managed in clinical practice by optimizing nutrition, or if needed, temporary discontinuation of omaveloxolone.

The observed decreases in body weight have also been previously observed with an analog of omaveloxolone. Decreases in body weight with bardoxolone were accompanied by significant reductions in waist circumference and improved glycemic control. Multiple studies in nonclinical models of diabetes and obesity have demonstrated that omaveloxolone analogs reduce fatty acid synthesis and promote fatty acid oxidation, thereby providing substrates for energy production (Shin, 2009). These effects are dependent on the presence of Nrf2 and are associated with improved glucose tolerance and insulin sensitivity, reduced body fat, preservation of muscle mass, and increased metabolism and energy expenditure (Camer, 2015; Saha, 2010; Shin, 2009). The observed decreases in body weight may therefore be explained by Nrf2-dependent changes in lipid metabolism, fatty acid oxidation, and glycemic control that have been observed in animal studies with omaveloxolone and analogs.

Cardiovascular Safety

Cardiovascular safety was evaluated because cardiomyopathy is the most common cause of death in patients with FA. In addition, adverse cardiovascular events were observed in a previous bardoxolone clinical trial in patients with type 2 diabetes mellitus and Stage 4 CKD. Of note, risk factors for these events were identified and used as population selection criteria to mitigate cardiovascular risks in patients in subsequent studies. The entry criteria in omaveloxolone clinical trials were designed to mitigate potential cardiovascular risk for participants, and signals for heart failure were closely monitored during the studies.

Adverse Events Related to Cardiovascular Safety

In MOXIe Part 2, the number of patients reporting cardiac disorder treatment-emergent AEs (TEAEs) was similar for omaveloxolone-treated and placebo-treated patients. There were no omaveloxolone-treated patients reporting vascular disorder AEs compared with three placebo-treated patients. All cardiac disorder and vascular disorder AEs were mild or moderate in severity. Overall, no meaningful difference in cardiac AEs, including cardiac failure or fluid overload events was observed between omaveloxolone-treated and placebo-treated patients.

Blood Pressure (BP)

In MOXIe Part 2, on average, no changes from baseline in SBP or DBP were observed at Week 48 in patients randomized to omaveloxolone or placebo. The profile of blood pressure over time across other subgroups was similar to the changes described above.

Echocardiograms

In MOXIe Part 2, treatment with omaveloxolone did not result in meaningful changes in echocardiogram parameters relative to baseline or compared with placebo-treated patients.

Electrocardiograms

In MOXIe Part 2, treatment with omaveloxolone did not show meaningful changes in ECG parameters relative to either baseline or compared with placebo-treated patients.

Brain Natriuretic Peptide (BNP)

In MOXIe Part 2, mean (± SD) BNP was slightly higher in omaveloxolone-treated patients compared to placebo-treated patients at baseline (omaveloxolone = 31.8 ± 31.43; placebo = 18.3 ± 25.43). Small increases in BNP were observed with omaveloxolone treatment relative to placebo in MOXIe Part 2, with mean values returning to near baseline after withdrawal of drug. Mean (± SD) change from baseline at Week 48 was 6.8 ± 30.30 in omaveloxolone-treated patients compared to 1.0 ± 19.29 in placebo-treated patients. Overall, mean BNP values in omaveloxolone-treated patients remained below the ULN (<100 pg/ml), and only 2 (3.9%) patients had BNP values that exceeded 200 pg/mL through Week 48. No patients reported TEAEs for BNP elevations, and there was only one patient with a TEAE of N-terminal prohormone brain natriuretic peptide (NT-pro-BNP) increased. In this patient, no changes to dosing were made, and the patient had a normal BNP value at the last on-treatment visit at Week 48. There were no associated AEs of fluid overload or cardiac failure.

In patients experiencing weight loss from liraglutide treatment and bariatric surgery we observed modest increases in BNP. Further, BNP elevations associated with liraglutide treatment were correlated with reductions in weight and fat mass in patients (Li, 2014). BNP regulates energy expenditure by influencing several metabolic processes, such as triglyceride lipolysis in adipocytes, fatty acid oxidation by skeletal muscle, mitochondrial biogenesis, and mitochondrial respiration, which are all processes associated with Nrf2 activation (Coué, 2016; Engeli, 2012; Miyashita, 2009; Schlueter, 2014; Sengenès, 2002). BNP overexpression is associated with protection from obesity and insulin resistance in animals fed a high-fat diet (Miyashita, 2009). BNP levels are lower in patients with metabolic risk factors, including obesity, visceral fat, lipid profiles, metabolic syndrome, low physical activity level, insulin resistance, and chronic inflammation (Zois, 2014).

We hypothesize that, like the modest increases observed in other forms of weight loss, the profile and magnitude of BNP increases observed with omaveloxolone treatment are due to reductions in weight and improvements in metabolic parameters. Omaveloxolone and analogs are associated with improved glucose tolerance and insulin sensitivity, reduced body fat, preservation of muscle mass, and increased metabolism and energy expenditure (Camer, 2015; Saha, 2010a; Shin, 2009; Uruno, 2013). A high-fat-diet study in mice using omaveloxolone analogs demonstrated that decreased body weight gain caused by treatment with an omaveloxolone analog is associated with significantly increased cardiac BNP mRNA levels, along with protection from high-fat diet-induced cardiac hypertrophy.

Lipids

In MOXIe Part 2, omaveloxolone-treated patients had a higher incidence of total cholesterol and low-density lipoprotein (LDL) cholesterol values above the ULN. Patients treated with omaveloxolone showed

increases in LDL cholesterol of approximately 20 mg/dL at Week 48 that returned to baseline after withdrawal of drug, while values for placebo-treated patients did not change notably. The mean LDL cholesterol values were below 120 mg/dL at all time points for omaveloxolone-treated patients. Eight (19.0%) omaveloxolone-treated patients and 4 (9.1%) placebo-treated patients had increases in LDL cholesterol above the normal range while receiving treatment, indicating that increases in LDL cholesterol above the normal range occurred more frequently in omaveloxolone-treated patients. Omaveloxolone-treated adolescent patients showed smaller increases in LDL cholesterol at Week 48 than omaveloxolone-treated adult patients. No notable change in mean very LDL cholesterol was seen over the treatment period in omaveloxolone-treated patients, nor was there a difference compared with placebo-treated patients.

On average, patients treated with omaveloxolone showed a reduction in high-density lipoprotein (HDL) cholesterol of -5.43 mg/dL at Week 48 and a reduction of -2.5 mg/dL after the four-week off-treatment period. Changes in HDL cholesterol below or above the normal range did not occur more frequently in omaveloxolone-treated patients.

The effects of omaveloxolone and analogs on serum lipids have been investigated in nonclinical models and are associated with metabolic effects of omaveloxolone, including mobilization and metabolism of stored lipids resulting in decreased adiposity, increased mitochondrial function, and increased energy production. For example, treatment with an omaveloxolone analog in a mouse model of high-fat diet-induced obesity resulted in reduced body and adipose mass and decreased hepatic lipid accumulation, coupled with increases in energy expenditure. However, these mice also had minor increases in serum total, LDL, and HDL cholesterol. All of these changes were attenuated in Nrf2-null mice, suggesting that the broad effects on lipid homeostasis associated with treatment were due to activation of Nrf2 (Shin, 2009). Furthermore, in a mouse model of nonalcoholic steatohepatitis, a 3-week treatment with omaveloxolone decreased hepatic fat deposition, hepatocellular ballooning, inflammatory cell infiltration, and collagen deposition, along with improved glucose control and decreases in liver and serum triglycerides. These changes were associated with small but significant increases in LDL cholesterol with omaveloxolone treatment (Reisman, 2020). Collectively, these nonclinical results suggest that elevations in serum lipid parameters can occur despite overall improvement in lipid homeostasis and are related to activation of Nrf2.

Infections and Infestations

Infections and infestations were prespecified and evaluated because the anti-inflammatory effects associated with Nrf2 activation could possibly lead to a decreased immune response.

In MOXIe Part 2, the number of patients with infections and infestation TEAE were balanced between omaveloxolone-treated patients and placebo-treated patients. None of the AEs were considered severe, and there was only 1 patient reporting two SAEs in the omaveloxolone group. The number of infection-related AEs was also similar across omaveloxolone and placebo groups in adolescent patients. Furthermore, no meaningful differences in immune cell (eg, white blood cell, lymphocytes, monocytes, neutrophils, eosinophils, basophils) counts were seen between omaveloxolone- and placebo-treated patients.

Omaveloxolone for Other Neurological Indications

Omaveloxolone is a promising platform molecule. Because mitochondrial dysfunction is a key feature of many neurological and neuromuscular diseases, we believe omaveloxolone may be broadly applicable to treat such diseases by activating Nrf2 to normalize and improve mitochondrial function and ATP production.

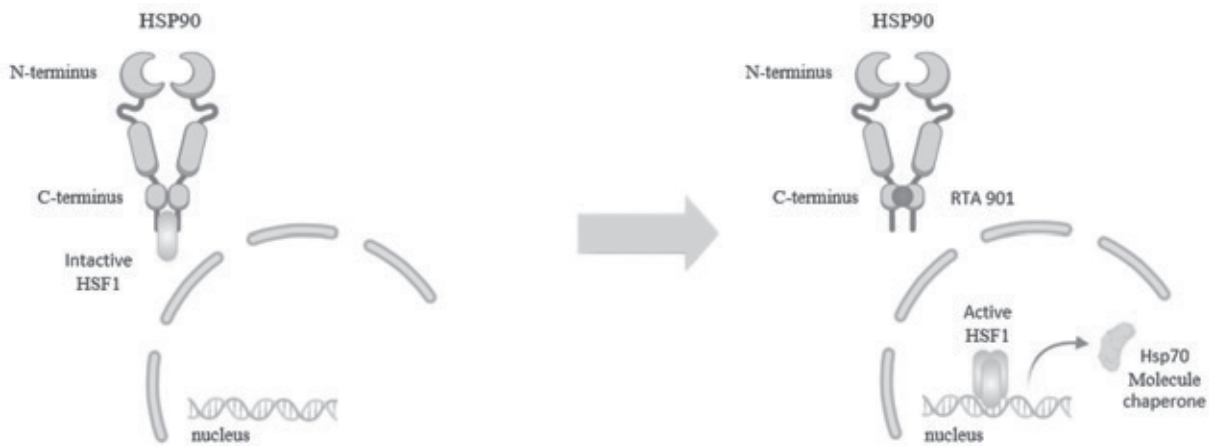
Based on our understanding of the pathophysiology of neurological diseases, characterized by mitochondrial dysfunction, inflammation, and oxidative stress, we believe omaveloxolone may be applicable to diseases such as progressive supranuclear palsy, Parkinson’s disease, frontotemporal dementia, Huntington’s disease, ALS, Alzheimer’s disease, and epilepsy. Consistent with this, we have observed promising activity of omaveloxolone and our other Nrf2 activators in preclinical models of many of these diseases.

Our Nrf2 activators reduced seizure frequency in refractory, progressive epilepsy models and restored mitochondrial function in patient biopsy samples and preclinical models of FA, ALS, familial and sporadic Parkinson's disease, and frontotemporal dementia. In clinical trials, improvements in neuromuscular function have been observed in FA patients treated with omaveloxolone as assessed by mFARS, 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 omaveloxolone has the potential to treat a number of neurological and neuromuscular diseases that currently have few or no effective therapies, and we plan to pursue the development of omaveloxolone and our other Nrf2 activators for one or more of these diseases.

RTA 901 in Neurological Diseases

RTA 901 is the lead product candidate from our Hsp90 modulator program, which includes highly potent and selective C-terminal modulators of Hsp90. We have observed favorable activity of RTA 901 in a range of preclinical models of neurological disease, including models of diabetic neuropathy, neuroinflammation, and neuropathic pain.

Historically, other companies have explored N-terminal Hsp90 inhibitors for cancer therapeutics; however, this approach has been associated with multiple adverse effects including peripheral neuropathy and ocular toxicity. Binding at the C-terminus of Hsp90 leads to increased transcription of Hsp70, a cytoprotective and molecular chaperone gene, which facilitates cell survival in response to stress without the deleterious activities of N-terminal inhibition.



In preclinical rodent disease models, we observed that RTA 901 administered orally once-daily rescued existing nerve function, restored thermal and mechanical sensitivity, and improved nerve conductance velocity and mitochondrial function. These effects are dose-dependent, reversible, and HSP70-dependent.

We completed a Phase 1 SAD/MAD trial of oral, once-daily RTA 901 in healthy adult volunteers to evaluate the safety, tolerability, and PK profile. The PK was approximately dose-proportional up to the highest doses evaluated with a half-life ranging from two to nine hours. Human exposures easily exceeded the exposures necessary for efficacy in multiple animal models. No safety or tolerability concerns were reported. We plan to initiate additional Phase 1 studies to evaluate the PK and drug-drug interaction potential of RTA 901 in the first half of 2022 and a randomized, placebo-controlled Phase 2 study in DPNP in the second half of 2022.

There are about four million patients with moderate to severe DPNP in the United States, and about two million adult patients diagnosed with DPNP seek treatment annually.

We are the exclusive licensee of RTA 901 and have worldwide commercial rights.

Programs in Chronic Kidney Disease

We and our strategic collaborator are developing bardoxolone for the treatment of CKD in multiple indications, including CKD caused by Alport syndrome, ADPKD, and type 1 and 2 diabetic CKD. We received a CRL from the FDA in February 2022 with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome. We will continue to work with the FDA to confirm our next steps on our Alport syndrome program. Kyowa Kirin, our strategic collaborator in CKD, is currently conducting its registrational AYAME trial of bardoxolone in diabetic (types 1 and 2) CKD in Japan. Kyowa Kirin expects last patient out in the second half of 2022.

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). eGFR is an estimate of GFR that nephrologists use to track the decline in kidney function and progression of CKD. When GFR gets too low, patients develop ESKD and require dialysis or a kidney transplant to survive. 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. 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 lives. These patients may suffer side effects due to dialysis. Dialysis also increases the likelihood of serious and life-threatening complications, such as cardiovascular disease (CVD). The five-year survival rate for hemodialysis patients is approximately 45%. As per the 2021 Annual Data Report published by the United States Renal Data System, the number of patients with ESKD in the United States has nearly doubled in the last two decades, comprising an estimated 783,000 patients as of 2019. Approximately 30% of these patients suffer from a rare form of CKD. In 2019, total Medicare fee-for-service (FFS) spending for all beneficiaries who had CKD was over $124 billion, of which $51 billion was spent on patients with ESKD. In 2018, the total Medicare FFS spending for all beneficiaries who had CKD was about $117 billion, representing an increase of about 6% in expenditure in 2019.

Rationale for the Development of Bardoxolone for the Treatment of CKD

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.

Bardoxolone suppresses inflammatory pathways that contribute to kidney function loss by increasing Nrf2 activity. Nrf2 has been shown to protect the kidney in preclinical studies that are the subject of many peer-reviewed manuscripts. We believe that by promoting the Nrf2-dependent resolution of inflammation and rescue of mitochondrial dysfunction, bardoxolone treatment addresses a final common pathway of kidney function loss triggered by a variety of insults and improves kidney function by increasing the effective glomerular filtration surface area, reducing inflammation, and preventing fibrosis.

Bardoxolone in Patients with CKD Caused by Alport Syndrome

Based on the results of our Phase 3 CARDINAL clinical trial, on March 1, 2021, we submitted our NDA for bardoxolone for the treatment of CKD caused by Alport syndrome to the FDA. On April 26, 2021, the FDA

accepted for filing our NDA, set the PDUFA date for February 25, 2022, and stated that the FDA also planned to hold an advisory committee meeting to discuss the application. On December 8, 2021, the Cardiovascular and Renal Drugs Advisory Committee voted no on the question of whether the provided evidence demonstrated that bardoxolone is effective in slowing the progression of CKD in patients with Alport syndrome and that its benefits outweigh its risks.

On February 25, 2022, we received a CRL from the FDA with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome. We will continue to work with the FDA to confirm our next steps on our Alport syndrome program.

Regarding non-U.S. regulatory applications for bardoxolone in the treatment of patients with CKD caused by Alport syndrome, on October 28, 2021, we submitted an MAA to the EMA and on July 27, 2021, our strategic collaborator in CKD in Japan, Kyowa Kirin, submitted an NDA in Japan to the MHLW. Both applications are currently under review.

We recently received the 120-day LOQ from the EMA. We are in the process of reviewing the questions and preparing our responses.

Overview of Alport Syndrome

Alport syndrome is a rare, genetic form of CKD caused by mutations in the genes encoding type IV collagen, which is a major structural component of the GBM in the kidney. The kidneys of patients with Alport syndrome progressively lose the capacity to filter waste products out of the blood, which can lead to ESKD and the need for chronic dialysis treatment or a kidney transplant. Alport syndrome affects both children and adults and can manifest as early as the first decade of life and causes average annual declines in eGFR of approximately four to five mL/min/1.73 m^2. In patients with the most severe forms of the disease, approximately 50% progress to dialysis by age 25, 90% by age 40, and nearly 100% by age 60. There are currently no approved therapies to treat CKD caused by Alport syndrome.

The Alport Syndrome Foundation estimates that Alport syndrome affects approximately 30,000 to 60,000 people in the United States. According to data provided by IQVIA in 2020, there are approximately 14,000 projected patients diagnosed with Alport syndrome in all stages of CKD in the United States. However, recent literature suggests that a large number of patients with Alport syndrome are either undiagnosed or mis-diagnosed with other forms of CKD.

Clinical Updates in Alport Syndrome

On November 9, 2020, we announced that the Phase 3 CARDINAL study met its primary and key secondary endpoints at the end of Year 2. The Phase 3 portion of CARDINAL was an international, multi-center, double-blind, placebo-controlled, randomized registrational trial that enrolled 157 patients with CKD caused by Alport syndrome at approximately 50 study sites in the United States, Europe, Japan, and Australia. Patients were randomized one-to-one to bardoxolone or placebo. At Week 100, in the intent to treat (ITT) population, which included eGFR values for patients who either remained on or discontinued study drug, patients treated with bardoxolone had a statistically significant improvement compared to placebo in mean change from baseline in eGFR of 7.7 mL/min/1.73 m^2 (p=0.0005). At Week 104 (four weeks after last dose in second year of treatment), patients in the ITT population treated with bardoxolone had a statistically significant improvement compared to placebo in mean change from baseline in eGFR of 4.3 mL/min/1.73 m^2 (p=0.023).

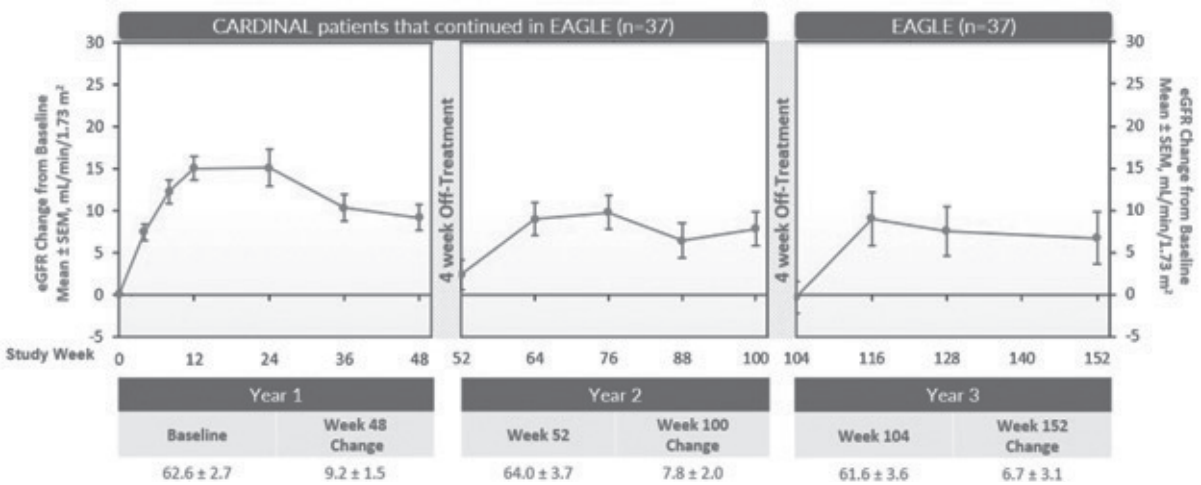
Bardoxolone was generally reported to be well tolerated in this study, and the safety profile was similar to that observed in prior trials. Eight patients (10%) receiving bardoxolone and 15 patients (19%) receiving placebo experienced a treatment-emergent SAE. No SAEs were reported in pediatric patients treated with bardoxolone. No fluid overload SAEs or major adverse cardiac events were reported in patients treated with bardoxolone. The

reported AEs were generally mild to moderate in severity, and the most common AEs observed more frequently in patients treated with bardoxolone compared to patients treated with placebo were muscle spasms and increases in aminotransferases, which are thought to be associated with the pharmacology of the drug.

Additionally, on November 9, 2020, we reported results from the long-term extension EAGLE study. EAGLE is an international, multi-center, open-label, extended access trial evaluating the longer-term safety and tolerability of bardoxolone in patients with CKD caused by Alport syndrome who participated in the CARDINAL trial or patients with ADPKD who participated in the FALCON trial. The change from baseline in eGFR was assessed for the 14 patients with Alport syndrome who were treated with bardoxolone for three years (two years in CARDINAL and one year in EAGLE), with four-week off-treatment periods occurring at Weeks 48 and 100. Bardoxolone treatment resulted in a mean increase from baseline in eGFR of 11.5 mL/min/1.73 m^2 at Year 1, 13.3 mL/min/1.73 m^2 at Year 2, and 11.0 mL/min/1.73 m^2 at Year 3.

In February 2022, we provided the FDA with an update on results from patients with CKD caused by Alport syndrome in the ongoing EAGLE trial. Mean increases in eGFR were observed at Week 12, Week 24, and Week 48 relative to Day 0 (before treatment) in EAGLE in patients who previously received placebo and initiated treatment with bardoxolone in EAGLE. Patients who previously received bardoxolone for two years in CARDINAL experienced similar mean increases in eGFR at all timepoints.

For the 37 patients randomized to bardoxolone in CARDINAL who completed 48 weeks in EAGLE (bardoxolone-to-bardoxolone group), bardoxolone treatment resulted in a mean change from baseline in eGFR (relative to original CARDINAL baseline) of 9.2 mL/min/1.73 m^2 at Year 1, 7.8 mL/min/1.73 m^2 at Year 2, and 6.7 mL/min/1.73 m^2 at Year 3.



A subset of patients (n=18) completed 96 weeks of treatment in EAGLE, which amounts to approximately four years of total treatment, and had a mean ± standard error change from baseline eGFR in CARDINAL of 5.5 ± 3.5 mL/min/1.73 m^2. This sustained improvement of kidney function is notable when compared to the CARDINAL study population's expected yearly eGFR decline of 5.1 mL/min/1.73 m^2, which was calculated based on five-year historical eGFR data collected before patients entered the study. No new safety findings have been observed in EAGLE extension study.

Bardoxolone in Patients with CKD Caused by Autosomal Dominant Polycystic Kidney Disease

ADPKD is a rare and serious hereditary form of CKD caused by a genetic defect in *PKD1* or *PKD2* genes leading to the formation of fluid-filled cysts in the kidneys and other organs. Cyst growth can cause the kidneys to expand up to five to seven times their normal volume, leading to pain and progressive loss of kidney function. Inflammation appears to play a role in cyst growth and is associated with disease progression in ADPKD.

ADPKD affects both men and women of all racial and ethnic groups and is the leading inheritable cause of kidney failure with an estimated diagnosed population of 140,000 patients and an estimated prevalent population of 400,000 patients in the United States. Despite current standard-of-care treatment, an estimated 50% of ADPKD patients progress to ESKD and require dialysis or a kidney transplant by 60 years of age. The only therapy currently approved for ADPKD is JYNARQUE® (tolvaptan), developed by Otsuka Pharmaceuticals Co., Ltd., which was approved in the United States in 2018 to slow kidney function decline in adults at risk of rapidly progressing ADPKD.

In ADPKD, inflammation and mitochondrial dysfunction, processes known to be suppressed by Nrf2 activation, drive cysts growth in the kidney tubules. We have shown in preclinical cellular models that in primary and immortalized ADPKD cyst-derived cells, bardoxolone induces expression of Nrf2 target genes, reduces levels of MCP-1 (marker of inflammation), increases total cellular glutathione levels, reduces ROS levels, and improves mitochondrial function. Bardoxolone also reduces cyst formation in a cell-based cystogenesis model. These results suggest that activation of Nrf2 by bardoxolone may have the potential to improve the molecular features that are hallmarks of ADPKD.

We are currently enrolling patients in FALCON, an international, multi-center, randomized, double-blind, placebo-controlled trial studying the safety and efficacy of bardoxolone in patients with ADPKD randomized one-to-one to active drug or placebo. FALCON is enrolling patients in a broad range of ages, 18 to 70 years old, with an eGFR between 30 to 90 mL/min/1.73 m^2. We recently filed a protocol amendment with the FDA and requested a Type A meeting to discuss the overall ADPKD development program including the recently submitted major protocol amendment. The major protocol amendment changes include increases in the sample size from 550 to 850 patients, addition of adolescent (12 to 17 years) patients with ADPKD, removal of the off-treatment period (Week 48 – Week 52) during Year 1, change of the primary endpoint of off-treatment eGFR change from baseline at Week 52 (or four weeks after drug discontinuation in Year 1) to eGFR change from baseline at Week 108 (eight weeks after planned drug discontinuation at Week 100), addition of an exploratory endpoint of eGFR change from baseline at Week 112 (12 weeks after planned drug discontinuation at Week 100), and addition of a sub study with ambulatory blood pressure monitoring.

Pursuant to the protocol amendment, patients will be treated with bardoxolone or placebo for 100 weeks followed by a twelve-week withdrawal period. The trial will remain blinded until study completion. All patients will be asked to return at Week 108 independent of the time of study drug discontinuation. In November 2021, we announced a plan to increase the FALCON sample size from 550 to 700 patients. In order to maintain power, with changes in the primary endpoint, the sample size is increased from 550 to 850 patients in our recently submitted protocol amendment. The secondary endpoint is the eGFR change from baseline at Week 100. The SAP, detailing the proposed analyses, has also been submitted. More than 500 patients are currently enrolled in the study.

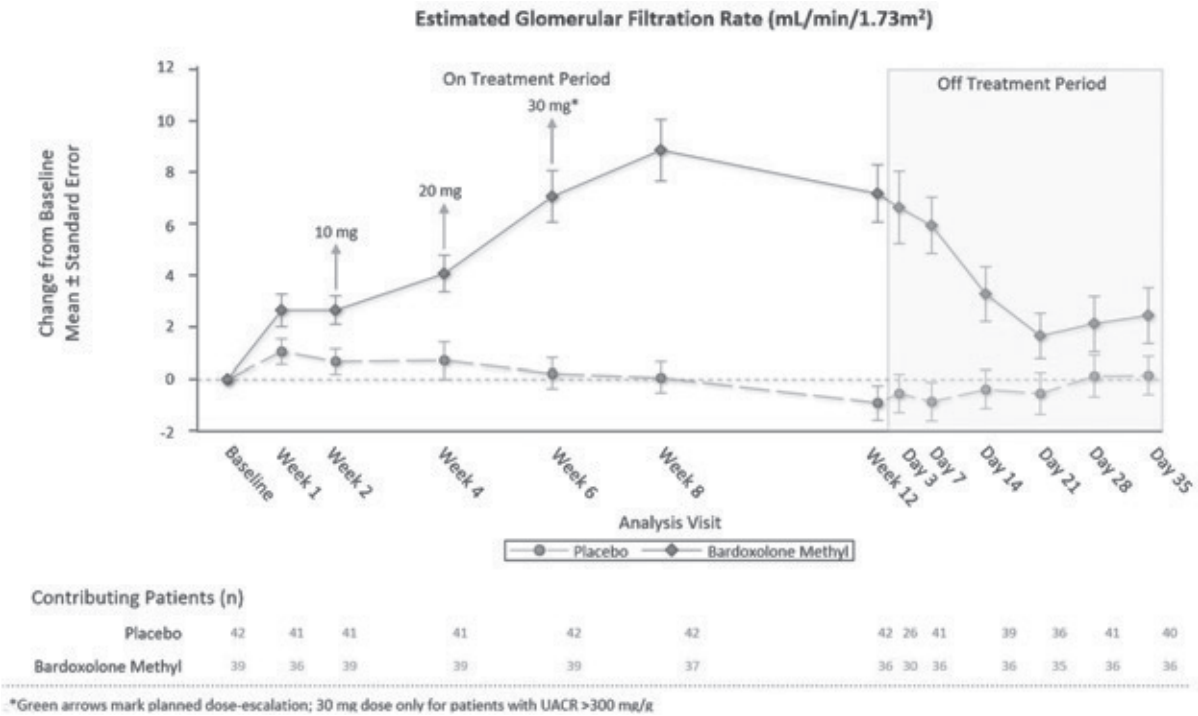
Bardoxolone in CKD Patients at Risk of Rapid Progression

MERLIN was a proof of concept, multi-center, double-blind, placebo-controlled, Phase 2 trial to evaluate the safety and efficacy of bardoxolone in patient populations with CKD secondary to varying etiologies at risk of rapid progression. MERLIN enrolled patients from ages 18 to 75 years old, with eGFR ≥ 20 to < 60 mL/min/1.73 m^2, and other risk factors for rapid progression of kidney disease. Eighty-one patients were enrolled and randomized one-to-one to either bardoxolone or placebo. The primary endpoint was the change in eGFR from baseline after 12 weeks of treatment, and the secondary endpoint was the change in eGFR from baseline after 12 weeks of treatment by CKD etiology. MERLIN also incorporated an exploratory efficacy endpoint of change in eGFR from baseline at off-treatment Days 3, 7, 14, 21, 28, and 35 to examine the time period for resolution of the acute PD effect of bardoxolone.

MERLIN met the primary endpoint at Week 12. Treatment with bardoxolone resulted in a higher mean eGFR change from baseline compared to placebo, with a placebo-corrected statistically significant mean

difference of 7.71 mL/min/1.73 m^2 (n=81, p < 0.0001, CI: 5.18, 10.24) at Week 12. When eGFR data were broken down by different etiologies of CKD, MMRM analysis results favored bardoxolone over placebo in all subgroups. A similar magnitude of eGFR change compared to placebo was observed in patients with diabetic CKD (placebo-corrected difference: 7.51 mL/min/1.73 m^2; n=33; p=0.0010), and in patients with CKD caused by various other etiologies (placebo-corrected difference: 7.61 mL/min/1.73 m^2; n=28; p=0.0009). We observed that patients with CKD at risk of rapid progression caused by hypertension also showed a nominal but not statistically significant mean change from baseline compared to placebo, with a placebo-corrected mean difference of 6.35 mL/min/1.73 m^2 in eGFR (n=20; p=0.1482).

The change in eGFR in patients treated with bardoxolone was maximal in MERLIN at Week 8, two weeks after the last planned dose titration at Week 6. Mean eGFR change from baseline began to decrease within three days after the planned cessation of treatment at Week 12. The maximum decrease in off-treatment eGFR change from baseline occurred 21 days after the last dose. Overlapping confidence intervals support consistency in the change from baseline for Days 14, 21, 28, and 35 off-treatment. A statistically significant difference in mean eGFR change from baseline was observed for the bardoxolone group compared to the placebo group through Day 14 off-treatment, with a placebo-corrected mean difference of 3.70 mL/min/1.73 m^2 (p = 0.0040, CI: 1.22, 6.18). At Day 21, off treatment and beyond, there was no significant placebo-corrected difference between the placebo and bardoxolone groups, suggesting the acute effects of bardoxolone had resolved by Day 21 off-treatment.



Consistent with previous studies, treatment with bardoxolone at doses up to 30 mg and for up to 12 weeks was generally safe and well tolerated. Furthermore, there was no imbalance in cases of volume overload and were no cases of congestive heart failure or increases in blood pressure noted in the bardoxolone group. There were no clinically meaningful overall trends in laboratory values or electrocardiograms, and there were no deaths in this study.

Four out of 81 patients had SAEs (one in the placebo group and three in the bardoxolone group), none of which were assessed as related to study treatment. Most TEAEs were mild to moderate in severity. As reported in other clinical trials with bardoxolone, muscle spasms were the most commonly reported TEAE and were

equivalent in frequency between the placebo and bardoxolone groups. Five patients in the bardoxolone group had dose de-escalations or delays in dose-escalation due to TEAEs. No placebo patients and seven out of 39 (17.9%) bardoxolone patients discontinued study treatment before Week 12. Reasons included AEs (four patients), non-compliance with study treatment (two patients), and withdrawal by patient (one patient).

As observed in previous studies increases in aminotransferases were transient, asymptomatic and were not associated with any evidence of liver injury. Increases with aminotransferases were not associated with increases in total bilirubin and no patient met Hy's Law criteria. Mean decreases from baseline in weight were observed in patients treated with bardoxolone. Treatment with bardoxolone resulted in increases in urinary albumin-to-creatinine ratio (UACR) over the course of eight weeks, plateauing through Week 12. UACR trended back towards baseline during the off-treatment period. When adjusted for eGFR, ratios of eGFR to UACR were unchanged, suggesting that increases in UACR are attributed to the increases in eGFR observed with bardoxolone.

The MERLIN data were submitted as an amendment to our NDA. However, the FDA did not accept this amendment as a major amendment.

Bardoxolone in Patients with Rare Forms of CKD

PHOENIX was a Phase 2, open-label, multi-center trial evaluating the safety and efficacy of bardoxolone in patients with ADPKD, IgA nephropathy (IgAN), type 1 diabetic CKD (T1D CKD), or focal segmental glomerulosclerosis (FSGS) completed in 2019. In each of these cohorts, bardoxolone treated patients experienced a statistically significant increase from baseline in mean eGFR after 12 weeks of treatment. Based on the outcome of AYAME and FALCON trials, and our discussions with the FDA regarding the bardoxolone program, we will decide future development plans for bardoxolone in patients with additional forms of CKD including patients at risk of rapid progression.

AYAME Trial in Diabetic CKD Conducted by Kyowa Kirin

Upon completion of the Phase 2 TSUBAKI study, Kyowa Kirin's clinical study of bardoxolone in patients with Stage 3 and 4 diabetic CKD in Japan, and after discussions with the PMDA, Kyowa Kirin initiated a Phase 3 outcomes trial called AYAME in patients with Stage 3 or 4 diabetic CKD in Japan. The primary endpoint is time to onset of a ≥ 30% decrease in eGFR from baseline or ESKD. The secondary endpoints are time to onset of a ≥ 40% decrease in eGFR from baseline or ESKD, time to onset of a ≥ 53% decrease in eGFR from baseline or ESKD, time to onset of ESKD, and change in eGFR from baseline at each evaluation time point. Kyowa Kirin completed patient enrollment in AYAME in June 2019 and expects the last patient out in the second half of 2022.

RTA 1700 Series

In addition to our lead programs, we are developing a proprietary series of RORÎ³t inhibitors for the potential treatment of a broad range of autoimmune, inflammatory, and fibrotic diseases. We conducted a Phase 1 trial to evaluate the safety, tolerability, and PK profile of RTA 1701 in healthy adult volunteers. RTA 1701 had no safety concerns, was well tolerated, and we observed an acceptable PK profile. Plasma concentrations were achieved that are associated with efficacy in preclinical models of autoimmune disease. Due to RTA 1701's ADME (absorption, distribution, metabolism, and excretion) properties and the potential for drug-drug interactions at clinically relevant concentrations, we have discontinued the development of RTA 1701 and are proceeding with the development of follow-on molecules in the 1700 series. We remain committed to developing RORγt inhibitors for the treatment of autoimmune, inflammatory, and fibrotic diseases. We retain all rights to our RORγt inhibitors, which are not subject to any existing commercial collaborations.

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 third-party manufacturing strategy enables us to efficiently direct financial resources to the research, development, and commercialization of product candidates rather than diverting resources to internally develop manufacturing facilities. We source our materials (whether they are of natural or chemical origin) globally, utilizing a network of qualified, established third-party vendors. Prior to commercialization, it is common that a product candidate's supply chain contains single-sourced suppliers. Second source supplier identification and implementation strategies, as well as inventory safety stock, are used to mitigate supply chain risks at the appropriate stage of product development. As our product candidates advance through development, we expect to enter into commercial supply agreements with key suppliers and manufacturers and continue to strategically build inventory and redundancy in suppliers, as appropriate, to fulfill and secure the ongoing and planned preclinical, clinical, and, if our product candidates are approved for marketing, commercial supply needs for us and our collaborators.

Manufacturing Preparations for Omaveloxolone in Neurological Diseases

Our manufacturing and quality teams are in place for the current stage of program development with plans to grow as needed to support future commercial supply and distribution of omaveloxolone. We are on track for planned clinical drug supplies, with a supply chain strategy to adequately support potential future clinical and commercial demand. We have completed registration batches for drug substance and drug product. In addition, we believe the synthesis from regulatory starting material to drug substance can be manufactured at scale, resulting in a commercially competitive cost of goods.

Manufacturing Preparations for Bardoxolone in Rare CKD

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 of bardoxolone. We have completed process validation batches for drug substance and drug product. In addition, we believe that the synthesis from regulatory starting material to drug substance can be manufactured at scale, resulting in a commercially competitive cost of goods.

Sales and Marketing

We are in the process of building the commercial infrastructure in the United States necessary to effectively support the commercialization of our product candidates, if and when we receive regulatory approval of such product candidates in the United States.

Outside of the United States, where appropriate and depending on the terms of our contractual arrangements, we plan, either alone, or with new collaboration partners, to commercialize our products. Our strategic collaborator Kyowa Kirin has all rights to commercialize bardoxolone in its territories. We are refining our strategy and market assessments with respect to a potential launch in the EU, and we plan to continue to evaluate market opportunities for our products in other global markets.

Commercial infrastructure for orphan products typically consists of a targeted, specialty sales force that calls on a limited and focused group of physicians and personnel involved in sales management, internal sales support, marketing, patient access, and distribution. One challenge unique to rare-disease commercialization is patient identification 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, 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.

Sales and Marketing Preparations for Omaveloxolone in FA

Commercial launch preparation will advance with regulatory progress. Our ability to launch omaveloxolone is dependent on the successful filing and defense of an NDA and MAA and approval by the FDA and EMA, respectively. We have hired commercial leadership and will build the teams, infrastructure, systems, and processes necessary for the launch of omaveloxolone. This will include sales, marketing, market access, patient support, and distribution. Additionally, we plan to expand quality and compliance functions to support commercialization.

Sales and Marketing Preparations for Bardoxolone in Rare CKD

We have paused our commercial planning efforts until we have a clear regulatory path forward for bardoxolone in rare CKD. Our ability to launch bardoxolone is dependent on the acceptance and successful defense of an NDA and MAA and approval by the FDA and EMA, respectively. If our commercial planning efforts resume, we have plans to establish a distribution network that would enable us to deliver product across Europe with a small initial footprint.

Medical Affairs

In neurological disease, we are continuing our efforts to educate physicians on the hallmarks of FA and the differentiating symptoms that discriminate patients with FA from patients with similar neurological diseases. Our medical affairs activities in the United States for bardoxolone in our CKD program have been paused. Our K**ID**neyCode™ genetic testing program has been terminated.

Competition

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 FA for which we are developing omaveloxolone, in DPNP for which we are developing RTA 901, and in CKD for which we are developing bardoxolone.

Omaveloxolone in Friedreich's Ataxia

There are currently no therapies approved for FA. If omaveloxolone 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.

We are aware of only one program, vatiquinone from PTC Therapeutics Inc., in Phase 3 stage of development. Additionally, competitor product candidates MIN-102 from Minoryx Therapeutics, MIB-626 from MetroBiotech, LLC, JOTROL (JOT-101) from Jupiter Neurosciences, Inc., and elamipretide from Stealth BioTherapeutics Corp. are in Phase 2 clinical development for FA. We are aware of only one program, CTI-1601 from Larimar Therapeutics, Inc., in Phase 1 clinical development. In addition, Biohaven Pharmaceutical Holding Company Ltd.'s Troriluzole is in Phase 3 development for the treatment of patients with Spinocerebellar ataxia (SCA). Biohaven has expressed an intention to explore the development of Troriluzole for other ataxias, which may include FA pending the outcome of the ongoing clinical studies in SCA. If approved and launched commercially, omaveloxolone may face competition from these product candidates. Some of these product candidates may enter the market prior to omaveloxolone, and some of these product candidates could limit the market or level of reimbursement available for omaveloxolone if it is commercialized.

RTA 901 in Diabetic Peripheral Neuropathic Pain

Currently, there are four drugs and two devices that are approved for treatment of DPNP in the United States including Lyrica®, Cymbalta®, Nucynta®, an opioid, and Qutenza®, a capsaicin patch applied once every three

months. Intellis™ and Vanta™ by Medtronic Plc. and Senza® by Nevro Corp. are two implantable spinal cord stimulation systems approved for treatment of chronic pain associated with diabetic peripheral neuropathy (DPN). Tarlige® by Daiichi Sankyo Company Ltd. is a gabapentinoid that is approved for DPNP in Japan. In addition, current treatment guidelines from the American Diabetes Association and the American Academy of Neurology also recommend the off-label use of gabapentin and tricyclic antidepressants.

We are aware of multiple drugs in advanced clinical development for DPNP including Engenesis (VM202) by Helixmith Co. in Phase 3, HSK-16149 by Sichuan Haisco Pharmaceutical Co. in Phase 2/3 (China), and 16 additional programs in Phase 2 clinical trials including LX9211 by Lexicon Pharmaceuticals Inc., MEDI7352 by AstraZeneca Plc, Elismetrep (MT8554) by Mitsubishi Tanabe Pharma (Europe), PGDN-20WS by Pure Green Pharmaceuticals, YJ-001 by Zhejiang Pharmaceutical (China), BAY2395840 by Bayer, LY3016859, LY3526318, and LY3556050 by Eli Lilly and Company, ETX-810 by Eliem Therapeutics Inc., Pirenzepine (WST-057) by WinSanTor Inc., NRD135S.E1 by Novaremed AG, NYX-2925 by Aptinyx Inc., Ricolinostat by Regenacy Pharmaceuticals, GRC 17536 by Glenmark Pharmaceuticals Ltd., and CNTX-6016 by Centrexion Therapeutics. AT-001 by Applied Therapeutics Inc. is also being investigated for DPN in a sub-study of a Phase 3 program in Diabetic Cardiomyopathy.

Bardoxolone in CKD

Currently, there are no approved therapies for CKD caused by Alport syndrome, and patients are commonly treated off-label with angiotensin converting enzyme (ACE) inhibitors or angiotensin 2 receptor blockers (ARBs). If bardoxolone is approved and launched commercially for patients with CKD caused by Alport syndrome, it may face market competition. We are aware of at least three therapies for the treatment of Alport syndrome currently in Phase 2 of clinical development including an injectable product candidate, lademirsen (RG-012) from Sanofi S.A, atrasentan in patients with one of several forms of CKD including Alport syndrome from Chinook Therapeutics Inc., and sparsentan in pediatric patients with proteinuric glomerular diseases including Alport syndrome from Travere Therapeutics Inc.

Currently, there is one drug specifically approved and multiple therapies in late-stage clinical development for the treatment of patients with ADPKD. In 2018, Otsuka Pharmaceuticals Co., Ltd. received approval by the FDA to market JYNARQUE® to slow kidney function decline in adults at risk of rapidly progressing ADPKD. We are aware of one program in Phase 3 stage of development which is Palladio Biosciences' study of lixivaptan for treating patients with ADPKD. Other products under clinical development for ADPKD include GLPG2737 by Galapagos NV in Phase 2, Tesevatinib by Kadmon, a Sanofi company, in Phase 2, Xrx-008 by Xortx Therapeutics Inc. in Phase 2, and AL01211 by Acelink Therapeutics in Phase 1.

We are also aware of multiple drugs that are either approved or in clinical development programs in Type 2 diabetic CKD (T2D CKD), hypertensive, and other forms of CKD. These include the SGLT2 inhibitors, Jardiance® and Farxiga® developed by Boehringer Ingelheim and Eli Lilly and Company, and by AstraZeneca, respectively which are in development for patients with CKD with and without T2D. In April 2021, Farxiga® received FDA approval to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. AstraZeneca has not said whether any patients with CKD caused by Alport syndrome were enrolled in the DAPA-CKD trial; however, the trial did enroll patients with IgAN and other forms of glomerulonephritis. The DAPA-CKD study excluded patients with ADPKD and T1D CKD. Farxiga® may be used to treat patients with CKD due to rare and common forms of CKD including Alport syndrome. Additionally, Jardiance® is currently being tested in EMPA-KIDNEY, a Phase 3 trial in patients with various forms of CKD, excluding ADPKD and T1D CKD. Results from the EMPA-KIDNEY trial are expected in the fourth quarter of 2022. Additionally, Bayer Healthcare, in November 2021, announced the initiation of the FIONA Phase 3 study to investigate finerenone for the treatment of pediatric patients with CKD and severely increased proteinuria. The study may enroll patients with Alport syndrome or ADPKD. Kerendia® (finerenone) received FDA approval in July 2021 to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with T2D CKD.

Collaborations

Kyowa Kirin Agreement

In December 2009, we entered into an agreement with Kyowa Kirin, under which we provided Kyowa Kirin the right to develop and commercialize bardoxolone 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 (the Kyowa Kirin Agreement). These indications include, among others, CKD. Total consideration under this agreement could reach $272.0 million in upfront and milestone payments, of which we have received $85.0 million. Additionally, Kyowa Kirin is required to pay us royalties on net sales of licensed product sold by Kyowa Kirin, 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.

Kyowa Kirin 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. Under this agreement, we are obligated to use commercially reasonable efforts to supply Kyowa Kirin with clinical supply of licensed product required for Kyowa Kirin's development in the licensed territory, and we are obligated to negotiate and execute commercial supply agreements with Kyowa Kirin. Also, Kyowa Kirin has allowed us to conduct clinical activities in certain rare forms of kidney disease in Japan and has reimbursed us the majority of the costs for CARDINAL in Japan and is assuming some of the costs of patients in Japan for the FALCON trial. In addition, Kyowa Kirin is the in-country caretaker for FALCON in Japan.

The Kyowa Kirin Agreement will terminate automatically when the royalty term expires in all of Kyowa Kirin's territory. A royalty term expires in a country on the later of the expiration of all patents in such country or 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, Kyowa Kirin may terminate the agreement at will upon advance written notice. In the event of any termination of the agreement by us for Kyowa Kirin's uncured breach, bankruptcy, or insolvency or by Kyowa Kirin at will, Kyowa Kirin will transfer and assign to us the regulatory filings for bardoxolone and will license to us the relevant trademarks used with the products in their respective territories.

Amended and Restated License Agreement with AbbVie

In September 2010, we entered into a license agreement with AbbVie (the AbbVie License Agreement), under which we provided AbbVie the exclusive right to develop and commercialize bardoxolone or other molecules for renal, metabolic, and cardiovascular indications, including CKD, in all other countries outside the United States not previously licensed to Kyowa Kirin under the Kyowa Kirin Agreement.

In December 2011, we entered into a collaboration agreement with AbbVie (the Collaboration Agreement) under which we provided AbbVie the right to jointly research, develop, and commercialize all second- and later-generation Nrf2 activators, including omaveloxolone, for all indications other than renal, cardiovascular, and metabolic indications.

In October 2019, we entered into an Amended and Restated License Agreement with AbbVie (the Reacquisition Agreement), under which we reacquired the development, manufacturing, and commercialization rights concerning our proprietary Nrf2 activator product platform originally licensed to AbbVie under the AbbVie License Agreement and the Collaboration Agreement. Under the Reacquisition Agreement, the AbbVie License Agreement and the Collaboration Agreement were amended, resulting in AbbVie granting its exclusive sublicenses back to us, such that we reacquired the worldwide rights to bardoxolone, excluding certain Asian countries previously licensed to Kyowa Kirin, and the worldwide rights to omaveloxolone and the second-generation activators. In exchange for such rights, we agreed to pay AbbVie a total of $330.0 million, all of which has subsequently been paid. In addition, AbbVie will receive an escalating, low single-digit royalty on

worldwide net sales, on a product-by-product basis, of omaveloxolone and certain next-generation Nrf2 activators. AbbVie will not receive royalties on bardoxolone sales. By reacquiring our rights, we were relieved from our obligations under the AbbVie License Agreement and the Collaboration Agreement.

As a result of the $330.0 million having been paid to AbbVie, the licenses granted to AbbVie and the sublicenses granted to us with respect to omaveloxolone and bardoxolone and certain next-generation Nrf2 activators have terminated, with all rights reverting to us.

Development and Commercialization Funding Agreement with Blackstone Life Sciences

On June 24, 2020, we closed a Development and Commercialization Funding Agreement (the Development Agreement) with an affiliate of Blackstone Life Sciences, LLC (BXLS) that provides funding for the development and commercialization of bardoxolone for the treatment of CKD caused by Alport syndrome, ADPKD, and certain other rare CKD indications. The Development Agreement includes a $300.0 million payment by the Blackstone affiliate in return for various percentage royalty payments on worldwide net sales of bardoxolone by Reata and its licensees, other than Kyowa Kirin. The royalty percentage will initially be in the mid-single digits and in future years can vary between higher-mid single digit percentages to low-single digit percentages depending on various milestones, including indication approval dates, cumulative royalty payments, and cumulative net sales. Pursuant to the Development Agreement, we have granted BXLS a security interest in substantially all of our assets. In addition, concurrent with the Development Agreement, we entered into a common stock purchase agreement (the Purchase Agreement) with affiliates of BXLS to sell an aggregate of 340,793 shares of the Company's Class A common stock at $146.72 per share for a total of $50.0 million.

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 in the ordinary course of our business, principally in our research and development expenses. 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 United States Department of Justice (DOJ) or other governmental entities.

United States Product Approval Process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act (FFDCA). Pharmaceutical products are also subject to regulation by other governmental agencies, such as, but not limited to, the Federal Trade Commission, the Office of Inspector General 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 good laboratory practice (GLPs);
- The submission to the FDA of an investigational new drug (IND) application for human clinical testing, which must become effective before any human clinical trial commences;
- Approval by an institutional review board (IRB) or ethics committee representing each clinical site before each clinical trial may be initiated;

- Adequate and well-controlled human clinical trials to establish the safety and efficacy of the product and conducted in accordance with good clinical practice (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 current good manufacturing practice (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, 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 AEs), 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.

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 the 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 (DSMB) 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 $3.1 million for fiscal year 2022. 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 risk evaluation and mitigation strategy (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 CRL 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 with the exception of 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.

Fast Track Designation, Accelerated Approval, and Priority Review

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 more frequent interactions with the FDA and rolling review (submission of portions of an application before the complete marketing application is submitted).

Under the Fast Track and accelerated approval programs, 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 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.

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 a manner consistent with the provisions of the approved labeling. 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. It also requires state licensing of 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 on 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 into law on November 27, 2013, imposes new obligations on manufacturers of prescription finished pharmaceutical drug products, among others, related to product tracking and tracing, identification, verification, illegitimate production notification, and other elements. Among the requirements of this federal law, manufacturers are required to provide certain information regarding the drug product to 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 the DSCSA, manufacturers have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, illegitimate, 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, and some requirements are already in effect. 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 logistics providers (3PLs). 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 standards for wholesalers, current state licensing requirements typically remain in effect, although the DSCSA expressly preempts those state statutes and regulations that require 3PLs to maintain wholesale drug distributor licenses. The FDA published its Proposed Rule on February 4, 2020, titled "National Standards for the Licensure of Wholesale Drug Distributors and Third-Party Logistics Providers." When finalized, the rule establishes among other things a national licensing standard for wholesale drug distributors and 3PLs. It is difficult to predict when FDA will publish the final rule. Once the final rule is published, the licensing standards will take effect one year after publication for 3PLs and two years after publication for wholesale drug distributors.

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, recommending, or arranging for the purchase, lease, or order of any good, facility, item, or service reimbursable under Medicare, Medicaid, or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value, including, for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests, and providing anything at less than its fair market value. The federal Anti-Kickback Statute has been interpreted to apply to certain arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and our practices may not in all cases meet all of the criteria for a statutory exception or safe harbor protection. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the federal Anti-Kickback Statute. Instead, the legality of the

arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. The intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (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. Health Insurance Portability and Accountability Act of 1996 (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 Health Information Technology for Economic and Clinical Health Act (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, 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 Center for Medicare and Medicaid Services (CMS) related to certain payments or other transfers of value made or distributed to physicians, physician assistants, certain types of advanced practice nurses, 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.

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. 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. Significant uncertainty thus 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 EU member states and China, the pricing of prescription drugs is subject to government control. In some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, EU member states have options 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 total cost of a medicinal product placed on its 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. The Biden 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.

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 expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program, imposed a significant annual, nondeductible fee on companies that manufacture or import certain branded prescription drug products, and enacted substantial provisions affecting compliance, which may affect our business practices with healthcare practitioners. 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. For example, on September 9, 2021, the Biden administration published a wide-ranging list of policy proposals, most of which would need to be carried out by Congress, to reduce drug prices and drug payment. The Department of Health and Human Services'(HHS) plan includes, among other reform measures, proposals to lower prescription drug prices, including by allowing Medicare to negotiate prices and disincentivizing price increases, and to support market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase price transparency. Many similar proposals, including the plans to give Medicare Part D authority to negotiate drug prices, require drug manufacturers to pay rebates on drugs whose prices increase greater than the rate of inflation, and cap out-of-pocket costs, have already been included in policy statements and legislation currently being considered by Congress. It is unclear to what extent these and other statutory, regulatory, and administrative initiatives will be enacted and implemented. 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 Tax Cuts and Jobs Act of 2017 (2017 Tax Act) was signed into law, which eliminated certain requirements of the PPACA, including the individual mandate. On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the PPACA will remain in effect in its current form. It is possible that the PPACA will be subject to judicial or Congressional challenges in the future. It is uncertain how any such challenges and the healthcare measures of the Biden administration will impact 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 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. The Medicare reductions will phase back in starting with a 1% reduction in effect from April 1, 2022 to June 30, 2022 before increasing to the full 2% reduction. Also, in January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several types of health care providers. Further, former President Trump and President Biden both issued Executive Orders intended to favor government procurement from domestic manufacturers.

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, contained 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 could 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 the EU, a sponsor must submit a clinical trial application (CTA), much like an IND, prior to the commencement of human clinical trials and receive authorization from the relevant authorities. The new EU Regulation on Clinical Trials, which became applicable on January 31, 2022, imposes additional requirements in relation to human clinical trials.

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.

In the EU, a company may submit an MAA either under a centralized, decentralized, mutual recognition or national procedure. The centralized procedure is compulsory for medicinal products that (1) are derived from biotechnology processes, (2) contain a new active substance for certain specific indications, (3) are orphan medicinal products or (4) are advanced therapy medicinal products, such as gene or cell therapy medicines; and optional for certain other medicinal products for example because they involve a new active substance or are highly innovative. Under the centralized procedure, a marketing application is submitted to the EMA where it will be evaluated by the Committee for Medicinal Products for Human Use and a favorable opinion typically results in the grant by the EC of a single marketing authorization that is valid for all EU member states within 67 days of receipt of the opinion. The initial marketing authorization is valid for five years, but once renewed is usually valid for an unlimited period. The decentralized procedure provides for approval of a new medicinal product by one or more "concerned" member states based on an assessment of an application performed by one member state, known as the "reference" member state. Under the decentralized approval procedure, an applicant submits an application, or dossier, and related materials to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the EC, whose decision is binding on all member states. The mutual-recognition procedure enables a company to seek recognition of a marketing authorization granted in one member state in other EU member states. The national procedure allows a company to apply for a national marketing authorization in a single EU country under its national authorization procedures.

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 new chemical entity (NCE), never previously approved by FDA either alone or in combination with another active moiety. No application or an abbreviated new drug application (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), on a worldwide basis, encompasses more than 900 granted patents and more than 260 pending patent applications, including more than 550 granted patents and more than 160 pending patent applications related to omaveloxolone, RTA 901, bardoxolone, and the RTA 1700 class of compounds. More than 200 granted patents and more than 50 pending applications claim additional structural classes of Nrf2 activators, providing further protection for the franchise and a potential source of additional development candidates. Four issued United States patents, more than ten issued foreign patents, and several pending United States and foreign patent applications contain composition of matter claims to RTA 901 and related compounds. The RTA 1700 class of compounds is covered by more than 40 granted United States and foreign patents and several pending applications.

Fundamental composition of matter patents and applications claiming omaveloxolone have an expiration date in 2033. These patents and applications also contain claims to therapeutic uses of omaveloxolone. The fundamental United States composition of matter patent claiming RTA 901, and its foreign equivalents, have an expiration date in 2033. Our later-expiring granted patents with claims to compositions of matter for bardoxolone, 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 bardoxolone, including the commercial formulation, has an expiration date of 2030. Other granted patents and pending patent applications relating to specific uses of bardoxolone, including the treatment of CVD and CKD, have expiration dates ranging from 2029 to 2034. Patents and pending applications covering the RTA 1700 class of compounds, 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.

Omaveloxolone Patent Portfolio

Omaveloxolone is protected by three families of patents. The first, filed in April 2009, contains composition of matter claims that encompass omaveloxolone and many related compounds. This family includes five issued United States patents and a number of granted patents in foreign jurisdictions including Canada, China, Eurasia, Europe, Japan, and Mexico. Additional United States and foreign applications from this family are pending. The second family, filed in April 2013, is specifically focused on omaveloxolone and includes composition of matter claims and method of use claims. The initial United States patent from this family was issued on March 31, 2015. The issued claims include composition of matter claims to omaveloxolone without regard to morphic form, claims to several distinct morphic forms of omaveloxolone, 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 also been granted in Europe. The Japanese and Chinese applications have also granted. A third patent family, filed by AbbVie in April 2014 and being assigned to us under the Reacquisition Agreement, claims additional morphic forms of omaveloxolone.

The most relevant granted United States patents with claims covering omaveloxolone are listed below, along with their projected expiration dates. As discussed below for bardoxolone, if omaveloxolone is approved for marketing in the United States, we may be eligible for term extension under the Hatch-Waxman Act for a granted United States patent containing claims covering omaveloxolone. Similar term extensions may be available in Europe, Japan, and certain other foreign jurisdictions. The amount of any such term extension, and the identity of the patent to which it would apply, depend 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
9,701,709	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 the Patent Cooperation Treaty application filed in 2013. Patents from this family have been granted in the United States, Australia, Canada, China, Eurasia, Europe, Japan, Korea, Mexico, and New Zealand. Applications are pending in Europe, China,

Mexico, and several other countries. Patents are granted on three United States continuation applications, while a fourth United States continuation application is pending. Patented 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. A second family of patents, filed in 2019 in more than 20 territories, provides additional composition of matter protection for RTA 901. Patents from this family will expire in 2039 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
10,590,157	C-Terminal Hsp90 Inhibitors	February 8, 2033
10,882,881	C-Terminal Hsp90 Inhibitors	February 8, 2033
10,717,755	Co-crystal Forms of a Novobiocin Analog and Proline	February 1, 2039

Bardoxolone Patent Portfolio

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

Two families of composition of matter patents contain claims that cover bardoxolone. The original patent family containing claims to bardoxolone 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 bardoxolone has an expiration date in 2022. Corresponding patents granted in Canada, Europe (validated in multiple European Patent Convention (EPC) member states), and Japan expired in 2019. Exclusive of any patent term extension, the granted United States patents containing claims covering specific forms of bardoxolone, 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, United States patents claiming bardoxolone have longer terms than the corresponding foreign patents. This results from the USPTO’s grant of patent term adjustments to offset examination delays originating at the USPTO. Analogous adjustments are generally not available under foreign patent laws. If bardoxolone is approved for marketing in the United States, under the Hatch-Waxman Act we may be eligible for up to five years patent term extension for a granted United States patent containing claims covering bardoxolone. Unlike patent term adjustments, 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, depend upon several factors including the duration of the development program and the date of marketing approval. See “Business—Government Regulation—United States Patent Term Restoration and Regulatory Exclusivity for Approved Products.”

We also own or exclusively license various United States and foreign granted patents and pending patent applications containing claims covering formulations of bardoxolone, including the planned commercial

formulation, and methods of using bardoxolone for the treatment of multiple diseases including PH, pulmonary arterial hypertension (PAH), endothelial dysfunction (an essential component of many cardiovascular disorders including PAH), CVD, CKD, Alport syndrome, metabolic disorders, and obesity.

The most relevant granted United States patents with composition of matter or method of use claims covering bardoxolone 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
8,088,824	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
9,757,359	Synthetic triterpenoids and methods of use in the treatment of disease	January 12, 2029
10,953,020	Methods of Treating Alport Syndrome Using Bardoxolone Methyl or Analogs Thereof	November 8, 2037

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

2014 University of Kansas License

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, including RTA 901, 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 retained limited rights related to research and educational use of compounds claimed in patents that name NIH as an assignee. In July 2020, Reata voluntarily terminated the license that involved both the University of Kansas and NIH. This license did not involve any patents that claim compounds in development by Reata or under consideration for development. The remaining license, which exclusively involves the University of Kansas as the licensor (the KU license), includes patents that claim RTA 901 and potential back-up or follow-on compounds, and remains in full force and effect.

The KU license 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.

The KU license 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.

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 bardoxolone, 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 pay 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 $27.2 million in development and sublicense payments under the license.

We have a continuing obligation to use best efforts to commercialize the licensed technology. The license is effective until the last expiration of a claim in a licensed patent that covers the licensed product or 20 years if no

licensed patent covers the licensed product. The license can be terminated by the licensors for our material breach subject to a specified notice and cure period based on the nature of the breach, if we become insolvent or enter bankruptcy or receivership proceedings, if we fail to provide satisfactory evidence that we are exercising best efforts to commercialize a licensed invention, or if two payments are late or unpaid within a twelve-month period. Upon any termination of the license, we grant licensors a non-exclusive, sublicenseable license to any improvements that we make to the licensed technology, including those that we license from third parties, subject to a mutually agreed royalty.

2012 Amendment to the 2004 Dartmouth and MD Anderson License

In July 2012, the parties executed an amendment to the 2004 license. This amendment provides, among other terms, that we will pay to the licensors a low single-digit royalty on net sales of certain Nrf2 activator compounds covered by the Collaboration Agreement, including omaveloxolone, that are claimed in certain patents and patent applications that are wholly owned by or assigned to us as identified in the Collaboration Agreement.

2021 Amendment to the 2004 Dartmouth and MD Anderson License

In August 2021, the parties executed an amendment to the 2004 license. This amendment, among other terms, provides consent to an internal restructuring by the Company of certain of its intellectual property rights, facilitates the potential monetization by Dartmouth of its rights to royalties under the 2004 license, clarifies the applicability of certain running royalty payment obligations with respect to certain compounds, and specifies the dispute resolution procedure regarding a dispute between the Company and Licensors as to whether the Company is obligated under the 2012 amendment to the 2004 license to pay licensors a low single-digit royalty on sales of products containing bardoxolone.

2009 Dartmouth License

In 2009, we entered into an agreement with Dartmouth, pursuant to which Dartmouth granted us an exclusive, worldwide, sublicenseable license to Dartmouth's rights in patents and patent applications jointly owned by us and Dartmouth claiming the use of bardoxolone 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. To date, we have made $11.3 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.

2021 Amendment to the 2009 Dartmouth License

In August 2021, the parties executed an amendment to the 2009 license. This amendment, among other terms, provides consent to an internal restructuring by the Company of certain of its intellectual property rights, facilitates the potential monetization by Dartmouth of its rights to royalties under the 2009 license, clarifies that there is no minimum royalty provision, and adds provisions regarding the defense of certain patent rights.

Third-Party Filings

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.

Human Capital Management

As of December 31, 2021, we had 346 full-time and three part-time employees. 67 of our employees hold Ph.D. or M.D. degrees, with 241 employees engaged in research and development activities. None of our employees is represented by a labor union, and none of our employees has entered into a collective bargaining agreement with us. We consider our overall employee relations to be good.

Diversity and inclusion

We are committed to creating and maintaining a diverse and inclusive work force. We believe our company is stronger because of the variety of our employees' experiences and backgrounds.

COVID-19 employee safety and benefits

When COVID-19 emerged as a global pandemic in the first quarter of, 2020, Reata was quick to respond and was an early adopter of a work-from-home policy, with the exception of the laboratory that continued to operate throughout under strict safety protocols. For all remote employees, we provided appropriate workstation equipment as well as training and resources to support employees' mental and emotional wellbeing. In the second quarter of 2021, Reata relaxed its policy and permitted employees to return to the office if requested. Although the Omicron variant has temporarily caused us to restrict office attendance, employees have typically agreed to a modified work schedule with management with approximately 100 employees attending the office on a regular basis. Since the onset of the pandemic, we have continued to provide full pay and benefits to employees unable to work due to illness from COVID-19, as well as those managing childcare issues or caring for ill family members.

Community engagement, social and relationship capital

Although the pandemic has significantly impacted our ability to conduct in-person community activities, we have continued to support the North Texas community as much as practical. Our two key initiatives in 2021 were teams assisting the North Texas Food Bank in packaging up food for local families in need, and employees across the organization supported the Salvation Army Angel Tree Program. With a planned gradual return to the office in mid-2022, Reata plans to expand its volunteering program to support the local community as it recovers from the economic and social challenges created by the pandemic.

Compensation and benefits, health and wellness

We strive to provide competitive compensation and benefit programs that help meet the varying needs of our employees. Our competitive total rewards package includes market competitive salaries, performance related bonuses, and a long-term incentive program that provides all employees the opportunity to benefit from equity ownership through annual grants in Reata restricted stock units (RSUs) and stock options. Given the highly competitive market we are experiencing, Reata conducts regular market assessments and in 2021 made a number of compensation adjustments to attract and retain talent.

Reata provides comprehensive benefit offerings, including health insurance, dental, vision, and a number of optional benefits. Reata also offers a childcare Flexible Spending Account (FSA) and contributes into a healthcare FSA or a Health Savings Account. Reata also offers a 401(k) plan with an employer match. In 2021, Reata expanded its family leave program to provide up to nine weeks paid leave for an expectant mother and two weeks paid leave for a father/domestic partner.

Growth and development

Reata's revised grade structure provides a foundation for career development. Coupled with career guides, employees will be able to identify potential career paths within the organization and understand what personal development initiatives they should adopt to improve career advancement opportunities. Reata utilizes an online performance management process that aligns employee goals with those of their respective function and the broader organization. Tuition reimbursement is also made available to employees wishing to pursue additional qualifications.

Communications and engagement

We employ a variety of tools to facilitate open and direct communications across our organization. These include open forums with executives, townhall meetings, social events, and opportunities to participate in cross-functional teams and committees. Since the onset of the pandemic, we have adapted these forums to allow for virtual connection. We refine our employee programs through employee engagement surveys as well as follow up pulse surveys. The executive leadership team reviews annual survey results and ensures action plans are implemented to further increase employee engagement.

Conduct and ethics

Our board of directors and senior management strongly support a no-tolerance stance for workplace harassment, biases, and unethical behavior. All employees are required to undertake annual training and abide by, review, and confirm compliance with, among other policies, our Code of Ethics and Business Conduct policy, Healthcare Compliance policies, and preventing harassment in the workplace policies.

Executive Officers and Directors

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

Name	Position
J. Warren Huff	Chief Executive Officer and Chairman of the Board of Directors
Manmeet S. Soni	Chief Operating Officer, Chief Financial Officer, and President
Colin Meyer, M.D.	Chief Innovation Officer and Executive Vice President
Dawn C. Bir	Chief Commercial Officer and Executive Vice President
Michael D. Wortley	Chief Legal Officer and Executive Vice President
Samina Khan, M.D.	Chief Medical Officer and Senior Vice President
Andrea L. Loewen	Senior Vice President, Global Regulatory Affairs
Martin W. Edwards, M.D. (2)(3)(4)	Director
William D. McClellan, Jr. (1)(2)(5)	Director
R. Kent McGaughy, Jr. (2)(4)(5)	Director
Jack B. Nielsen (2)(3)	Director
William E. Rose (1)(2)	Director
Christy J. Oliger (1) (3) (5)	Director
Shamim Ruff (1)(3)(4)	Director

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

Executive Officers

J. Warren Huff is the Chairman and Chief Executive Officer of Reata. He has served as our sole Chief Executive Officer and as Chairman of the Board since our founding in 2002 and as our President until February 2022. Prior to founding Reata, Mr. Huff served as Chief Executive Officer in a number of biotechnology 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.

Manmeet S. Soni is Reata's President, Chief Operating Officer and Chief Financial Officer and oversees manufacturing, quality assurance, global alliances, program management, business development, corporate strategy, finance, accounting, treasury, tax, corporate communications, investor relations and information technology. He joined Reata in August 2019 as Chief Financial Officer, Executive Vice President, and assumed the additional role of Chief Operating Officer in June 2020. In February 2022, Mr. Soni was promoted to President. Prior to joining Reata, Mr. Soni served as Senior Vice President and Chief Financial Officer of Alnylam Pharmaceuticals, Inc. from May 2017 until August 2019. From March 2016 to February 2017, Mr. Soni served as the Executive Vice President, Chief Financial Officer and Treasurer of ARIAD Pharmaceuticals, Inc., a publicly held biopharmaceutical company, when ARIAD was acquired by Takeda Pharmaceutical Company Limited. Mr. Soni continued as an employee of ARIAD through May 2017. Previously, Mr. Soni served as Chief Financial Officer and Treasurer of Pharmacyclics, Inc., a publicly held biopharmaceutical company, until its acquisition by AbbVie in 2015. Prior to joining Pharmacyclics, Mr. Soni worked at ZELTIQ Aesthetics Inc., a publicly held medical technology company as corporate controller. Prior to ZELTIQ, Mr. Soni worked at PricewaterhouseCoopers in their Life Science and Venture Capital Group. Mr. Soni currently serves as a member of the board of directors of Pulse Biosciences, Inc., and Summit Therapeutics plc, and previously served as a

member of the board of directors of Arena Pharmaceuticals, Inc., each of which is a publicly traded company. Mr. Soni graduated from Hansraj College at Delhi University in India. He is a certified public accountant (CPA) and Chartered Accountant from the Institute of Chartered Accountants of India.

Colin J. Meyer, M.D. joined Reata as one of our first employees in 2003, served as Chief Medical Officer until July 2020 and was appointed Chief Research and Development Officer in July 2020. Beginning in February 2022, his title was changed to Chief Innovation Officer to reflect his focus on providing strategic input on our portfolio of potential products, including indication expansion of our clinical programs, early-stage development and identifying new technology platforms, as well as supporting our regulatory submissions. 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.

Dawn C. Bir joined Reata as Chief Commercial Officer in September 2016 to develop and oversee marketing, market access, sales, training and commercial operations. Prior to joining Reata, Ms. Bir most recently served as Vice President of Sales with Pharmacyclics, LLC. From February 2013 to September 2016, she built and led their first hematology national sales organization of sales representatives, division managers and regional sales directors responsible for the launch of IMBRUVICA® in the 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. She currently serves as a member of the board of directors of Geron Corporation, a publicly traded clinical stage pharmaceutical company. Ms. Bir holds a B.S. in Biology from Binghamton University.

Michael D. Wortley joined Reata as Chief Legal Officer in April 2015. Prior to joining Reata, Mr. Wortley was an attorney at Vinson & Elkins L.L.P. from 1995 to March 2015, serving in various capacities, including Chief Operating Partner of the firm and Managing Partner of the Dallas office, and, prior to 1995, at Johnson & Wortley, P.C., serving as Chairman of the Board and President. He currently serves as a member of the board of directors of Pioneer Natural Resources Company, a publicly traded 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.

Samina Khan, M.D. joined Reata as Chief Medical Officer in July 2020. Prior to joining Reata, she served as Clinical Development Team Lead at Mitsubishi Tanabe Pharma America, Inc. from May 2017 to July 2020. From March 2015 to April 2017, Dr. Khan served as Vice President, Clinical Development at Quark Pharmaceuticals, Inc. Prior to March 2015, Dr. Khan served in leadership positions at Abbott Laboratories and AbbVie Inc. Dr. Khan attended Fatima Jinnah Medical University. She completed her residency and fellowship at Tufts Medical Center program and served as an Assistant Professor of Medicine at Tufts University School of Medicine. She also received post-graduate training in rheumatology/immunology. Dr. Khan received an M.P.H. from Harvard Medical School of Public Health and an M.B.A. from Brandeis University.

Andrea L. Loewen joined Reata in February 2020 and serves as the Senior Vice President, Global Regulatory Affairs. She has more than 30 years of regulatory experience in drug development and commercial life cycle management primarily working in neurology, oncology, metabolic, renal, and rare diseases. Prior to joining Reata, Ms. Loewen served as Vice President, Global Regulatory Affairs and Quality at Retrophin (now Travere Therapeutics) from 2017 to 2020. In this role she helped to develop multiple late-stage rare disease programs, including negotiating several phase 3 studies with global health authorities in renal and neurology indications, and managed global life cycle management and label expansion for several marketed drugs. Prior to this, Ms. Loewen served as Vice President, Regulatory Affairs and Quality at Vital Therapies from 2013 to 2017. Ms. Loewen started her career at Baxter Healthcare and has held increasing management roles in Regulatory Affairs including a 10-year tenure at Biogen and serving as Head of Global Regulatory Affairs at Shire

Pharmaceuticals. Ms. Loewen earned a Bachelor's degree in Biology from Gustavus Adolphus College and a Master's degree from Pepperdine University.

Non-Employee Directors

Dr. Martin W. Edwards has served as a member of the Board since August 2020. Since 2003, until his retirement in September 2020, Dr. Edwards held various positions at Novo Holdings A/S, a life sciences investment firm, and most recently as a part-time Senior Partner. Earlier in his career, he was Corporate VP and Global Head of Drug Development for Novo Nordisk A/S, where he led all aspects of pre-clinical and clinical drug development. Dr. Edwards currently serves as a member of the board of directors of public biotech companies Kalvista Pharmaceuticals, Inc., Verona Pharma plc, Inozyme Pharma, Inc., and Morphic Holding, Inc., as well as a private biotech company. Dr. Edwards previously served as a member of the board of directors of CoLucid Pharmaceuticals, Inc., a publicly traded company. Dr. Edwards qualified in physiology and medicine at the University of Manchester. Dr. Edwards was elected a Member of the Royal College of Physicians, a Member with distinction of the Royal College of General Practitioners, and a Fellow of the Faculty of Pharmaceutical Medicine, and holds an M.B.A. from the University of Warwick.

William D. McClellan, Jr. has served as a member of the Board since March 2017. Mr. McClellan has served as the Chief Financial Officer of Aerin Medical Inc. since January 2018. Mr. McClellan, 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, was the Chief Financial Officer and Executive Vice President, Finance at On-X Life Technologies Holdings, Inc. Prior to June 2004, Mr. McClellan, held financial and accounting positions at various healthcare and other companies and was a CPA 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 received a B.B.A. in accounting from Abilene Christian University and is a CPA.

R. Kent McGaughy, Jr. has served as a member of the Board since December 2004. Mr. McGaughy has been a partner in CPMG, Inc. since 2005. 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. and Instil Bio, Inc., each of which is a publicly traded company, and several private companies. Mr. McGaughy 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.

Jack B. Nielsen has served as a member of the Board since June 2006. Mr. Nielsen has served as a Managing Director at Vivo Capital LLC, a healthcare focused investment firm, since August 2017, and previously served as a consultant from March 2017 to July 2017. From 2001 to February 2017, Mr. Nielsen was with the Novo A/S (Novozymes) organization and its venture activities in several roles, most recently as a Senior Partner based in Copenhagen, Denmark. From 2006 to 2012, Mr. Nielsen was a Partner at Novo Ventures (US) Inc. in San Francisco, where he established the office which provides certain consultancy services to Novo A/S. He currently serves as a member of the board of directors of public biotech companies Aligos Therapeutics, Inc., ALX Oncology Holdings Inc., Harmony Biosciences Holdings, Inc., Instil Bio, Inc., and IO Biotech, Inc. Mr. Nielsen in the past has served as a member of the board of Akebia Therapeutics, Inc., Apollo Endosurgery, Inc., Crinetics Pharmaceuticals, Inc., and Merus, N.V., each of which is a publicly-traded company. He is currently a member of the board of directors of a number of private companies. Mr. Nielsen received an 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.

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 joining 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 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.

Christy J. Oliger has served as a member of the Board since April 2021. Ms. Oliger brings nearly 30 years of experience in the biopharmaceutical industry, serving in various commercial roles at Genentech, Inc. and Roche Holding AG from January 2000 until her retirement in July 2020, and at Schering-Plough Corporation from September 1992 until December 1999. Most recently, Ms. Oliger served as Senior Vice President, Oncology Business Unit Head, at Genentech, Inc. During her tenure at Genentech, Inc., Ms. Oliger held senior leadership roles across a variety of therapeutic areas, including oncology, neurology, rare diseases, respiratory, dermatology and immunology in hospital and specialty settings. She currently serves as a member of the board of directors of Karyopharm Therapeutics Inc., Replimune Group Inc., and Sierra Oncology, Inc., each of which is a publicly traded pharmaceutical company. Ms. Oliger received a B.A. in Economics from the University of California at Santa Barbara.

Shamim Ruff has served as a member of the Board since April 2021. Ms. Ruff brings over 30 years of experience in the biopharmaceutical industry, serving in various regulatory roles. Ms. Ruff has served as Chief Regulatory Affairs Officer and Senior Vice President, Head of Quality Assurance, at Stoke Therapeutics, Inc. since December 2018. From January 2013 to May 2018, Ms. Ruff served in various roles at Sarepta Therapeutics, Inc., including as Chief Regulatory Officer and Senior Vice President, Quality, from December 2015 to May 2018. Prior to her time at Sarepta Therapeutics, Inc, Ms. Ruff served in increasing senior regulatory roles at Sanofi, Amgen Inc., Abbott Laboratories, and AstraZeneca PLC. Ms. Ruff holds a bachelor's degree in Chemistry and Biology from the University of Leicester, UK, and a master's degree in Analytical Chemistry from the University of Loughborough, UK. Additionally, she is a Chartered Chemist and Member of the Royal Society of Chemistry.

Corporate Information

We were formed in Delaware in 2002 and maintain our principal corporate offices at 5320 Legacy Dr., Plano, Texas 75024. 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 Securities Exchange Act of 1934 (Exchange Act) as soon as reasonably practicable after we electronically file such material with, or furnish it to, the United States Securities and Exchange Commission (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 "Cautionary Note Regarding Forward-Looking Statements" and "Risk Factor Summary" 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, omaveloxolone and bardoxolone, 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 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 Kyowa Kirin, 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, 2021, 2020, and 2019, our net loss was $297.4 million, $247.8 million, and $290.2 million, respectively. As of December 31, 2021, we had an accumulated deficit of $1,255.6 million and capital resources consisting of cash and cash equivalents of $590.3 million. Despite the potential to receive development cost sharing, milestone, and other payments from Kyowa Kirin, we anticipate that we will continue to incur losses for the foreseeable future, and we anticipate these losses will increase as we continue our development of, seek regulatory approval for, and potentially commercialize 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. 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 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.

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, manufacturing and supplying products and product candidates for ourselves and our collaborators, and hiring personnel to prepare for commercialization of our product candidates. 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, royalty sales, collaboration arrangements, 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 and 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.

In connection with the Development Agreement, upon approval of bardoxolone in the United States or certain specified European countries, we agreed to make royalty payments on our world-wide net sales, excluding net sales made by Kyowa Kirin, to BXLS. We granted BXLS a security interest in substantially all of our assets. The Development Agreement also contains negative covenants that may restrict our ability to pursue our business strategies, including, among other things, to obtain additional financing or reasonable terms for additional financing.

In June 2020, we entered into the Development Agreement pursuant to which BXLS paid us a $300 million development payment in exchange for our agreement to make payments to BXLS equal to various single-digit

percentages of world-wide net sales of bardoxolone by us and any of our licensees, excluding net sales made by Kyowa Kirin. Subject to approval of bardoxolone for the treatment of CKD caused by Alport syndrome or ADPKD in the United States or certain specified European countries, and BXLS not having achieved a certain internal rate of return on its investment, we are obligated to make certain minimum cumulative payment amounts in 2025 through 2033, but only until BXLS has achieved the internal rate of return target, after which the minimum payment obligations no longer apply.

BXLS was granted a security interest in substantially all of our assets. The Development Agreement also contains negative covenants that restrict us from (a) granting liens on certain of our assets, including liens on the bardoxolone intellectual property collateral, except for certain permitted liens, (b) incurring indebtedness, except for certain permitted indebtedness which will include certain secured indebtedness, and (c) entering into development or commercialization license transactions with respect to bardoxolone in the United States, France, Germany, Italy, Spain, or the United Kingdom, except that we are permitted to enter into any such development or commercialization license transactions freely with certain pharmaceutical companies, including those companies that have annual sales in excess of an agreed threshold. These restrictions could inhibit our ability to pursue our business strategies and may limit our ability to, among other things, incur indebtedness, encumber assets, dispose 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. If we default under our obligations under the Development Agreement, we will be obligated to pay BXLS liquidated damage payments in excess of the development payment paid by BXLS.

Risks Related to the Development and Commercialization of Our Product Candidates

We are substantially dependent on the success of our lead product candidates, omaveloxolone and bardoxolone. We have received a CRL from the FDA with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome.

To date, we have invested a substantial portion of our efforts and financial resources in the research and development of omaveloxolone and bardoxolone, which are currently our lead product candidates. These are our lead product candidates that have advanced into registrational clinical development, but there can be no assurance that further clinical trials will not be required, or that regulatory delays will not be incurred. It could be years before the trials required for their approval are completed, if ever. We recently received a CRL from the FDA with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome. We will continue to work with the FDA to confirm our next steps on our Alport syndrome program. There is a high degree of risk that other regulatory agencies, such as the EMA, may be influenced by the CRL from the FDA and the negative vote at the Advisory Committee meeting for bardoxolone in patients with CKD caused by Alport syndrome. However, in any event, the development program for bardoxolone has been substantially delayed, and there is a high degree of risk that bardoxolone will not be approved in the future for any indication in the United States or elsewhere. Furthermore, these negative outcomes regarding bardoxolone may cause the FDA and regulators in other jurisdictions, such as the EMA, to be skeptical in their future review of other drug products which we develop and for which we submit for approval. 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 commercialization of omaveloxolone and bardoxolone. We may need to complete additional or larger and more extensive controlled clinical trials to validate the results observed in clinical trials to date to continue further development and seek regulatory approval of these product candidates. We have announced positive results from our MOXIe trial of omaveloxolone in patients with FA. We began submitting an NDA for

omaveloxolone in patients with FA in January 2022 and plan to complete the submission by the end of the first quarter of 2022. However, there can be no assurance that the NDA will be accepted by the FDA, or, if accepted, that the NDA will be approved by the FDA. Furthermore, there is a risk that the FDA will not agree that the data submitted in the NDA support full approval of the NDA; in this event, the FDA could determine that the data support accelerated approval under Subpart H or do not support any type of approval. An accelerated approval would require that we agree to conduct a post-approval confirmatory clinical trial. 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 omaveloxolone and bardoxolone will depend on a number of factors, many of which are beyond our control.

The clinical and commercial success of omaveloxolone and bardoxolone 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 omaveloxolone and bardoxolone, 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 the FDA or other regulatory authorities will accept NDAs for approval of our product candidates;
- 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 additional, 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, United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), PMDA, and Australian Therapeutic Goods Administration (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, MHRA, 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 or manufacturers 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 may not be indicative of the results that may be obtained in larger registrational clinical trials, which may delay or prevent obtaining regulatory approval.

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Success in preclinical studies and early clinical trials may not be predictive of results in larger clinical trials, and successful results from early or small clinical trials may not be replicated or show as favorable an outcome in larger clinical trials, even if successful. For example, we have previously endeavored to develop bardoxolone for the treatment of T2D CKD. While bardoxolone 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 Phase 2 clinical programs with omaveloxolone and bardoxolone 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 omaveloxolone and bardoxolone 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 AEs, including possible drug-drug interactions, which may negatively affect their safety profile.

We initiated the rolling submission of an NDA for omaveloxolone in patients with FA in January 2022 and plan to complete the submission by the end of the first quarter of 2022. There can be no assurance that the FDA will accept the NDA for filing or that the NDA will be approved. The FDA had originally indicated that we must conduct another clinical trial of omaveloxolone in patients with FA prior to seeking approval, prior to indicating thereafter that an NDA filing would be an acceptable next step in the regulatory process. However, there can be no assurance that the FDA will not determine that another clinical trial must be conducted. Furthermore, the FDA could determine that an accelerated approval regulatory pathway for omaveloxolone in patients with FA is the most appropriate approval pathway, which will require us to conduct another clinical trial as a post-marketing requirement. The results of this trial may not be sufficient to support or maintain approval of omaveloxolone for treatment of patients with FA.

Preliminary discussions with the EMA indicated that additional nonclinical or clinical studies may be required in advance of a MAA for FA in the EU. 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 any potential advantages that we believe bardoxolone may have for our current clinical programs will be substantiated by each of 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 that our previous data in our Phase 2 and Phase 3 trials and our trials in T2D CKD may predict effects in our registrational trial in patients with CKD caused by ADPKD or other forms of CKD. Additionally, we have discussed CKD caused by Alport syndrome trial data with the FDA, EMA and the PMDA and ADPKD trial data with the FDA. Discussions with the FDA of the two-year results of our CARDINAL Phase 3 trial in patients with CKD caused by Alport syndrome will continue after our receipt in February 2022 of a CRL from the FDA in connection with the FDA's review of the NDA for bardoxolone in patients with CKD caused by Alport syndrome. The EMA is reviewing our MAA for CKD caused by Alport syndrome in the EU. 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.

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, or after achieving positive

results in pivotal trials, and we have had, and may face, similar setbacks. In addition, the patient populations under investigation with omaveloxolone and bardoxolone have many co-morbidities that may cause severe illness or death, which may be attributed to omaveloxolone and bardoxolone in a manner that negatively affects the safety profile of our product candidate. If the results of our ongoing or future clinical trials for omaveloxolone and bardoxolone 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 due to a number of factors, including failure to enroll sufficient number of patients in our clinical trials in a timely manner, or these studies may not be completed at all.

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

- reach timely agreement on acceptable terms with prospective contract research organization (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.

We experienced trial enrollment delays in our Phase 3 ADPKD trial, and a termination of a Phase 3 trial in pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH), due to the COVID-19 pandemic.

We recently have experienced and may continue to experience slowing of patient enrollment or higher patient discontinuations in our ongoing Phase 3 FALCON study and long-term extension EAGLE study, due to the safety concerns raised during the FDA Advisory Committee Meeting and based on the CRL received for our NDA for bardoxolone for the treatment of patients with CKD caused by Alport Syndrome.

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.

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 bardoxolone 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 omaveloxolone and bardoxolone due to unforeseen factors beyond our control. Most 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.

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 AEs and SAEs.

Clinical trials of our product candidates may not uncover all possible AEs 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 omaveloxolone and bardoxolone 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.

If we, our collaborators, or our third-party manufacturers cannot manufacture our product candidates or products at sufficient yields and quantities, 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 quality, 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 contract manufacturing organizations (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, adverse geo-political events, pandemics, 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 one registrational trial and have completed pivotal trials in patients with Alport syndrome caused by CKD and FA, specific labeling language has not yet been discussed with regulatory authorities. For both omaveloxolone and bardoxolone, 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.

Other than the recent submission of an NDA with the FDA and an MAA with the EMA for bardoxolone in patients with CKD caused by Alport syndrome, and our current rolling submission of an NDA with the FDA for omaveloxolone in patients with FA, we have never submitted an NDA, MAA, or other marketing applications and may be unable to do so efficiently or at all for omaveloxolone, bardoxolone, 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 trials for omaveloxolone and bardoxolone, and we may need to conduct additional Phase 2 trials before initiating additional Phase 3 clinical trials with omaveloxolone and bardoxolone. The conduct of Phase 3 trials and the submission of an NDA, MAA, or other marketing application is a complicated process. We have limited experience in preparing, submitting, and prosecuting regulatory filings, and, other than the recent submission of an NDA with the FDA and an MAA with the EMA for bardoxolone in patients with CKD caused by Alport syndrome, and our current rolling submission of an NDA with the FDA for omaveloxolone in patients with FA, we 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 or our collaborators 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 bardoxolone, we are currently dependent in certain territories on the commercialization capabilities of our collaborator, Kyowa Kirin. If Kyowa Kirin 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 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, develop, obtain regulatory approval of, and commercialize drugs before we do, or develop drugs that are safer, more effective, or less costly.

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.

For our development program in FA, if omaveloxolone is approved and launched commercially it may face market competition. Although there are no currently approved therapies for this condition, there are several competitors who purport to be developing products in this space.

We are aware of only one program, vatiquinone from PTC Therapeutics Inc., in Phase 3 stage of development. Additionally, competitor product candidates MIN-102 from Minoryx Therapeutics, MIB-626 from

MetroBiotech, LLC, JOTROL (JOT-101) from Jupiter Neurosciences, Inc., and elamipretide from Stealth BioTherapeutics Corp. are in Phase 2 clinical development for FA. We are aware of only one program, CTI-1601 from Larimar Therapeutics, Inc., in Phase 1 clinical development. In addition, Biohaven Pharmaceutical Holding Company Ltd.'s Troriluzole is in Phase 3 development for the treatment of patients with SCA. Biohaven has expressed an intention to explore the development of Troriluzole for other ataxias, which may include FA pending the outcome of the ongoing clinical studies in SCA. If approved and launched commercially, omaveloxolone may face competition from these product candidates. Some of these product candidates may enter the market prior to omaveloxolone, and some of these product candidates could limit the market or level of reimbursement available for omaveloxolone if it is commercialized.

RTA 901 may face similar competitive risks as omaveloxolone. We are aware of other HSP90 inhibitors being developed for neurological indications, including arimoclomol and PU-AD by Orphazyme AS and Samus Therapeutics Inc, respectively. If approved and launched commercially, RTA 901 may face competition by these product candidates. Some of these product candidates may enter the market prior to RTA 901 and some of these product candidates could limit the market or level of reimbursement available for RTA 901 if they are commercialized. We plan to develop RTA 901 for patients with DPNP. Currently, there are four drugs and two devices that are approved for treatment of DPNP in the United States including Lyrica®, Cymbalta®, Nucynta®, an opioid, and Qutenza®, a capsaicin patch applied once every three months. Intellis™ and Vanta™ by Medtronic Plc. and Senza® by Nevro Corp. are two implantable spinal cord stimulation systems approved for treatment of chronic pain associated with DPN. Tarlige® by Daiichi Sankyo Company Ltd. is a gabapentinoid that is approved for DPNP in Japan. In addition, current treatment guidelines from the American Diabetes Association and the American Academy of Neurology also recommend the off-label use of gabapentin and tricyclic antidepressants.

We are aware of multiple drugs in advanced clinical development for DPNP including Engenesis (VM202) by Helixmith Co. in Phase 3, HSK-16149 by Sichuan Haisco Pharmaceutical Co. in Phase 2/3 (China), and 16 additional programs in Phase 2 clinical trials including LX9211 by Lexicon Pharmaceuticals Inc., MEDI7352 by AstraZeneca Plc, Elismetrep (MT8554) by Mitsubishi Tanabe Pharma (Europe), PGDN-20WS by Pure Green Pharmaceuticals, YJ-001 by Zhejiang Pharmaceutical (China), BAY2395840 by Bayer, LY3016859, LY3526318, and LY3556050 by Eli Lilly and Company, ETX-810 by Eliem Therapeutics Inc., Pirenzepine (WST-057) by WinSanTor Inc., NRD135S.E1 by Novaremed AG, NYX-2925 by Aptinyx Inc., Ricolinostat by Regenacy Pharmaceuticals, GRC 17536 by Glenmark Pharmaceuticals Ltd., and CNTX-6016 by Centrexion Therapeutics. AT-001 by Applied Therapeutics Inc. is also being investigated for DPN in a sub-study of a Phase 3 program in Diabetic Cardiomyopathy.

If bardoxolone is approved and launched commercially for patients with CKD caused by Alport syndrome, it may face market competition. Currently, there are no approved therapies for CKD caused by Alport syndrome, and patients are commonly treated off-label with ACE inhibitors or ARBs. We are aware of at least three therapies for the treatment of Alport syndrome currently in Phase 2 of clinical development including an injectable product candidate, lademirsen (RG-012) from Sanofi S.A, atrasentan in patients with one of several forms of CKD including Alport syndrome from Chinook Therapeutics Inc., and sparsentan in pediatric patients with proteinuric glomerular diseases including Alport syndrome from Travere Therapeutics Inc.

If bardoxolone is approved and launched commercially for patients with ADPKD, it would launch into a landscape with at least one approved product and multiple products in clinical development. In 2018, Otsuka Pharmaceuticals Co., Ltd. received approval by the FDA to market JYNARQUE® to slow kidney function decline in adults at risk of rapidly progressing ADPKD. We are aware of one program in Phase 3 stage of development which is Palladio Biosciences' study of lixivaptan for treating patients with ADPKD. Other products under clinical development for ADPKD include GLPG2737 by Galapagos NV in Phase 2, Tesevatinib by Kadmon, a Sanofi company, in Phase 2, Xrx-008 by Xortx Therapeutics Inc. in Phase 2, and AL01211 by Acelink Therapeutics in Phase 1.

We are also aware of multiple drugs that are either approved or in clinical development programs in T2D CKD, hypertensive, and other forms of CKD. These include the SGLT2 inhibitors, Jardiance® and Farxiga® developed by Boehringer Ingelheim and Eli Lilly and Company, and by AstraZeneca, respectively which are in development for patients with CKD with and without T2D. In April 2021, Farxiga® received FDA approval to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. AstraZeneca has not said whether any patients with CKD caused by Alport syndrome were enrolled in the DAPA-CKD trial; however, the trial did enroll patients with IgAN and other forms of glomerulonephritis. The DAPA-CKD study excluded patients with ADPKD and T1D CKD. Farxiga® may be used to treat patients with CKD due to rare and common forms of CKD including Alport syndrome. Additionally, Jardiance® is currently being tested in EMPA-KIDNEY, a Phase 3 trial in patients with various forms of CKD, excluding ADPKD and T1D CKD. Results from the EMPA-KIDNEY trial are expected in the fourth quarter of 2022. Additionally, Bayer Healthcare, in November 2021, announced the initiation of the FIONA Phase 3 study to investigate finerenone for the treatment of pediatric patients with CKD and severely increased proteinuria. The study may enroll patients with Alport syndrome or ADPKD. Kerendia® (finerenone) received FDA approval in July 2021 to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with T2D CKD.

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 product development, including 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 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.

Failure to gain market acceptance of our product candidates, if approved, may adversely affect our business and financial condition.

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 have been 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

We may seek collaborations with third parties, in addition to our collaboration with Kyowa Kirin, with development, regulatory, and commercial expertise for our current and future product candidates. If we fail to maintain or establish such collaborations, or such collaborations are not successful, it may disrupt our business or we may not be able to capitalize on the development and commercialization of our current and future product candidates.

We have entered into the Kyowa Kirin Agreement with respect to the development and commercialization by Kyowa Kirin of bardoxolone for renal, cardiovascular, diabetes, and certain related metabolic indications in certain territories in Asia. If Kyowa Kirin were to elect not to participate in the development and commercialization of all of our bardoxolone indications or to determine that their collaboration with us is no longer a strategic priority, were unable to perform their obligations under the Kyowa Kirin Agreement, or if a successor were to reduce their level of commitment to their collaboration with us, our ability to develop and commercialize our product candidates could suffer. In addition, our Kyowa Kirin collaboration is, and any future collaboration may be, exclusive and preclude us from entering into additional collaboration agreements with other parties in the area or field of exclusivity. Also, when we reacquired our development, manufacturing, and commercialization rights to bardoxolone, omaveloxolone, and other Nrf2 activators from AbbVie in October 2019, we agreed not to enter into licensing agreements with respect to bardoxolone in AbbVie's former territory for a period of time, with certain exceptions. Kyowa Kirin has 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.

Our collaboration with Kyowa Kirin and potential other third parties for bardoxolone requires cooperation between the parties, and failure to do so can negatively affect the development and commercialization of certain of our product candidates. Multi-party decision-making is complex and involves significant time and effort. There can be no assurance that we and our collaborators will cooperate or reach consensus. Any disputes or lack of cooperation with our collaborators may negatively affect the timing or success of our planned clinical trials or commercialization plans.

If we fail to establish and maintain, or are prohibited from establishing, 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.

We rely on third parties to conduct 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 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, so we must rely on collaborators and outside vendors to manufacture supplies and process our product candidates. Outside of scale-up and validation activities, we have not yet routinely caused our product candidates to be manufactured or processed at a commercial scale and/or frequency 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. Similar actions may be taken by foreign regulatory authorities.

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 foreign regulatory authorities, 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 or foreign regulatory authorities could place significant restrictions on our company until deficiencies are remedied to their 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.

In most cases, we do not have long-term agreements with suppliers of drug substance, a drug product intermediate, or final drug product candidates. Additionally, we do not have long-term agreements with suppliers of certain components of our product candidates. To date, we primarily 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 long-term 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, and may not have, 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 could 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. Omaveloxolone, RTA 901, and bardoxolone are protected by granted United States and foreign patents claiming compositions of matter and methods of use. The RTA 1700 class of compounds 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, which can result in uncertainties. For example, 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 that we hold with respect to our product candidates is threatened, then 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 subsequently implemented a "first inventor to file" system under the Leahy-Smith America Invents Act (AIA), effective March 16, 2013. Effects of this system and other elements of the AIA are evolving, especially as the federal courts develop a body of case law around the statutory provisions of the AIA. Creating further uncertainty, such provisions include procedures for challenging issued patents and pending patent applications. We may become involved in opposition, *inter partes* review (IPR), or interference proceedings challenging our patents and patent applications or the patents and patent applications of others; the outcomes of any such proceedings are highly uncertain. For example, an unfavorable outcome 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, IPR, 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, IPR, 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 a material 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 global market.

The USPTO and foreign patent offices require maintenance fees and payments as well as continued compliance with 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. Non-compliance 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 a material 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 challenges. 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 USPTO in an IPR. If an IPR is instituted by the Patent Trial and Appeal Board (PTAB) at the USPTO, a court could stay the litigation pending a decision by the USPTO 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, which we have experienced, we will 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 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, MD Anderson, and the University of Kansas, which include descriptions of the termination provisions of these agreements. We currently have a dispute with MD Anderson and Dartmouth regarding whether, under the 2012 amendment to the 2004 license agreement, we are obligated to pay them a low single-digit royalty on sales of products containing bardoxolone. If the dispute is resolved in favor of MD Anderson and Dartmouth and a product containing bardoxolone is approved for sale, then we will incur additional royalty, which would have a negative impact on our operating results. 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. Even if we believe our completed, current, or planned clinical trials are successful, regulatory authorities may not agree that they provide adequate data on safety or efficacy or may require that we conduct confirmatory clinical trials either prior to approval or after market approval.

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. With the exception of an NDA filed with the FDA and an MAA filed with the EMA for bardoxolone in patients with CKD caused by Alport syndrome, and our current rolling submission of an NDA with the FDA for omaveloxolone in patients with FA, we have not submitted an NDA or 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 recent receipt of a CRL from the FDA with respect to the NDA for bardoxolone in patients with CKD caused by Alport syndrome puts our entire bardoxolone platform at a high degree of risk; there can be no assurance that bardoxolone will be approved for any indication.

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;
- internal FDA delays in the scheduling and conducting of on-site regulatory inspections due to pandemic-related circumstances (e.g., travel restrictions) or other federal, state, or local restrictions;
- 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, clinical, nonclinical, or CMC 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 completed, current, or planned clinical trials are successful, regulatory authorities may not agree that our completed clinical trials provide adequate data on safety or efficacy, which was the case in connection with the FDA's issuance of a CRL regarding our NDA for bardoxolone in patients with CKD caused by Alport syndrome. In addition, the FDA originally concluded that the results of our MOXIe Phase 2 clinical trial, while positive, were not sufficient to support approval of omaveloxolone for the treatment of patients with FA. Consequently, the FDA advised us that we needed to conduct a second clinical trial prior to submitting an NDA, prior to subsequently agreeing that we could proceed with the filing of an NDA for omaveloxolone in patients with FA. Certain of our Phase 3 clinical trials have been or may be 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 five in 10,000 persons in the EU 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 EC, including protocol assistance, access to the centralized authorization procedure, ten 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 bardoxolone for the treatment of CKD caused by Alport syndrome and ADPKD. We have also received orphan drug designation in Europe for bardoxolone for the treatment of Alport syndrome. We have also received orphan drug designation by the FDA and in Europe for omaveloxolone 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.

If our product candidates obtain marketing approval, we will be subject to more extensive healthcare laws, regulation, and enforcement, including United States healthcare reform and other changes, 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, physician assistants, certain types of advanced practice nurses, and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- state law equivalents of each of the above federal laws, such as the federal Anti-Kickback Statute and false claims laws, that may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or which otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information 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 and genetic 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, expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program, imposed a significant annual, nondeductible fee on companies that manufacture or import certain branded prescription drug products, and enacted substantial provisions affecting compliance, which may affect our business practices with healthcare practitioners. 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 and, due to subsequent legislative amendments to the statute will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. The Medicare reductions phase back in starting with a 1% reduction in effect from April 1, 2022 through June 30, 2022 before increasing to the full 2% reduction. Additionally, in January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several types of health care providers.

In addition, the Biden 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. For example, on September 9, 2021, the Biden administration published a wide-ranging list of policy proposals, most of which would need to be carried out by Congress, to reduce drug prices and drug payment. The HHS plan includes, among other reform measures, proposals to lower prescription drug prices, including by allowing Medicare to negotiate prices and disincentivizing price increases, and to support market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase price transparency. Many similar proposals, including the plans to give Medicare Part D authority to negotiate drug prices, require drug manufacturers to pay rebates on drugs whose prices increase greater than the rate of inflation, and cap out-of-pocket costs, have already been included in policy statements and legislation currently being considered by Congress. It is unclear to what extent these and other statutory, regulatory, and administrative initiatives will be enacted and implemented, and to what extent these or any future legislation or regulations by the Biden administration will have on our business or future product candidates. In addition, former President Trump and President Biden both issued Executive Orders intended to favor government procurement from domestic manufacturers. 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. On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the PPACA is unconstitutional in its entirety because the individual mandate was repealed by Congress. Thus, the PPACA will remain in effect in its current form. 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 U.S. 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, fines, penalties, or 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.

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, public health crises such as pandemics or epidemics, or systems failure including cybersecurity breaches; and
- compliance with evolving and expansive international data privacy laws, such as the EU GDPR.

For example, the U.K. has voluntarily departed from the EU, commonly referred to as "Brexit." 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.

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 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 retain senior management and key personnel, in particular our Chief Executive Officer, Chief Operating Officer and Chief Financial Officer, and Chief Innovation Officer, we may be unable to successfully develop our product candidates, conduct our clinical trials, and commercialize our product candidates.

We are highly dependent on our Chief Executive Officer, Warren Huff, our Chief Operating Officer and Chief Financial Officer, Manmeet Soni, and our Chief Innovation Officer, Colin Meyer. The loss of the services of Mr. Huff, Mr. Soni, 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.

Risks Related to Our Class A Common Stock

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 23, 2022, our executive officers and directors, together with their respective affiliates, collectively owned shares representing approximately 98.3% of our total Class B common stock, including shares subject to outstanding options that are exercisable within 60 days of such date, and approximately 13.6% of our total Class A common stock, including shares subject to outstanding options that

are exercisable and shares that will be settled upon the vesting of RSUs within 60 days of such date. 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 46.8% of the voting power of our outstanding capital stock.

Accordingly, these stockholders will be able to exert effective 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 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.

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. 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 net operating losses (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.

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

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.

In November 2019, we closed a follow-on underwritten public offering of 2,760,000 shares of our Class A common stock at $183.00 per share. In December 2020, we closed a follow-on underwritten public offering of 2,000,000 shares of our Class A common stock at $140.85 per share. Since our initial public offering (IPO) in May 2016 through February 23, 2022, our closing stock price has reached a low of $13.07 and a high of $247.74. Between January 1, 2021, and December 31, 2021, the closing price of shares of our Class A common stock declined by $94.92 per share.

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, which we experienced in December 2021 in connection with the negative vote by the FDA's advisory committee on bardoxolone in patients with chronic kidney disease caused by Alport syndrome;
- 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, including about merger or acquisition activity;
- 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;
- public health epidemics;
- 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, particularly companies in the life sciences industry such as us. 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. This could have a material, adverse effect on our business, financial condition and results of operations. See Note 15, *Commitments and Contingencies-Bardoxolone Securities Litigation* of Notes to Consolidated Financial Statements for a description of our securities 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.

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 23, 2022, we have 4,919,249 shares of Class B common stock outstanding representing 13.5% 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 4,423,719 shares of Class B common stock and 1,898,576 shares of Class A common stock as of February 23, 2022. Once we register these shares, they can be freely sold in the public market.

In addition, as of February 23, 2022, there are approximately 5,623,581 and 1,280,306 shares subject to outstanding options to purchase, and RSUs representing, shares of Class B and Class A common stock,

respectively, 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 Second Amended and Restated Long Term Incentive Plan (the LTIP 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.

General Risk Factors

If we fail to comply with United States and certain foreign government 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 United States federal, state, and local laws and foreign government 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.

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, manufacturers, suppliers, and other third parties, including, but not limited to, software as a service (SaaS) providers 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 issues to our clinical data, or disruption of the manufacturing process, we could incur liability, remediation costs, and increased cybersecurity protection costs, 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.

We are increasingly dependent upon technology systems and data to operate our business. Our ability to effectively manage our business depends on the security, reliability, and availability of our technology systems and data. Cyber-attacks are increasing in their frequency, sophistication, and intensity, while also becoming increasingly difficult to detect. They are often carried out by motivated, well-resourced, skilled, and persistent actors, including nation states, organized crime groups, "hacktivists", and employees or contractors acting with malicious intent. Cyber-attacks could include the deployment of harmful malware and key loggers, ransomware, a denial-of-service attack, a malicious website, the use of social engineering, impersonation, telephony and/or e-mail spear phishing, and other means to compromise the confidentiality, integrity, and availability of our technology systems, data, and other corporate information assets. E-mail fraud, including various types of business email compromise, may cause payments or information to be transmitted to unintended recipients. Cyber-attacks could also include supply chain attacks, which could cause delays in the manufacturing of our products or products produced for contract manufacturing. While we have not experienced a system failure, accident, cyber-attack or security breach that has resulted in a material loss of assets or operational capabilities to date, there can be no assurance that our efforts will prevent additional future cyber-attacks and/or security breaches in our systems that could materially and adversely affect our business, assets, or operations, even as we continue to strengthen the security posture of our infrastructure, systems, and corporate cybersecurity training. In addition, our liability insurance is not sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related incidents.

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. Despite having mechanisms in place to ensure system redundancy, resiliency, and data and system backups, 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 that we have in place, including those of our third-party SaaS service providers, 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, catastrophic events, such as power loss, natural disasters, terrorism, public health crises such as pandemics or epidemics, and similar unforeseen events beyond our control, could adversely affect our employees and our clinical study operations, including forcing us to stop a trial and start over. Additionally, parties in our supply chain may be operating from single sites, increasing their vulnerability to such events. If such an event were to affect our employees, our clinical study operations, or our supply chain, it could have a material adverse effect on our business, results of operations, and financial condition.

The COVID-19 outbreak has caused and could continue to cause disruptions in our business and operating results, including our clinical development activities.

The pandemic resulting from the global outbreak of COVID-19 has had and could continue to have a negative impact on our business and operating results. Although no longer in place, we implemented work-from-home measures and additional safety protocols to protect employees and the broader community and to ensure business continuity in the early stage of the pandemic. We limited on-site staff to only those required to execute their job responsibilities, including limiting in-person meetings and travel. We may need to reinstate these measures if there are additional major outbreaks of COVID-19 in the future.

We conduct clinical studies in many countries around the world that are being impacted by the COVID-19 pandemic. Regulatory agencies, governments, and health care providers have implemented restrictive measures, including but not limited to "shelter-in-place" orders, travel restrictions, and business closures, designed to reduce potential exposure to the virus, particularly for patients at increased risk of severe illness. For each clinical development program, we are working with health care providers to implement changes that mitigate risk to patients; comply with regulatory, institutional, and government guidance; and maintain the integrity of our ongoing clinical studies. These concerns led us to pause enrollment in our FALCON trial, which has subsequently resumed enrollment, to stop our CATALYST and RANGER trials, and to adapt procedures for our remaining ongoing trials to address restrictions on travel and concerns for patient safety. For example, we implemented the use of at-home visits as an alternative to in-clinic visits when necessary to collect blood draws and to assess patient safety and arranged for home delivery of the study drug to patients.

As the global outbreak of COVID-19 continues to rapidly evolve, the duration and ultimate impact of COVID-19 on our business is highly uncertain and subject to change. At this time, we do not believe that the COVID-19 pandemic will have a significant impact on our ability to conduct our operations. Should the COVID-19 outbreak cause further or extended disruptions at our clinical trial sites or safety concerns regarding our patients, our clinical development activities could be more significantly affected. In addition, our ability to obtain raw materials, supplies, and component parts necessary to manufacture clinical supplies, our ability to deliver clinical drug to our patients in our clinical trials, and our ability to establish commercial supply capacity may be negatively impacted. To date, the COVID-19 outbreak has neither impeded our CMOs' ability to conduct their business, nor our ability to execute our third-party manufacturing strategy, but it has modified the way that we interact with and provide oversight to our third-party vendors. On-site visits for critical activities are conducted when allowable by vendor procedures, and local, state, federal, and international laws, as well as routine virtual oversight through various technology platforms. In some instances, we have had to conduct vendor audits virtually, which could result in our inability to identify material issues at a vendor's site. Since the COVID-19 outbreak is fluid, there is no guarantee that our manufacturing strategy will not be negatively impacted by how the outbreak evolves over time. The outbreak could cause health concerns with our personnel, including our executives, which could lead to reductions in the efficiency of our operations. The outbreak has caused and could continue to cause significant disruption of global financial markets, which may reduce our ability to access capital, which would negatively affect our liquidity. While we will continue to develop plans to help mitigate the potential negative impact of a continued or expanded COVID-19 outbreak, and any future pandemic, on our business and operating results, our efforts may not prevent our business from being adversely affected.

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

As a public company, we incur significant legal, insurance, accounting, and other expenses. The Sarbanes-Oxley Act of 2002 (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.

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.

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 principal executive offices are located in Plano, Texas, where we lease approximately 122,000 square feet of office space. This lease expires in August 2022. We also lease approximately 34,890 square feet of additional office and laboratory space in Irving, Texas. This lease expires in October 2024, with an option to extend for a fixed twelve-month period. In October 2019, we entered into a lease agreement with TC Legacy Land Venture, LLC (the 2019 Lease Agreement), to lease a single-tenant and build-to-suit building of approximately 327,400 square feet of office and laboratory space located in Plano, Texas with an initial lease term of 16 years beginning in June 2022 with an option to renew up to ten years. However, we have paused our buildout of the build-to-suit building and are seeking tenants for some or all of that space. 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.

For a discussion of material pending legal proceedings, please read Note 15, *Commitments and Contingencies – Bardoxolone Securities Litigation*, of Notes to Consolidated Financial Statements included in this Annual Report on Form 10-K, which is incorporated into this item by reference.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our 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.

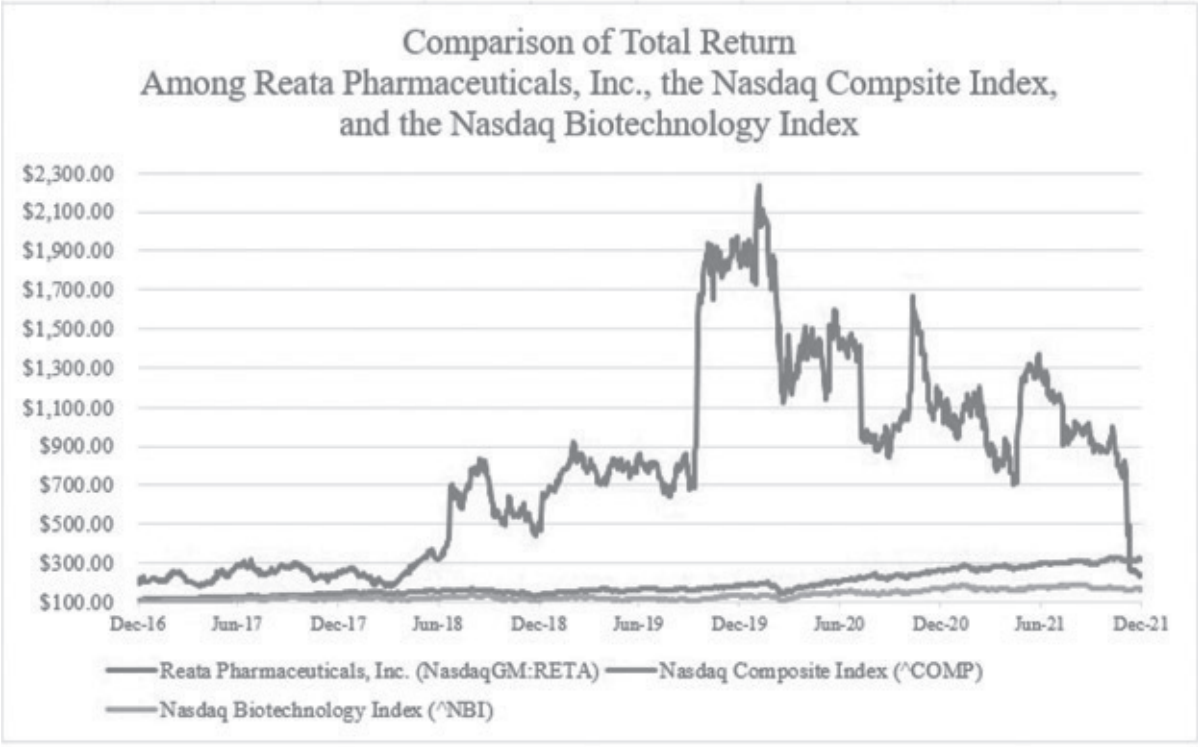
Stockholders

As of February 23, 2022, there were 380 and 85 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 December 31, 2016, through December 31, 2021, to two indices: the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes an initial investment of $100 on December 31, 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 (Securities Act), or the Exchange Act,

whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



		December 31					
$100 investment in stock or index	**Ticker**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Reata Pharmaceuticals, Inc.	RETA	$100.00	$256.06	$507.23	$1,848.37	$1,117.72	$238.43
Nasdaq Composite Index	^IXIC	$100.00	$141.03	$135.56	$ 183.31	$ 263.30	$319.62
Nasdaq Biotechnology Index	^NBI	$100.00	$116.67	$105.79	$ 131.61	$ 165.41	$164.36

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.

Issuer's Purchases of Equity Securities

None.

Item 6. [Reserved.]

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 on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, 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 "Cautionary 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. Our discussion and analyses below are focused on our 2021, 2020, and 2019 financial results, including comparisons of our year-over-year performance between these years.

Overview

We are a clinical-stage biopharmaceutical company focused on identifying, developing, and commercializing innovative therapies that change patients' lives for the better. We concentrate on small-molecule therapeutics with novel mechanisms of action for the treatment of severe, life-threatening diseases with few or no approved therapies. Our lead programs are omaveloxolone in FA and bardoxolone in rare forms of CKD. Both of our lead product candidates activate the transcription factor Nrf2 to normalize mitochondrial function, restore redox balance, and resolve inflammation. Because mitochondrial dysfunction, oxidative stress, and inflammation are features of many diseases, we believe omaveloxolone, bardoxolone, and our next-generation Nrf2 activators have many potential clinical applications. We possess exclusive, worldwide rights to develop, manufacture, and commercialize omaveloxolone, bardoxolone, and our next-generation Nrf2 activators, excluding certain Asian markets for bardoxolone in certain indications, which are licensed to Kyowa Kirin. In addition, we are developing RTA 901, the lead product candidate from our Hsp90 modulator program, in neurological indications. We are the exclusive licensee of RTA 901 and have worldwide commercial rights.

Collaborations Update

In October 2019, we and AbbVie entered into the Reacquisition Agreement, under which we reacquired the development, manufacturing, and commercialization rights provided in the AbbVie License Agreement and the Collaboration Agreement. Under the Reacquisition Agreement, the AbbVie License Agreement and the Collaboration Agreement were amended, resulting in AbbVie granting its exclusive sublicenses back to us, such that we reacquired the worldwide rights to bardoxolone, excluding certain Asian countries previously licensed to Kyowa Kirin, and the worldwide rights to omaveloxolone and certain next-generation Nrf2 activators. By reacquiring our rights, we were relieved from our obligations under the AbbVie License Agreement and the Collaboration Agreement.

In exchange for such rights, we agreed to pay AbbVie $330.0 million, all of which has subsequently been paid. Additionally, we will pay AbbVie an escalating, low single-digit royalty on worldwide net sales, on a product-by-product basis, of omaveloxolone and certain next-generation Nrf2 activators.

As a result of the $330.0 million having been paid to AbbVie, the licenses granted to AbbVie and the sublicenses granted to us with respect to omaveloxolone and bardoxolone and certain next-generation Nrf2 activators have terminated, with all rights reverting to us.

Liability Related to Sale of Future Royalties

On June 24, 2020, we closed on the Development Agreement with an affiliate of BXLS, which provided funding for the development and commercialization of bardoxolone for the treatment of CKD caused by Alport

syndrome, ADPKD, and certain other rare CKD indications in return for future royalties. The Development Agreement included a $300.0 million payment by an affiliate of BXLS in return for various percentage royalty payments on worldwide net sales of bardoxolone, if and when approved in the United States or certain specified European countries, by Reata and its licensees, other than Kyowa Kirin. Pursuant to the Development Agreement, we have granted BXLS a security interest in substantially all of our assets.

In addition, concurrent with the Development Agreement, the Company entered into the Purchase Agreement with affiliates of BXLS to sell an aggregate of 340,793 shares of the Company's Class A common stock at $146.72 per share for a total of $50.0 million.

Corporate Overview

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 Kyowa Kirin, from sales of our securities, with secured loans, and from a strategic financing from BXLS. 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 Kyowa Kirin and reimbursements of expenses under the terms of our agreement with Kyowa Kirin. We have incurred losses in each year since our inception, other than in 2014. As of December 31, 2021, we had $590.3 million of cash and cash equivalents and an accumulated deficit of $1,255.6 million. We continue to incur significant research and development and other expenses related to our ongoing operations. Despite the potential to receive future payments from Kyowa Kirin, 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, seek regulatory approval for, and potential commercialization of our product candidates. If we do not successfully develop and obtain regulatory approval of our existing product candidates or any future product candidates and effectively manufacture, market, and sell any products that are approved, we may never generate revenue from product sales. Furthermore, even if we do generate revenue from product sales, we may never again achieve or sustain profitability on a quarterly or annual basis. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our failure to become and remain profitable could depress the market price of our Class A common stock and could impair our ability to raise capital, expand our business, diversify our product offerings, or continue our operations.

The probability of success for each of our product candidates and clinical programs and our ability to generate product revenue and become profitable depend upon a variety of factors, including the quality of the product candidate, clinical results, investment in the program, competition, manufacturing capability, commercial viability, and our collaborators' ability to successfully execute our development and commercialization plans. We will also require additional capital through equity, debt, or royalty financings or collaboration arrangements in order to fund our operations and execute on our business plans, and there is no assurance that such financing or arrangements 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 on Form 10-K.

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 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 the Kyowa Kirin Agreement, the AbbVie License Agreement, and the Collaboration Agreement and consists of upfront payments and milestone payments. License revenue recorded with respect to the Kyowa Kirin Agreement, the AbbVie License Agreement, and the Collaboration Agreement consists solely of the recognition of deferred revenue. Under our revenue recognition policy, collaboration revenue associated with upfront, non-refundable license payments received under our license and collaboration agreements are deferred and recognized ratably over the expected term of the performance obligations under each agreement. Under the Reacquisition Agreement, we no longer have performance obligations under the AbbVie License Agreement and the Collaboration Agreement. Under the Kyowa Kirin Agreement, we only expect to recognize the deferred revenue through mid-2022.

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, 2021, we have incurred a total of $1,089.9 million in research and development expense, a majority of which relates to the development of omaveloxolone and bardoxolone. 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;
- the cost of development, scale up, and process validation activities to support product registration; 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 highly judgmental and 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.

To date, we have not experienced material 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, Kyowa Kirin has allowed us to conduct clinical studies of bardoxolone in certain rare forms of kidney diseases in Japan and has reimbursed us the majority of the costs for our CARDINAL study in Japan. Kyowa Kirin is the in-country caretaker in our FALCON study in Japan and we are reimbursing Kyowa Kirin for the costs of a certain number of patients in the study.

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

	Years Ended December 31		
	2021	2020	2019
		(in thousands)	
Bardoxolone	$ 50,827	$ 50,836	$ 47,994
Omaveloxolone	12,935	25,231	23,992
RTA 901	5,642	4,189	1,859
Other research and development expenses[(1)]	86,589	78,824	54,264
Total research and development expenses	$155,993	$159,080	$128,109

(1) RTA 1701 expenses have been included in other research and development expenses due to development updates in the program. See discussion in *Other Clinical Programs* section above.

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 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 premiums, 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 (Expense), Net

Other income (expense) includes interest and gains earned on our cash and cash equivalents, interest expense on term loans, amortization of debt issuance costs, imputed interest on long term payables, loss on extinguishment of debt, gain on termination of lease, foreign currency exchange gains and losses, gains and losses on sales of assets, and non-cash interest expense on liability related to the sale of future royalties.

Benefit from (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. During 2020, we recognized a tax benefit and receivable of $22.2 million associated with the ability to carryback an applicable prior year's net operating losses to a preceding year to generate a refund under the Coronavirus Aid, Relief, and Economic Security Act (the CARES Act). The Company received the tax refund in 2021. Realization of deferred tax assets is generally dependent upon future earnings by jurisdiction, of which the timing and amount are uncertain for the majority of our deferred tax assets, and valuation allowances are maintained against them. Changes in valuation allowances also affect the tax provision.

Results of Operations

Comparison of the Years Ended December 31, 2021, 2020, and 2019

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

	2021	Change %	2020	Change %	2019
	(in thousands, except for percentage data)				
Collaboration revenue					
License and milestone	$ 8,040	71	$ 4,701	(81)	25,276
Other revenue	3,450	(20)	4,318	**	1,241
Total collaboration revenue	11,490	27	9,019	(66)	26,517
Expenses					
Research and development	155,993	(2)	159,080	24	128,109
Reacquired license rights	—	—	—	(100)	124,398
General and administrative	99,002	32	75,128	29	58,298
Depreciation	1,203	6	1,136	22	932
Total expenses	256,198	9	235,344	(25)	311,737
Other income (expense), net	(53,128)	21	(43,914)	**	(4,942)
Loss before taxes on income	(297,836)	10	(270,239)	7	(290,162)
Benefit from (provision for) taxes on income	450	(98)	22,487	**	(8)
Net loss	$(297,386)	20	$(247,752)	(15)	$(290,170)

** Percentage not meaningful

Revenue

License and milestone revenue represented approximately 70%, 52%, and 95% of total revenue for the years ended December 31, 2021, 2020, and 2019, respectively, and consisted primarily of the recognition of deferred revenue. License and milestone revenue increased by 71% during 2021 compared to 2020, and consisted of the recognition of Kyowa Kirin revenue. The increase in license and milestone revenue is primarily due to the achievement of a $5.0 million regulatory milestone in 2021. Upon achievement of the milestone, we recorded $4.7 million in collaboration revenue, representing a cumulative catch-up for the portion of service period relating to our performance obligation that was satisfied in prior periods.

License and milestone revenue decreased by 81% during 2020 compared to 2019, primarily due to the Reacquisition Agreement in October 2019, which ended our performance obligations under the Collaboration Agreement and resulted in the writing off of the related remaining deferred revenue balance, after which no further revenue was recognized. Total revenue of $4.7 million was recognized in 2020 from deferred revenue related to the Kyowa Kirin Agreement.

Other revenue decreased by $0.9 million during 2021 compared to 2020, primarily due to a decrease in reimbursements of expenses from Kyowa Kirin for manufacturing expenses incurred.

Other revenue increased by $3.1 million during 2020 compared to 2019, primarily due to an increase in reimbursements of expenses from Kyowa Kirin for manufacturing and non-clinical study expenses incurred.

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

	2021	2020	2019
		(in thousands)	
License and milestone			
AbbVie collaboration agreement	$ —	$ —	$20,588
Kyowa Kirin agreement	8,040	4,701	4,688
Total license and milestone	$ 8,040	$4,701	$25,276
Other revenue	3,450	4,318	1,241
Total collaboration revenue	$11,490	$9,019	$26,517

The following table summarizes our expenses, in thousands and as a percentage of total expenses, for the years ended December 31:

	2021	% of Total Expenses	2020	% of Total Expenses	2019	% of Total Expenses
	(in thousands, except for percentage data)					
Research and development	$155,993	60%	$159,080	67%	$128,109	40%
Reacquired license rights	$ —	—	$ —	—	$124,398	40%
General and administrative	99,002	39%	75,128	32%	58,298	19%
Depreciation	1,203	1%	1,136	1%	932	1%
Total expenses	$256,198		$235,344		$311,737	

Research and Development Expenses

Research and development expenses decreased by 2% during 2021 compared to 2020. The decrease was primarily due to timing of manufacturing activities related to omaveloxolone. The remaining changes included decreased stock-based compensation expense due to accelerated expense recognized during 2020, offset by an increase in personnel and personnel-related costs to support our product development activities.

Research and development expenses increased by 24% during 2020 compared to 2019. The increase is primarily due to $30.2 million in increased personnel and equity compensation expenses to support growth of our development activities, including accelerated recognition of stock-based compensation expense as a result of the death of an executive and employees who entered into consulting agreements at the termination of employment. The remaining changes included increased manufacturing and regulatory costs to support product registration, increased clinical pharmacology and toxicity study expenses for our RTA 901 program, offset by a decrease in clinical study expenses related to PAH studies terminated in the first quarter 2020, and decreased medical affairs and research expenses.

Research and development expenses, as a percentage of total expenses, was 60%, 67%, and 40% for 2021, 2020, and 2019, respectively. The decrease in 2019 compared to 2021 and 2020 was primarily due to the reacquired license rights expense of $124.4 million incurred during 2019, resulting in higher total operating expenses.

Reacquired License Rights

The reacquired license rights expense incurred in 2019 was due to the Reacquisition Agreement we entered into with AbbVie in October 2019 to reacquire the development, manufacturing, and commercialization rights provided in the AbbVie License Agreement and the Collaboration Agreement.

General and Administrative Expenses

General and administrative expenses increased by 32% during 2021 compared to 2020. The increase was primarily due to increased spend related to commercial readiness activities, personnel and personnel-related costs to support growth in our development activities, and insurance premiums.

General and administrative expenses increased by 29% during 2020 compared to 2019. The increase was primarily due to $17.9 million in increased personnel and stock-based compensation expenses in preparation for commercial launch readiness and to support growth in our development activities and $1.2 million in increased insurance expenses, which were offset by a $1.4 million in decreased marketing and commercialization expenses.

General and administrative expenses, as a percentage of total expenses, were 39%, 32%, and 19% for 2021, 2020, and 2019, respectively. The decrease in 2019 compared to 2021 and 2020 was primarily due to the reacquired license rights expense of $124.4 million incurred during 2019, resulting in higher total operating expenses.

Other Income (Expense), Net

Other income (expense), net increased by $9.2 million during 2021 compared to 2020. The increase was primarily due to increased non-cash interest expense on liability related to the sale of future royalties and decreased interest income earned due to lower market rates, offset by decreased interest expense and loss on extinguishment of debt due to the payoff on our Term Loans in 2020.

Other income (expense), net increased by $39.0 million during 2020 compared to 2019. The increase was primarily due to $21.9 million from non-cash interest expense on liability related to the sale of future royalties, $11.2 million from loss on debt extinguishment, and $3.7 million of additional interest expense attributable to additional borrowings under the Term B Loan drawn in December 2019 and the payable due to collaborator related to the Reacquisition Agreement in October 2019, and offset by a decrease of $1.3 million for a gain on lease termination.

Benefit from (Provision for) Taxes on Income

Benefit from taxes on income decreased by $22.0 million during 2021 compared to 2020 and increased by $22.5 million during 2020 compared to 2019, which was primarily due to a tax benefit recognized in 2020 related to a carryback claim associated with the CARES Act.

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, the sale of royalty interests, and secured loans. To date, we have raised gross cash proceeds of $476.6 million through the sale of convertible preferred stock and $785.0 million from payments under license and collaboration agreements. We also obtained $1,222.1 million in net proceeds from our IPO, follow-on offerings, and the sale of our Class A common stock under the Purchase Agreement, and $299.0 million in net proceeds from the sale of future royalties under the Development Agreement. We have not generated any revenue from the sale of any products. As of December 31, 2021, we had available cash and cash equivalents of approximately $590.3 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:

	2021	2020	2019
		(in thousands)	
Net cash (used in) provided by:			
Operating activities	$(235,701)	$(322,340)	$(251,151)
Investing activities	(1,329)	(927)	(2,673)
Financing activities	9,138	477,093	580,358
Net change in cash and cash equivalents	$(227,892)	$ 153,826	$ 326,534

Operating Activities

Net cash used in operating activities was $235.7 million for the year ended December 31, 2021, consisting primarily of net loss of $297.4 million adjusted for non-cash items including stock-based compensation expense of $56.8 million, non-cash interest expense on liability related to sale of future royalty of $46.7 million, depreciation and amortization expense of $7.8 million, and a net decrease in operating assets and liabilities of $49.6 million. The significant items in the change in operating assets that impacted our use of cash in operations were a decrease in income tax receivable of $22.2 million, an increase in accounts payable $8.7 million due to timing of payments, a decrease in payable to collaborators of $80.0 million for a payment made in December 2021 under the Reacquisition Agreement, and a decrease in deferred revenue of $3.0 million.

Net cash used in operating activities was $322.3 million for the year ended December 31, 2020, consisting primarily of net loss of $247.8 million adjusted for non-cash items including stock-based compensation expense of $57.6 million, non-cash interest expense on liability related to sale of future royalty of $21.9 million, loss on extinguishment of debt of $11.2 million, depreciation and amortization expense of $8.7 million, gain on lease termination of $1.3 million, and a net decrease in operating assets and liabilities of $172.7 million. The significant items in the change in operating assets that impacted our use of cash in operations were an increase in income tax receivable of $22.2 million, an increase in accounts payable $2.9 million due to timing of payments, a decrease in payable to collaborators of $150.0 million for a payment made on June 30, 2020 under the Reacquisition Agreement, and a decreased in deferred revenue of $4.7 million.

Net cash used in operating activities was $251.2 million for the year ended December 31, 2019, consisting primarily of net loss of $290.2 million adjusted for non-cash items including stock-based compensation expense of $26.4 million, depreciation and amortization expense of $2.3 million, and a net increase in operating assets and liabilities of $10.3 million. The significant items in the change in operating assets that impacted our use of cash in operations include increases in accrued direct research and other current and long-term liabilities of $8.1 million due to activities directly related to our clinical trials and other activities to support our registrational trials, operating lease liability of $3.8 million, an increase in payables to collaborators of $216.9 million primarily due to the remaining payable due to AbbVie for the reacquisition of development, manufacturing, and commercialization rights, a decrease in accounts payable of $2.1 million due to timing of payments, and a decrease in deferred revenue of $216.3 million. The decrease in deferred revenue is due to the ratable recognition of approximately $25.2 million in revenue offset by the write off of the $191.1 million deferred revenue balance related to the Collaboration Agreement, after our performance obligations were terminated under the Reacquisition Agreement.

Investing Activities

Net cash used in investing activities was $1.3 million, $0.9 million, and $2.7 million for the years ended December 31, 2021, 2020, and 2019, respectively, primarily due to purchases of property and equipment.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2021 was $9.1 million, primarily consisting of option exercises.

Net cash provided by financing activities for the year ended December 31, 2020 was $477.1 million, primarily due to net proceeds of $277.5 million from our follow-on public offering, $349.0 million in net proceeds received under the Purchase Agreement and Development Agreement with BXLS, and $17.8 million from options exercised, offset by $167.2 million to pay off our Term Loans.

Net cash provided by financing activities for the year ended December 31, 2019 was $580.4 million, primarily due to net proceeds of $492.4 million from our follow-on public offering, $75.0 million from the First Amendment to the Amended and Restated Loan and Security Agreement (the Amended Restated Loan Agreement), and $13.4 million from options exercised.

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.

In October 2019, we entered into the 2019 Lease Agreement, relating to a new headquarter building lease of approximately 327,400 square feet of office and laboratory space located in Plano, Texas.

- In December 2021, we obtained control of the building, and, accordingly, we recorded related right-of-use assets and the lease liabilities during the fourth quarter of 2021.
- We have paused the tenant improvement activities for the new headquarter building and are attempting to sublease the building. At this point, we will not spend the earlier-planned $50 million in capital expenditures. If at a future date, we determine to move into the building, capital expenditures will need to be incurred based on our occupancy requirements at that time.
- The initial term of the lease is 16 years, with up to ten years of extension at our option. The annual base rent payment, which will begin in June 2022, will be determined based on the project cost, subject to an initial annual cap of approximately $13.3 million. Beginning in the third lease year, the base rent will increase 1.95% per annum each year. In addition to the annual base rent, we will pay for taxes, insurance, utilities, operating expenses, assessments under private covenants, maintenance and repairs, certain capital repairs and replacements, and building management fees.

In July 2021, Kyowa Kirin announced the submission of an NDA in Japan for bardoxolone for improvement of renal function in patients with Alport syndrome. We earned a $5.0 million milestone related to this event that was received and began to be recognized in the third quarter of 2021.

In December 2020, we closed a follow-on underwritten public offering of 2,000,000 shares of our Class A common stock for gross proceeds of $281.7 million. Net proceeds to us from the offering were approximately $277.5 million, after deducting underwriting discounts and commissions and offering expenses.

In June 2020, we closed on the Development Agreement and Purchase Agreement, each dated June 10, 2020, under which certain BXLS entities paid us an aggregate of $350.0 million in exchange for future royalties on bardoxolone and an aggregate of 340,793 shares of our Class A common stock at $146.72 per share.

In June 2020, we paid off our Term Loans with Oxford Finance LLC and Silicon Valley Bank, which included payments for principal of $155.0 million, prepayment fees of $5.4 million, exit fees of $6.7 million, and accrued and unpaid interest of $1.0 million.

In March 2020, the United States enacted the CARES Act. Under its provisions, we recognized a tax benefit and receivable of $22.2 million associated with the ability to carryback an applicable prior year's net operating losses to a preceding year to generate a refund.

Our longer term liquidity requirements will require us to raise additional capital, such as through additional equity, debt, or royalty financings or collaboration arrangements. Our future capital requirements will depend on many factors, including the receipt of milestones under our Kyowa Kirin Agreement and the timing of our expenditures related to clinical trials. We believe our existing cash and cash equivalents will be sufficient to enable us to fund our operations through the fourth quarter of 2024. However, we anticipate opportunistically raising additional capital before that time through equity offerings, collaboration or license agreements, additional debt financings, or royalty financings 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, debt, or royalty financing. Additional securities may include common stock, preferred stock, or debt securities. We may explore strategic collaborations or license arrangements for any of our product candidates. 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, loans, royalty financings, and collaboration or license transactions. The outbreak of COVID-19 has caused significant disruption of global financial markets, which may reduce our ability to access capital, which could negatively affect our liquidity. 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 or obtain royalty financing, 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 or royalty financing 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 collaboration with Kyowa Kirin 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 or 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 any potential loss or corruption of our information or data in a cyberattack on our computer systems or those of our suppliers, vendors, or collaborators who store or transmit our data;
- the costs associated with being a public company;
- any additional costs we incur, or delays in clinical trials we experience, associated with the COVID-19 pandemic; 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

We have various contractual obligations and other commitments that require payments at certain specified periods. The following table summarizes our contractual obligations and commitments as of December 31, 2021:

	Payments due by period				
	Less than 1 year	**1 to 3 years**	**4 to 5 years**	**6 years and beyond**	**Total**
	(unaudited, in thousands)				
Operating lease obligations[1]	$8,686	$13,452	$27,697	$183,223	$233,058
Total contractual obligations	$8,686	$13,452	$27,697	$183,223	$233,058

(1) Above table assumes one year rent abatement is applied beginning in June 2023 following FDA approval of omaveloxolone

Clinical Trials

As of December 31, 2021, 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 on Form 10-K, 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.

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.

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.

Liability Related to Sale of Future Royalties

On June 24, 2020, we closed on the Development Agreement with certain BXLS entities, which provided funding for the development and commercialization of bardoxolone for the treatment of CKD caused by Alport syndrome, ADPKD, and certain other rare CKD indications in return for future royalties. We accounted for the Development Agreement as a sale of future revenues resulting in a debt classification, primarily because we have significant continuing involvement in generating the future revenue on which the royalties are based. The debt will be amortized under the effective interest rate method and, accordingly, we are recognizing non-cash interest expense over the estimated term of the Development Agreement. The liability related to the sale of future royalties, and the debt amortization, are based on our current estimate of future royalties expected to be paid over the estimated term of the Development Agreement. We will periodically assess the expected royalty payments and, if materially different than our previous estimate, will prospectively adjust and recognize the related non-cash interest expense. The transaction costs associated with the liability will be amortized to non-cash interest expense over the estimated term of the Development Agreement.

Revenue Recognition

We recognize revenue generated primarily from licensing fees received under our collaborative licensing agreements in prior years with AbbVie and currently with Kyowa Kirin and reimbursements for expenses from Kyowa Kirin. 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, we assess the goods or services promised within each contract, determine those that are performance obligations, and assess whether each promised good or service is distinct. We then recognize 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 our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue 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, we utilize 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. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement that includes milestone payments, we evaluate whether the milestones are considered probable of being achieved and estimate 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 us) is included in the transaction price, which is then allocated to each performance obligation. Milestone payments that are not within our control, 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, we re-evaluate the probability of achievement of such development milestones and, if necessary, adjust our 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, we recognize 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, we have 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. We assess if these options provide a material right to the licensee and, if so, they are accounted for as separate performance obligations. If we are 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* of Notes of Consolidated Financial Statements contained in this Annual Report on Form 10-K. Our revenue to date has been generated primarily from licensing fees received under our collaborative licensing agreements with AbbVie and Kyowa Kirin and reimbursements for expenses from Kyowa Kirin. 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.

Income Taxes

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

Realization of deferred tax assets is generally dependent upon future earnings by jurisdiction, if any, the timing and amount of which are uncertain. As of December 31, 2021, based on known factors, for the majority of our deferred tax assets, we cannot conclude that it is more likely than not that they will be utilized, and we have recorded valuation allowances to offset these deferred tax assets.

We account for uncertain tax positions in accordance with the provisions of Accounting Standards Codification (ASC) 740, *Income Taxes*. We recognize tax benefit for uncertain tax positions if we believe it is

more likely than not that the position will be upheld on audit based solely on the technical merits of the tax position. We evaluate uncertain tax positions after consideration of all available information. As of December 31, 2021, the interest accrued related to provision uncertain tax positions was immaterial.

Stock-Based Compensation

We measure and recognize compensation expense for all stock option 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.

Stock option and RSU awards have been granted to nonemployees, in connection with research and consulting services provided to us, and to employees, under our LTIP Plan. Equity awards generally vest over terms of four or five years. For employees, stock-based compensation expense is recorded ratably through the vesting period for each stock option or tranche of restricted stock award. For option and RSU awards with performance conditions, we evaluate the probability of the number of shares that are expected to vest and adjust compensation expense to reflect the number of shares expected to vest and the cumulative vesting period met to date.

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

	Years Ended December 31		
	2021	2020	2019
Dividend yield	— %	— %	— %
Volatility	69.71%	73.46%	73.73%
Risk-free interest rate	0.69%	1.44%	2.18%
Expected term of options (in years)	5.65	5.86	6.23
Weighted average grant date fair value	$120.97	$196.96	$69.76

Leases

We determine if an arrangement is a lease at inception. Lease assets represents our right to use an underlying asset for the lease term, and lease liabilities represent our obligation to make lease payments arising from the lease. These assets and liabilities are initially recognized at the lease commencement date based on the present value of lease payments over the lease term calculated using its incremental borrowing rate based on the information available at commencement unless the implicit rate is readily determinable. Lease assets also include upfront lease payments, lease incentives paid, and direct costs incurred and exclude lease incentives received. The lease term used to calculate the lease assets and related lease liabilities includes the options to extend or terminate the lease when it is reasonably certain that we will exercise those options. Lease expense for operating leases is recognized on a straight-line basis over the expected lease term as an operating expense while the expense for finance leases is recognized as depreciation expense over the expected lease term unless there is a transfer of title or purchase option reasonably certain of exercise.

We will account for each separate lease component separately from the nonlease components. The depreciable life of lease assets and leasehold improvements is limited by the expected lease term unless there is a transfer of title or purchase option reasonably certain of its exercise.

Leases with an initial term of 12 months or less are not recorded on the balance sheet, and the expense for these short-term leases and operating leases is recognized on a straight-line basis over the lease term.

Key assumptions and judgments included in the determination of the lease liability include the discount rate applied to the present value of the future lease payments, and the exercise of renewal options. Our leases do not provide information about the rate implicit in the lease; therefore, we utilize an incremental borrowing rate to calculate the present value of our future lease obligations. The incremental borrowing rate represents the rate of interest we would have to pay on a collateralized borrowing, for an amount equal to the lease payments, over a similar term and in a similar economic environment.

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 $590.3 million at December 31, 2021, 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. There have been no changes since the end of the last fiscal year in our primary market risk exposures or the management of those exposures, and we do not expect future changes in these exposures.

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 on Form 10-K. 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, 2021. 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, 2021, 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) and 15(d)-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 (COSO framework) to evaluate the effectiveness of internal control over financial reporting. Management believes that the COSO framework is a suitable framework for its evaluation of financial reporting because it is free from bias, permits reasonably consistent qualitative and quantitative measurements of our internal control over financial reporting, is sufficiently complete so that those relevant factors that would alter a conclusion about the effectiveness of our internal control over financial reporting are not omitted, and is relevant to an evaluation of internal control over financial reporting.

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, 2021, based on those criteria.

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 quarter ended December 31, 2021, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Attestation Report of the Registered Public Accounting Firm

The effectiveness of the Company's internal control over financial reporting has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their attestation report appearing below, which expresses an unqualified opinion on the effectiveness of the Company's internal control over financial reporting as of December 31, 2021.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on Internal Control over Financial Reporting

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

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and 2020, the related consolidated statements of operations, stockholders' equity (deficit), and cash flows, for each of the three years in the period ended December 31, 2021, and the related notes and our report dated February 28, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

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

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

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

Definition and Limitations of Internal Control Over Financial Reporting

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

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

/s/ Ernst & Young LLP

Dallas, Texas

February 28, 2022

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

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 2022 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 2022 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.

Information concerning our equity compensation plan at December 31, 2021, was as follows:

Equity Compensation Plans

The table below discloses information as of December 31, 2021, with respect to our equity compensation plans and outstanding stock options granted pursuant to individual compensation arrangements.

Plan Category	Number of shares of Class A common stock and 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:	5,552,325	$83.27	2,836,302
Total	5,552,325	$83.27	2,836,302

(1) Represents 4,743,180 stock options and 809,145 RSUs outstanding under the LTIP Plan. Of the total 4,743,180 stock options, 1,019,603 stock options are exercisable for shares of our Class A common stock, and 3,723,577 stock options are exercisable for shares of our Class B common stock. Of the total 809,145 RSUs, 742,499 RSUs represent shares of our Class A common stock, and 66,646 RSUs represent shares of our Class B common stock.

(2) Represents the number of securities remaining available under the LTIP Plan as of December 31, 2021. On January 1 of each calendar year, the total number of shares of stock reserved and available for issuance shall automatically increase by an amount equal to 4% 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 reserved shares for any year.

The remaining information required by Item 12 is incorporated by reference to the relevant information contained under the caption “Security Ownership Of Certain Beneficial Owners And Management” in our proxy statement related to the 2022 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 2022 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 2022 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 (PCAOB ID: 42)

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	
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	
4.3	Description of Registrant's Securities.	10-K	001-37785	4.3	02/19/2020	
Agreements with Executive Officers and Directors						
10.1+	Indemnification Agreement by and between the Registrant and J. Warren Huff, together with a schedule identifying other substantially identical agreements between the Registrant and the persons identified on the schedule and identifying the material differences between each of the agreements and the filed Indemnification Agreement.	S-1	333-208843	10.1	05/20/2016	
10.2+	Indemnification Agreement by and between the Registrant and Dawn C. Bir dated September 6, 2016.	10-Q	001-37785	10.1	11/14/2016	
10.3+	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+	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	
10.5+	Amended and Restated Employment Agreement, by and between the Registrant and Dawn C. Bir, dated as of June 14, 2017.	S-3	333-218915	10.3	06/23/2017	
10.6+	Amended and Restated Employment Agreement, by and between the Registrant and Colin Meyer, dated as of June 14, 2017.	S-3	333-218915	10.4	06/23/2017	
10.7+	Amended and Restated Employment Agreement, by and between the Registrant and Michael D. Wortley, dated as of June 14, 2017.	S-3	333-218915	10.7	06/23/2017	

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.8+	Indemnification Agreement by and between the Company and Manmeet S. Soni dated August 28, 2019.	10-Q	001-37785	10.1	11/12/2019	
10.9+	Employment Agreement by and between the Company and Manmeet S. Soni dated August 28, 2019.	10-Q	001-37785	10.2	11/12/2019	
10.10+	Indemnification Agreement by and between the Company and Martin W. Edwards, dated as of August 3, 2020.	8-K	001-37785	10.1	7/30/2020	
10.11+	Indemnification Agreement by and between the Company and Christy J. Oliger, dated as of April 15, 2021.	10-Q	001-37785	10.1	5/6/2021	
10.12+	Indemnification Agreement by and between the Company and Shamim Ruff, dated as of April 15, 2021.	10-Q	001-37785	10.2	5/6/2021	
10.13+	Indemnification Agreement by and between the Company and Samina Khan, dated as of February 24, 2020.					X
10.14+	Indemnification Agreement by and between the Company and Andrea Loewen, dated as of February 24, 2020.					X
10.15+	Employment Agreement by and between the Company and Samina Khan, dated as of July 7, 2020.					X
10.16+	Employment Agreement by and between the Company and Andrea Loewen, dated as of February 24, 2020.					X
Patent and License Agreements						
10.17	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	
10.18	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	
10.19#	Fifth Supplement to Exclusive License and Supply Agreement, dated as of August 22, 2019, between Reata Pharmaceuticals, Inc. and Kyowa Hakko Kirin Co., Ltd.	8-K	001-37785	10.1	08/22/2019	
10.20#	Sixth Supplement to Exclusive License and Supply Agreement, dated as of August 22, 2019, between Reata Pharmaceuticals, Inc. and Kyowa Hakko Kirin Co., Ltd.	8-K	001-37785	10.2	08/22/2019	

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.21#	Amended and Restated License Agreement, dated as of October 9, 2019.	8-K	001-37785	10.1	10/10/2019	
10.22+#	Amendment No. 2 to the 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 August 17, 2021, as amended.	10-Q	001-37785	10.1	11/18/2021	
10.23+#	Amendment No. 2 to the Exclusive License Agreement between the Trustees of Dartmouth College and the Registrant, dated as of August 17, 2021, as amended.	10-Q	001-37785	10.2	11/18/2021	
10.24#	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.					X
10.25#	Exclusive License Agreement between the Trustees of Dartmouth College and the Registrant, dated as of December 16, 2009, as amended.					X
10.26#	Exclusive License Agreement between the KU Center for Technology Commercialization, Inc. and the Registrant, dated as of September 26, 2014.					X
10.27#	Exclusive License and Supply Agreement between the Registrant and Kyowa Hakko Kirin Co. Ltd., dated as of December 24, 2009.					X
10.28#	License Agreement between the Registrant and Abbott Pharmaceuticals PR Ltd., dated as of September 21, 2010.					X
10.29#	Collaboration Agreement between the Registrant and Abbott Pharmaceuticals PR Ltd., dated as of December 9, 2011.					X
10.30#	Third Supplement to Exclusive License and Supply Agreement, dated as of December 6, 2017, between Reata Pharmaceuticals, Inc. and Kyowa Hakko Kirin Co., Ltd.					X

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.31#	Fourth Supplement to Exclusive License and Supply Agreement, dated as of December 6, 2017, between Reata Pharmaceuticals, Inc. and Kyowa Hakko Kirin Co., Ltd.					X
Lease Agreements						
10.32	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	
10.33	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	
10.34	Lease Agreement, dated as of October 15, 2019.	8-K	001-37785	10.1	10/16/2019	
10.35	Expansion Agreement, dated as of October 15, 2019.	8-K	001-37785	10.2	10/16/2019	
10.36	Gateway Lease Expansion Agreement, dated December 12, 2019.	10-K	001-37785	10.39	2/19/2020	
10.37	First Amendment to Lease Agreement, dated as of May 27, 2020.	10-Q	001-37785	10.1	8/10/2020	
10.38	Lease Amendment No. 13, effective as of February 4, 2022, between Reata Pharmaceuticals, Inc. and SDCO Commerce I & II, Inc.					X
Equity Compensation Plans and Policies						
10.39+	Reata Pharmaceuticals, Inc. Second Amended and Restated Long Term Incentive Plan.	10-Q	001-358762	10.1	05/09/2019	
10.40+	Stock Option Agreement.	10-Q	001-358762	10.2	05/09/2019	
10.41+	Notice of Stock Option Grant forms for employees and director/consultants.	S-8	333-232009	4.5	06/13/2019	
10.42+	Restricted Stock Unit Agreement.	10-Q	001-37785	10.3	11/12/2019	
10.43+	Notice of Grant of Restricted Stock Units for employees.	10-K	001-37785	10.38	2/19/2020	
10.44+	Fourth Amended and Restated Non-Employee Director Compensation Policy, dated as of June 10, 2020.	10-Q	001-37785	10.4	8/10/2020	
10.45+	Fifth Amended and Restated Non-Employee Director Compensation Policy, dated as of December 2, 2020.	10-K	001-37785	10.37	3/01/2021	

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.46+	Notice of Grant of Restricted Stock Units for director/consultants, dated as of December 2, 2020.	10-K	001-37785	10.38	3/01/2021	
10.47+	Notice of Grant of Restricted Stock Units for employees, dated as of December 2, 2020.	10-Q	001-37785	10.3	05/06// 2021	
10.48*	Notice of Grant of Restricted Stock Units for employees, dated as of December 3, 2021.					X
10.49*	Notice of Grant of Restricted Stock Units Form for director/consultants, dated as of December 3, 2021.					X
10.50*	Sixth Amended and Restated Non-Employee Director Compensation Policy, dates as of December 17, 2021.					X
Other						
10.51†#	Common Stock Purchase Agreement between the Company and BXLS V – River L.P, dated as of June 10, 2020.	10-Q	001-37785	10.2	8/10/2020	
10.52†#	Development and Commercialization Funding Agreement between the Company and BXLS V – River L.P, dated as of June 10, 2020.	10-Q	001-37785	10.3	8/10/2020	
21.1	List of Subsidiaries.					X
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.					*
101.INS	Inline XBRL Instance Document.					X

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
101.SCH	Inline XBRL Taxonomy Extension Schema Document.					X
101.CAL	Inline XBRL Taxonomy Calculation Linkbase Document.					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.					X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.					X
101.PRE	Inline Taxonomy Extension Presentation Linkbase Document.					X
104	Cover Page Interactive Data File (embedded within the Inline XBRL document.					X

+ Indicates management contract or compensatory plan.

Information in this exhibit identified by brackets is confidential and has been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K because it is not material and is the type of information that the Company customarily treats as private or confidential. An unredacted copy of this exhibit will be furnished to the Securities and Exchange Commission on a supplemental basis upon request.

† Certain exhibits and schedules have been omitted pursuant to Item 601(a)(5) of Regulation S-K. A copy of any omitted schedule or exhibit will be furnished to the Securities and Exchange Commission upon request.

* 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, 2022

By: /s/ J. Warren Huff
J. Warren Huff
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	Chief Executive Officer and Chairman of the Board of Directors (*Principal Executive Officer*)	February 28, 2022
/s/ Manmeet S. Soni Manmeet S. Soni	Chief Operating Officer, Chief Financial Officer and President (*Principal Financial Officer*)	February 28, 2022
/s/ Bhaskar Anand Bhaskar Anand	Vice President, Chief Accounting Officer (*Principal Accounting Officer*)	February 28, 2022
/s/ Martin W. Edward, M.D. Martin W. Edward, M.D.	Member of the Board of Directors	February 28, 2022
/s/ William D. McClellan, Jr. William D. McClellan, Jr.	Member of the Board of Directors	February 28, 2022
/s/ R. Kent McGaughy, Jr. R. Kent McGaughy, Jr.	Member of the Board of Directors	February 28, 2022
/s/ Jack B. Nielsen Jack B. Nielsen	Member of the Board of Directors	February 28, 2022
/s/ Christy J. Oliger Christy J. Oliger	Member of the Board of Directors	February 28, 2022
/s/ William E. Rose William E. Rose	Member of the Board of Directors	February 28, 2022
/s/ Shamim Ruff Shamim Ruff	Member of the Board of Directors	February 28, 2022

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INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders 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, 2021 and 2020, 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, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 28, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

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

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

Critical Audit Matter

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

Provision for Unbilled Accrued Direct Research Liabilities

Description of the Matter

As described in Note 2 to the consolidated financial statements, the Company bases expense accruals related to clinical trials on estimates of the services performed and expenses incurred, pursuant to contracts with multiple research institutions. As of December 31, 2021, the Company had $14.2 million of accrued direct research liabilities, of which $11.8 million related to accruals for unbilled research and development expenses. The financial terms of these agreements vary from contract to contract, resulting in uneven billing and payment flows. At a given financial statement date, the Company accumulates and assesses unbilled research and development costs, inclusive of contract milestones, pass-through costs, and estimates of the total costs of unbilled patient visits for clinical trials.

Auditing management's accounting for and disclosure of unbilled accrued direct research liabilities was highly judgmental due to lag times in receiving research and development invoices, necessitating the Company to estimate unbilled costs.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the unbilled accrued direct research liabilities process. For example, we tested controls over management's review of the data inputs used in the estimation of the unbilled accrued direct research liability.

To test the Company's assumptions and related calculation of accrued direct research liabilities, our audit procedures included, among others, inquiring of management to corroborate our understanding of the inputs and data used to calculate the accrual, including gaining an understanding of the current status and enrollment timelines for each material clinical trial and the current status of other research and development related purchase orders. For each material clinical study, we confirmed the terms of the agreement in effect as of December 31, 2021 with the related invoice processor and clinical sites, as well as significant inputs contributing to the amount accrued, such as lifetime-to-date patient visit costs and amounts invoiced, and compared them to actual inputs used by the Company to calculate the unbilled liability related to each clinical trial. In addition, we performed procedures to evaluate the completeness and accuracy of material unbilled accrued direct research liability components and tested cash payments subsequent to December 31, 2021 that could potentially impact the year-end balances. We also performed analytical procedures to evaluate whether appropriate relationships existed between the unbilled accrued direct research liabilities and drug development costs compared to historical trends.

/s/ Ernst & Young LLP

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

Dallas, Texas

February 28, 2022

Reata Pharmaceuticals, Inc.

Consolidated Balance Sheets
(in thousands, except share data)

	December 31, 2021	December 31, 2020
Assets		
Cash and cash equivalents	$ 590,258	$ 818,150
Prepaid expenses and other current assets	6,217	6,960
Income tax receivable	—	22,228
Total current assets	596,475	847,338
Property and equipment, net	11,604	4,912
Operating lease right-of-use assets	126,777	5,208
Other assets	160	140
Total assets	$ 735,016	$ 857,598
Liabilities and stockholders' equity		
Accounts payable	13,505	4,790
Accrued direct research liabilities	14,249	14,023
Other current liabilities	21,450	19,423
Operating lease liabilities, current	3,142	2,841
Payable to collaborators	—	73,437
Deferred revenue	1,648	4,688
Total current liabilities	53,994	119,202
Other long-term liabilities	—	3,029
Operating lease liabilities, noncurrent	132,891	2,482
Liability related to sale of future royalties, net	362,142	315,454
Total noncurrent liabilities	495,033	320,965
Commitments and contingencies		
Stockholders' equity:		
Common stock A, $0.001 par value: 500,000,000 shares authorized; issued and outstanding – 31,478,197 and 31,109,154 at December 31, 2021 and December 31, 2020, respectively	31	31
Common stock B, $0.001 par value: 150,000,000 shares authorized; issued and outstanding – 4,919,249 and 5,044,931 at December 31, 2021 and December 31, 2020, respectively	5	5
Additional paid-in capital	1,441,584	1,375,640
Accumulated deficit	(1,255,631)	(958,245)
Total stockholders' equity	185,989	417,431
Total liabilities and stockholders' equity	$ 735,016	$ 857,598

See accompanying notes.

Reata Pharmaceuticals, Inc.

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

	Years Ended December 31		
	2021	2020	2019
Collaboration revenue			
License and milestone	$ 8,040	$ 4,701	$ 25,276
Other revenue	3,450	4,318	1,241
Total collaboration revenue	11,490	9,019	26,517
Expenses			
Research and development	155,993	159,080	128,109
Reacquired license rights	—	—	124,398
General and administrative	99,002	75,128	58,298
Depreciation	1,203	1,136	932
Total expenses	256,198	235,344	311,737
Other income (expense), net	(53,128)	(43,914)	(4,942)
Loss before taxes on income	(297,836)	(270,239)	(290,162)
Benefit from (provision for) taxes on income	450	22,487	(8)
Net loss	$ (297,386)	$ (247,752)	$ (290,170)
Net loss per share—basic and diluted	$ (8.19)	$ (7.35)	$ (9.54)
Weighted-average number of common shares used in net loss per share basic and diluted	36,321,351	33,709,480	30,414,203

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 Capital	Total Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount	Shares	Amount			
Balance at January 1, 2019	24,000,683	$ 24	5,728,175	$ 6	$ 435,452	$ (420,323)	$ 15,159
Compensation expense related to stock-based compensation	—	—	—	—	26,381	—	26,381
Exercise of options	—	—	707,849	—	13,445	—	13,445
Public offering of common stock, net of offering costs	2,760,000	3	—	—	491,932	—	491,935
Conversion of common stock Class B to Class A	1,117,867	1	(1,117,867)	(1)	—	—	—
Other shareholder transactions	—	—	—	—	107	—	107
Net loss	—	—	—	—	—	(290,170)	(290,170)
Balance at December 31, 2019	27,878,550	$ 28	5,318,157	$ 5	$ 967,317	$ (710,493)	$ 256,857
Compensation expense related to stock-based compensation	—	—	—	—	57,633	—	57,633
Exercise of options	—	—	616,585	1	17,819	—	17,820
Public offering of common stock, net of offering costs	2,000,000	2	—	—	277,473	—	277,475
Issuance of Common Stock	340,793	—	—	—	55,398	—	55,398
Conversion of common stock Class B to Class A	889,811	1	(889,811)	(1)	—	—	—
Net loss	—	—	—	—	—	(247,752)	(247,752)
Balance at December 31, 2020	31,109,154	$ 31	5,044,931	$ 5	$1,375,640	$ (958,245)	$ 417,431
Compensation expense related to stock-based compensation	—	—		—	56,806	—	56,806
Exercise of options	—	—	234,216	—	9,138	—	9,138
Issuance of common stock upon vesting of restricted stock units	—	—	9,145	—	—	—	—
Conversion of common stock Class B to Class A	369,043	—	(369,043)	—	—	—	—
Net loss	—	—		—	—	(297,386)	(297,386)
Balance at December 31, 2021	31,478,197	31	4,919,249	5	1,441,584	(1,255,631)	185,989

See accompanying notes.

Reata Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Years Ended December 31		
	2021	2020	2019
Operating activities			
Net loss	$(297,386)	$(247,752)	$(290,170)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	1,203	1,136	932
Amortization of debt issuance costs and imputed interest	6,563	7,545	1,374
Non-cash interest expense on liability related to sale of future royalty	46,688	21,884	—
Stock-based compensation expense	56,806	57,633	26,381
Loss on extinguishment of debt	—	11,183	—
Gain on lease termination	—	(1,286)	—
Changes in operating assets and liabilities:			
Income tax receivable and payable	22,217	(22,217)	—
Prepaid expenses, other current assets and other assets	750	222	(59)
Accounts payable	8,713	2,879	(2,114)
Accrued direct research, other current and long-term liabilities	1,346	2,090	8,140
Operating lease obligations	439	(956)	3,835
Payable to collaborators	(80,000)	(150,000)	216,862
Deferred revenue	(3,040)	(4,701)	(216,332)
Net cash used in operating activities	(235,701)	(322,340)	(251,151)
Investing activities			
Purchases of property and equipment	(1,329)	(927)	(2,673)
Net cash used in investing activities	(1,329)	(927)	(2,673)
Financing activities			
Proceeds from issuance of common stock, net	—	333,278	492,453
Payments on deferred offering costs	—	(405)	(71)
Payments on long-term debt	—	(167,170)	75,000
Payments on deferred issuance costs	—	—	(576)
Exercise of options	9,138	17,820	13,445
Proceeds from sale of future royalties, net	—	293,570	107
Net cash provided by financing activities	9,138	477,093	580,358
Net decrease in cash and cash equivalents	(227,892)	153,826	326,534
Cash and cash equivalents at beginning of year	818,150	664,324	337,790
Cash and cash equivalents at end of period	$ 590,258	$ 818,150	$ 664,324
Supplemental disclosures			
Cash paid for interest	$ —	$ 8,021	$ 8,207
Non-cash activity:			
Accrued deferred offering cost	$ —	$ 102	$ 447
Right-of-use assets obtained in exchange for lease obligations	$ 124,479	$ 4,756	$ 9,068
Purchases of equipment in accounts payable, accrued direct research, other current, and long-term liabilities	$ 295	$ 29	$ 302
Acquisition of property and equipment through tenant improvement allowance	$ 8,702	$ 2,402	$ —

See accompanying notes.

1. Description of Business

Reata Pharmaceuticals, Inc.'s (Reata, the Company, we, us, or our) mission is to identify, develop, and commercialize innovative therapies that change patients' lives for the better. The Company focuses on 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 programs are omaveloxolone in a rare neurological disease called Friedreich's ataxia (FA) and bardoxolone methyl (bardoxolone) in rare forms of chronic kidney disease (CKD). Both of the Company's lead product candidates activate the transcription factor Nrf2 to normalize mitochondrial function, restore redox balance, and resolve inflammation. Because mitochondrial dysfunction, oxidative stress, and inflammation are features of many diseases, the Company believes omaveloxolone, bardoxolone, and our next-generation Nrf2 activators have many potential clinical applications. Reata possesses exclusive, worldwide rights to develop, manufacture, and commercialize omaveloxolone, bardoxolone, and our next-generation Nrf2 activators, excluding certain Asian markets for bardoxolone in certain indications, which are licensed to Kyowa Kirin Co., Ltd. (Kyowa Kirin). In addition, we are developing RTA 901, the lead product candidate from our Hsp90 modulator program, in neurological indications. We are the exclusive licensee of RTA 901 and have worldwide commercial rights.

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.

Prior period reclassifications

Certain prior period amounts in the consolidated financial statements have been reclassified to conform to the current period presentation. Specifically, Operating lease right-of-use assets, Operating lease liabilities, current and Operating lease liabilities, noncurrent have been reclassed out of Other assets, Other current liabilities and Other long-term liabilities in prior periods to conform with current period presentation on the consolidated balance sheets.

2. Summary of Significant Accounting Policies

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.

C*ash 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.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation. 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
Manufacturing equipment	10 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 recorded as depreciation expenses in the consolidated statements of operations.

Impairment of Long-Lived Assets

The Company periodically evaluates its long-lived assets for potential impairment in accordance with ASC Topic 360, *Property, Plant and Equipment*. Potential impairment is assessed when there is evidence that events or changes in circumstances indicate that the carrying amount of an asset may not be recovered. Recoverability of these assets is assessed based on undiscounted expected future cash flows from the assets, considering a number of factors, including past operating results, budgets and economic projections, market trends, and product development cycles. If impairments are identified, assets are written down to their estimated fair value. The Company has not recognized any impairment charges in 2021, 2020, or 2019.

Liability Related to Sale of Future Royalties

On June 24, 2020, the Company closed on the Development and Commercialization Funding Agreement with an affiliate of Blackstone Life Sciences, LLC (BXLS), which provided funding for the development and commercialization of bardoxolone for the treatment of CKD caused by Alport syndrome, autosomal dominant polycystic kidney disease (ADPKD), and certain other rare CKD indications in return for future royalties (the Development Agreement). The Company accounted for the Development Agreement as a sale of future revenues resulting in a debt classification, primarily because the Company has significant continuing involvement in generating the future revenue on which the royalties are based. The debt will be amortized under the effective interest rate method and, accordingly, the Company is recognizing non-cash interest expense over the estimated term of the Development Agreement. The liability related to sale of future royalties, and the debt amortization, are based on the Company's current estimate of future royalties expected to be paid over the estimated term of the Development Agreement. The Company will periodically assess the expected royalty payments and, if materially different than its previous estimate, will prospectively adjust and recognize the related non-cash interest expense. The transaction costs associated with the liability will be amortized to non-cash interest expense over the estimated term of the Development Agreement. For a complete discussion of accounting for Development Agreement see, Note 6, *Liability Related to Sale of Future Royalties* of Notes to Consolidated Financial Statements contained in this Annual Report on Form 10-K.

Fair Value Measurements

The Company categorizes its financial instruments measured at fair value into a three-level fair value hierarchy that prioritizes the inputs used in determining the fair value of the asset or liability. The three levels of the fair value hierarchy are as follows:

- Level 1—Financial instruments that have values based on unadjusted quoted prices for identical assets or liabilities in an active market which the Company has the ability to access at the measurement date.
- Level 2—Financial instruments that have values based on quoted market prices in markets where trading occurs infrequently or that have values based on quoted prices of instruments with similar attributes in active markets.
- Level 3—Financial instruments that have values based on prices or valuation techniques that require inputs that are both unobservable and significant to the overall fair value measurement. These inputs reflect management's own assumptions about the assumptions a market participant would use in pricing the asset.

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 Kirin and reimbursements for expenses from Kyowa Kirin. 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* of Notes of Consolidated Financial Statements contained in this Annual Report on Form 10-K.

Acquired License Rights

All acquired license and sublicense costs that are in-process research and development, which were acquired directly in a transaction other than a business combination that does not have an alternative future use, are expensed as incurred. For a complete discussion of accounting for reacquisition of license rights in 2019, see Note 3, *Collaboration Agreements*.

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.

In December 2017, the Company and Kyowa Kirin entered into the Third Supplement to the Kyowa Kirin Agreement, which allows the Company to begin a portion of the registrational CARDINAL trial in Japan, for which Kyowa Kirin has reimbursed costs incurred of $3.0 million as of the end of December 31, 2021. The Company deemed that this was not a material modification to the Kyowa Kirin Agreement because no payment terms or deliverables were changed. The Company's expenses were reduced by $0.5 million for Kyowa Kirin's share of the study costs for twelve months ended December 31, 2019. No such credits were recorded in the twelve months ended December 31, 2020, or 2021, respectively.

In addition, we have also entered into cost sharing agreement for the FALCON trial and have recorded $1.4 million in expenses during the year ended December 31, 2021. No such costs were incurred in the twelve months ended December 31, 2019, or 2020, respectively.

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. Included within total accrued direct research liabilities is $11.8 million, which was accrued but unbilled, as of December 31, 2021.

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.

Patents

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

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 option and RSU 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 initial public offering (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.

Stock option and RSU unit awards have been granted to nonemployees, in connection with research and consulting services provided to the Company, and to employees, under its Second Amended and Restated Long Term Incentive Plan (the LTIP Plan). Equity awards generally vest over terms of four or five years. For employees and non-employees, stock-based compensation expense is recorded ratably through the vesting period for each stock option or tranche of RSU award. For performance-based awards, the Company evaluates the probability of the number of shares that are expected to vest and adjusts compensation expense to reflect the number of shares expected to vest and the cumulative vesting period met to date.

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. As of December 31, 2021, the interest accrued related to provision uncertain tax positions was immaterial.

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.

Leases

At the inception of an arrangement, the Company determines if an arrangement is, or contains, a lease based on the unique facts and circumstances present in that arrangement. Lease assets represent the Company's right to use an underlying asset for the lease term, and lease liabilities represent the obligation to make lease payments arising from the lease. These assets and liabilities are initially recognized at the lease commencement date based on the present value of lease payments over the lease term calculated using its incremental borrowing rate based on the information available at commencement unless the implicit rate is readily determinable. Lease assets also

include upfront lease payments, lease incentives paid, and direct costs incurred and exclude lease incentives received. The lease term used to calculate the lease assets and related lease liabilities includes the options to extend or terminate the lease when it is reasonably certain that the Company will exercise those options. Lease expense for operating leases is recognized on a straight-line basis over the expected lease term as an operating expense while the expense for finance leases is recognized as depreciation expense over the expected lease term unless there is a transfer of title or purchase option reasonably certain of exercise.

The Company accounts for each lease component separately from the nonlease components. The depreciable life of lease assets and leasehold improvements is limited by the expected lease term unless there is a transfer of title or purchase option reasonably certain of its exercise.

Leases with an initial term of 12 months or less are not recorded on the balance sheet, and the expenses for these short-term leases and operating leases are recognized on a straight-line basis over the lease term.

Key assumptions and judgments included in the determination of the lease liability include the discount rate applied to the present value of the future lease payments, and the exercise of renewal options. Our leases do not provide information about the rate implicit in the lease; therefore, we utilize an incremental borrowing rate to calculate the present value of our future lease obligations. The incremental borrowing rate represents the rate of interest we would have to pay on a collateralized borrowing, for an amount equal to the lease payments, over a similar term and in a similar economic environment.

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 RSUs 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, 2021, 2020, and 2019 was immaterial.

Recent Accounting Pronouncements Adopted

In December 2019, the Financial Accounting Standards Board (FASB) issued ASU 2019-12, Income Taxes (Topic 740), Simplifying the Accounting for Income Taxes. The FASB issued this update as part of its Simplification Initiative to improve areas of U.S. GAAP and reduce cost and complexity while maintaining usefulness. The main provision that impacts the Company is the removal of the exception to the incremental approach of intra-period tax allocation when there is a loss from continuing operations and income or gain from other items. ASU 2019-12 is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2020. The Company adopted this standard on January 1, 2021, and its adoption did not have material impact to the Company's consolidated financial statements and related disclosure.

3. Collaboration Agreements

Subsequent to the 2019 reacquisition of certain rights originally licensed to AbbVie (see "AbbVie" below), the Company's collaboration revenue and deferred revenue have been generated primarily from licensing fees and reimbursements for expenses received under our exclusive license with Kyowa Kirin Agreement (as defined below).

Kyowa Kirin

In December 2009, the Company entered into an exclusive license with Kyowa Kirin to develop and commercialize bardoxolone in the licensed territory (the Kyowa Kirin Agreement). The terms of the agreement include payment to the Company of a nonrefundable, up-front license fee of $35.0 million and additional development and commercial milestone payments. As of December 31, 2021, the Company has received $50.0 million related to regulatory development milestone payments from Kyowa Kirin and has the potential in the future to achieve another $47.0 million from regulatory milestones and $140.0 million from 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 Kyowa Kirin in the licensed territory. The Company is participating on a joint steering committee with Kyowa Kirin to oversee the development and commercialization activities related to bardoxolone. 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 Kyowa Kirin Agreement.

The up-front payment and regulatory milestones are accounted for as a single unit of accounting. The Company regularly evaluates its remaining performance obligation under the Kyowa Kirin Agreement. Accordingly, revenue may fluctuate from period to period due to changes to its estimated performance obligation period and variable considerations. The Company began recognizing revenue related to the up-front payment upon execution of the Kyowa Kirin Agreement.

In March 2021, the Company's performance obligation period under the Kyowa Kirin Agreement was extended to June 2022, which decreased quarterly revenue recognition by approximately $0.4 million prospectively.

On July 27, 2021, Kyowa Kirin, submitted an New Drug Application (NDA) in Japan to the Ministry of Health, Labour and Welfare (MHLW) for bardoxolone for improvement of renal function in patients with Alport syndrome. Based on this submission, the Company earned a $5.0 million milestone payment, variable consideration previously considered constrained, under the Kyowa Kirin Agreement. As a result, the Company recorded $4.7 million in collaboration revenue, a cumulative catch-up for the portion of this milestone that was satisfied in prior periods, and $0.3 million in deferred revenue that will be recognized over the remaining performance obligation period, ending in June 2022.

AbbVie

In September 2010, the Company entered into a license agreement with AbbVie (the AbbVie License Agreement) for an exclusive license to develop and commercialize bardoxolone in the Licensee Territory (as defined in the AbbVie License Agreement).

In December 2011, the Company entered into a collaboration agreement with AbbVie (the Collaboration Agreement) to jointly research, develop, and commercialize the Company's portfolio of second and later generation oral Nrf2 activators.

In October 2019, the Company and AbbVie entered into an Amended and Restated License Agreement (the Reacquisition Agreement) pursuant to which the Company reacquired the development, manufacturing, and commercialization rights concerning its proprietary Nrf2 activator product platform originally licensed to AbbVie in the AbbVie License Agreement and the Collaboration Agreement. In exchange for such rights, the Company agreed to pay AbbVie $330.0 million, all of which has subsequently been paid. Additionally, the Company will pay AbbVie an escalating, low single-digit royalty on worldwide net sales, on a product-by-product basis, of omaveloxolone and certain next-generation Nrf2 activators. The execution of the Reacquisition Agreement ended our performance obligations under the Collaboration Agreement.

The Company recognized interest expense related to the Reacquisition Agreement of approximately $6.6 million, $6.5 million and $1.4 million during twelve months ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2021, the Company has fully satisfied its payable to AbbVie.

4. Other Income (Expense), Net

	Years Ended December 31		
	2021	2020	2019
		(in thousands)	
Other income (expense), net			
Investment income	$ 177	$ 2,769	$ 6,248
Interest expense	(6,563)	(14,895)	(11,197)
Non-cash interest expense on liability related to sale of future royalty	(46,688)	(21,884)	—
Other income (expense)	(54)	1,279	7
Loss on extinguishment of debt	—	(11,183)	—
Total other income (expense), net	$(53,128)	$(43,914)	$ (4,942)

Investment Income

Interest income consists primarily of interest generated from our cash and cash equivalents.

Interest Expense

Interest expense consists primarily of the imputed interest from amounts due to AbbVie under the Reacquisition Agreement and interest on its Amended Restated Loan Agreement (Term Loans) which were paid in full in 2020.

Non-Cash Interest Expense on Liability Related to Sale of Future Royalties

Non-cash interest expense consists of recognition of interest expense based on the Company's current estimate of future royalties expected to be paid over the estimated term of the Development Agreement.

Other income (expense)

Other income (expense) consists primarily of gains and losses on foreign currency exchange, sales of assets, extinguishment of debt, and lease termination.

Other income of $1.3 million recorded in the twelve months ended December 31, 2020, related to a gain on the Company's lease termination due to the bankruptcy filing of its lessor.

Loss on Extinguishment of Debt

In June 2020, the Company paid off the Term Loans and recorded a loss on the extinguishment of debt of $11.2 million, which consisted primarily of prepayment fees, exit fees and unamortized debt issuance costs.

5. Term Loan

On October 9, 2019, the Company entered into the First Amendment to the Amended and Restated Loan and Security Agreement (the Amended Restated Loan Agreement), under which it borrowed $155.0 million as of December 20, 2019. On June 24, 2020, the Company paid off the total outstanding balance of the term loans under the Term Loans prior to the maturity date. The payoff consisted of (i) the outstanding principal balance of $155.0 million, (ii) exit fees of $6.7 million, which were partially accrued up to the date of repayment, (iii) prepayment fees of $5.4 million, and (iv) accrued and unpaid interest of $1.0 million. At the time of payoff, all liabilities and obligations under the Amended Restated Loan Agreement were terminated. The Company recognized approximately $8.4 million and $8.3 million in interest expense for the twelve months ended December 31, 2019, and 2020, respectively. No interest expense was recognized in 2021 as the term loan was paid off in June 2020.

6. Liability Related to Sale of Future Royalties

On June 24, 2020, the Company closed on the Development Agreement. The Development Agreement included a $300.0 million payment by an affiliate of BXLS in return for various percentage royalty payments on worldwide net sales of bardoxolone, once approved in the United States or certain specified European countries, by Reata and its licensees, other than Kyowa Kirin. The royalty percentage will initially be in the mid-single digits and, in future years, can vary between higher-mid single digit percentages to low-single digit percentages depending on various milestones, including indication approval dates, cumulative royalty payments, and cumulative net sales. Pursuant to the Development Agreement, we have granted BXLS a security interest in substantially all of our assets. After a bardoxolone product approval has been obtained by the Company, the Company is obligated to make certain minimum cumulative payment amounts in 2025 through 2033, but only until BXLS has achieved certain internal rate of return target.

In addition, concurrent with the Development Agreement, the Company entered into a common stock purchase agreement (the Purchase Agreement) with affiliates of BXLS to sell an aggregate of 340,793 shares of the Company's Class A common stock at $146.72 per share for a total of $50.0 million.

The Company concluded that there were two units of accounting for the consideration received, comprised of the liability related to the sale of future royalties and the common shares. The Company allocated the $300.0 million from the Development Agreement and $50.0 million from the Purchase Agreement between the two units of accounting on a relative fair value basis at the time of the transaction. The Company allocated $294.5 million, which includes $0.8 million in transaction costs incurred, in transaction consideration to the liability, and $55.5 million to the common shares. The Company determined the fair value of the common shares based on the closing stock price on the June 24, 2020, the closing date of the Development Agreement. The effective interest rate under the Development Agreement, including transaction costs, is 13.8%.

The following table shows the activity within the liability related to sale of future royalties for the twelve months ended December 31, 2021:

	Liability Related to Sale of Future Royalties
	(in thousands)
Balance at December 31, 2020	$ 316,305
Non-cash interest expense recognized	46,623
Balance at December 31, 2021	362,928
Less: Unamortized transaction cost	(786)
Carrying value at December 31, 2021	$ 362,142

7. Property and Equipment

Property and equipment consisted of the following as of December 31:

	2021	2020
	(in thousands)	
Computer equipment and software	$ 3,748	$ 3,306
Laboratory equipment	6,389	5,404
Office furniture	1,990	1,990
Office and other equipment	399	412
Leasehold improvements	14,127	7,829
Manufacturing equipment	213	163
	26,866	19,104
Less: accumulated depreciation	(15,262)	(14,192)
Property and equipment, net	$ 11,604	$ 4,912

8. Leases

The Company's headquarters are located in Plano, Texas, where it leases approximately 122,000 square feet of office space, with lease terms extending through August 31, 2022. The Company leases additional office and laboratory space of approximately 34,890 square feet located in Irving, Texas, with lease terms extending through October 31, 2022 with an option to renew up to six months. On February 4, 2022, the Company extended this lease agreement. See Note 17, *Subsequent Events.*

The Company has an additional lease of a single-tenant, build-to-suit building of approximately 327,400 square feet of office and laboratory space located in Plano, Texas with an initial lease term of 16 years. The Company entered into the lease agreement on October 15, 2019 (the 2019 Lease Agreement), and at the Company's option, it may renew the lease for two consecutive five-year renewal periods or one ten-year renewal period. The initial annual base rent will be determined based on the project cost, subject to an initial annual cap of approximately $13.3 million. Beginning in the third lease year, the base rent will increase 1.95% per annum each year. In addition to the annual base rent, the Company will pay for taxes, insurance, utilities, maintenance and repairs, and building management fees, all of which are variable in nature and were not included in the measurement of the lease liability. Under the First Amendment to the Lease Agreement executed in May 2020, the landlord will fund the Company's leasehold improvements up to $31.3 million, of which the Company has recorded approximately $8.7 million, as of December 15, 2021.

On December 15, 2021, the Company obtained control of the space, and, accordingly, we recorded related right-of-use assets and the lease liabilities during the fourth quarter of 2021. The Company recorded the liability associated with the 2019 Lease Agreement at the present value of the lease payments not yet paid, using the discount rate as of the commencement date. As the discount rate implicit in the 2019 Lease Agreement was not readily determinable, the Company utilized its incremental borrowing rate. The renewals are not assumed in the determination of the lease term, since they are not deemed to be reasonably assured at the inception of the lease. We recorded $124.5 million as a right-of-use asset, which represented a lease liability of $133.2 million, net of $8.7 million of lease incentives recognized as of December 31, 2021.

For the year ended December 31, 2021, the Company paid $3.2 million for amounts included in the measurement of lease liabilities. For the years ended December 31, 2021, 2020, and 2019, the Company recorded total rent expense of $3.6 million, $3.4 million, and $3.4 million, respectively.

Supplemental balance sheet and other information related to the Company's operating leases is as follows:

	As of December 31	
	2021	2020
Weighted-average remaining lease term (in years)	15.7	1.8
Weighted-average discount rate	6.6%	8.2%

Maturities of lease liabilities by fiscal year for the Company's operating leases:

	As of December 31, 2021 (in thousands)
2022	$ 9,798
2023 (1)	6,672
2024 (1)	6,802
2025	13,737
Thereafter	196,049
Total lease payments (1)	233,058
Less: Imputed interest	(97,025)
Present value of lease liabilities	$ 136,033

(1) Above table assumes one year rent abatement is applied beginning in June 2023 following United States Food and Drug Administration (FDA) approval of omaveloxolone.

9. Income Taxes

On March 27, 2020, the United States enacted the Coronavirus Aid, Relief, and Economic Security Act (the CARES Act). The CARES Act is an emergency economic stimulus package that includes spending and tax breaks to strengthen the U.S. economy and to provide assistance to individuals, families, and businesses affected by the coronavirus disease (COVID-19). Accordingly, under the provisions of the CARES Act, in March 2020, the Company recognized tax benefits and receivables totaling $22.2 million associated with the ability to carryback an applicable prior year's net operating losses to a preceding year, which had previously been fully reserved by its valuation allowance. During the second quarter of 2021, the Company received a total of $22.9 million from the IRS, comprising $22.2 million of the income tax receivable plus $0.7 million in interest.

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

	2021	2020	2019
U.S. federal income taxes	21 %	21 %	21 %
Federal and state tax credits	5 %	12	8
Stock-based compensation	(0)%	4	5
NOL carryback rate differential	— %	1	—
Foreign rate differential	(3)%	(2)	—
Change in valuation allowance	(23)%	(28)	(34)
Recorded federal income tax benefit	— %	8 %	— %

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):

	2021	2020
Deferred tax assets:		
Federal and state tax credits	$ 102,590	$ 87,056
Net operating loss	101,463	68,936
Accrued royalties	79,458	66,389
Intellectual property	60,753	62,838
Lease Liability	29,847	1,626
Stock-based compensation	23,677	15,158
Deferred revenue	362	987
Other	1,422	903
Deferred tax assets before valuation allowance	399,572	303,893
Less: Valuation allowance	(369,215)	(300,888)
Net deferred income tax assets	30,357	3,005
Deferred tax liabilities:		
Deferred purchase price	—	(1,127)
Right-of-use assets	(27,817)	(1,096)
Other	(2,424)	(659)
Net deferred tax assets	$ 116	$ 123

Deferred tax assets are regularly reviewed for recoverability by jurisdiction and valuation allowances are established based on historical and projected future taxable losses and the expected timing of the reversals of existing temporary differences. For the majority of its deferred tax assets, the Company cannot currently conclude that it is more likely than not that they will be utilized. Therefore, the Company has recorded valuation allowances against these deferred tax assets for 2021. 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 $68.3 million and $74.6 million in 2021 and 2020, respectively.

As of December 31, 2021, the Company had United States federal accumulated net operating losses of $350.6 million of which $0.4 million are subject to an annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended (Section 382). The Company has United States federal accumulated net operating losses of $59.6 million expiring between fiscal years 2023 and 2037, of which $59.2 million begin expiring in 2037. Under the Tax Cuts and Jobs Act of 2017 (the 2017 Tax Act), the remaining $291.0 million will be carried forward indefinitely but is limited to 80% of our taxable income. As of December 31, 2021, the Company had net operating losses in Switzerland of $227.6 million expiring in 2028.

As of December 31, 2021, the Company has federal orphan drug tax credit, federal research and development tax credit, and state research and development tax credit carryforwards of $76.9 million, $19.3 million, and $6.3 million, respectively, with federal orphan drug and federal research and development tax credits expiring between years 2024 and 2041, of which $0.1 million expires in 2024 and the remainder begins expiring in 2030.

The Company's federal income tax returns for 2013, and 2018 through 2020 remain open to examination by the IRS.

10. 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, 2021, 2020, or 2019.

11. Licenses

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

Bardoxolone 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 July 2012, the Company amended the 2004 CDDO License Agreement, which provides, among other terms, that the Company will pay to the licensors a low single-digit royalty on net sales of certain Nrf2 activator compounds, including omaveloxolone, that are claimed in certain patents and patent applications that are wholly owned by or licensed to the Company. In 2021, the Company paid a development milestone and sublicense payments of $0.6 million under the agreement.

In August 2021, the Company amended the 2004 CDDO License Agreement. This amendment, among other terms, provides consent to an internal restructuring by the Company of certain of its intellectual property rights, facilitates the potential monetization by the Trustees of Dartmouth College (Dartmouth) of their rights to royalties under the license, clarifies the applicability of certain running royalty payment obligations with respect to certain compounds, and specifies the dispute resolution procedure regarding a dispute between the Company and Licensors as to whether the Company is obligated under the 2012 amendment to the 2004 CDDO License Agreement to pay the licensors a low single-digit royalty on sales of products containing bardoxolone.

In January 2009, the Company filed a patent application claiming the use of bardoxolone and related compounds in treating CKD, endothelial dysfunction, cardiovascular disease (CVD), 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 Dartmouth are co-owners of this patent application. In December 2009, the Company entered into an agreement with Dartmouth that provides the Company with an exclusive worldwide license to the academic institution's rights in these applications and any resulting patents (the 2009 License Agreement). The Company agreed to pay a limited super-royalty on product sales that occur during the effective term of the original patents, 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 2021, the Company paid a development milestone and sublicense payments of $0.4 million under the agreement.

In August 2021, the Company amended the 2009 License Agreement. These amendments, among other terms, provides consent to an internal restructuring by the Company of certain of its intellectual property rights, facilitates the potential monetization by Dartmouth of its rights to royalties under the 2009 License Agreement, clarifies that there is no minimum royalty provision, and adds provisions regarding the defense of certain patent rights.

Other Technologies

The Company has an exclusive technology and patent license agreement with the University of Kansas and the University of Kansas Medical Center (the University of Kansas) for certain patents and patent applications related to small molecule modulators of heat shock proteins, including RTA 901. The Company has the right to sublicense this patent. 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 license, 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 license.

12. Convertible Preferred Stock

Under our Thirteenth Amended and Restated Certificate of Incorporation, the Company has 100,000,000 undesignated shares of convertible preferred stock. As of December 31, 2021 and 2020, there were no shares of convertible preferred stock issued and outstanding.

13. Stock-Based Compensation

The LTIP Plan provides for awards of RSUs, nonstatutory stock options, incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the Code), and other incentive awards and rights to purchase shares of the Company's common stock. As of December 31, 2021, a total of

2,836,302 shares of common stock are reserved for future grant under the LTIP Plan. As of December 31, 2021, 809,145 RSUs and stock options to purchase 4,743,180 shares have been granted and are outstanding under the LTIP Plan.

The Company recognizes stock-based compensation expense for awards with service-based vesting conditions as an expense using the straight-line method. In the case of performance-based awards, compensation expense is recognized for awards when achievement of the underlying performance-based targets become probable, which have typically been in the same period as when the targets are achieved.

The following table summarizes time-based and performance-based stock compensation expense reflected in the consolidated statements of operations:

	Years Ended December 31		
	2021	2020	2019
		(in thousands)	
Research and development	$23,566	$28,114	$ 8,692
General and administrative	33,240	29,519	17,689
Total stock compensation expense	$56,806	$57,633	$26,381

Restricted Stock Units

RSUs, including service-based and performance-based awards, were granted under the LTIP Plan. The fair value of these RSUs is equal to the closing price of the Company's common stock at the date of grant multiplied by the number of shares subject to the RSU awards with forfeitures accounted for as they occur. The vesting is subject to the satisfaction of service requirements or the satisfaction of achieving certain performance targets.

The following table summarizes RSUs as of December 31, 2021, and changes during the year ended December 31, 2021 under the LTIP Plan:

	Number of RSUs	Weighted-Average Grant Date Fair Value
Outstanding at January 1, 2021	108,551	$115.54
Granted	758,246	64.65
Vested	(9,145)	164.39
Forfeited	(48,507)	122.40
Outstanding at December 31, 2021	809,145	$ 66.91

As of December 31, 2021, total unrecognized compensation expense related to service-based RSU and performance-based RSU awards that were deemed probable of vesting was approximately $36.6 million which is expected to be recognized over a weighted average of 3.1 years, which excludes 134,000 shares of unvested performance-based RSUs that were deemed not probable of vesting totaling unrecognized stock-based compensation expense of $13.9 million.

Stock Options

Stock options, including service-based and performance-based awards, were granted under the LTIP Plan. The Company estimates stock awards fair value on the date of grant using the Black-Scholes valuation, with the

vesting being subject to service requirements' satisfaction or achieving certain performance targets. The Company accounts for forfeitures when they occur.

The following table summarizes stock option activity as of December 31, 2021, and changes during the year ended December 31, 2021, under the LTIP Plan and standalone option agreements:

	Number of Options	Weighted-Average Price
Outstanding at January 1, 2021	4,306,269	$ 79.47
Granted	1,008,879	120.97
Exercised	(234,216)	39.05
Forfeited	(284,626)	127.43
Expired	(53,126)	199.82
Outstanding at December 31, 2021	4,743,180	$ 86.06
Exercisable at December 31, 2021	2,874,424	$ 56.21

As of December 31, 2021, total unrecognized compensation expense of $95.1 million related to stock options is expected to be recognized over a weighted average of 2.79 years, which excludes the unvested performance-based stock options that were deemed not probable of vesting as of December 31, 2021, constituting 467,850 shares with unrecognized stock-based compensation expense of $47.6 million.

At December 31, 2021, 4,743,180 stock options are fully vested or are expected to vest and have a weighted-average outstanding term of 7.0 years and a weighted-average exercise price of $86.06. Exercisable stock options have a weighted-average outstanding term of 6.1 years.

The total intrinsic value (the difference between market value and exercise prices of in-the-money options) of all outstanding options at December 31, 2021, 2020, and 2019, was $8.6 million, $269.4 million, and $659.3 million, respectively. The total intrinsic value of exercisable options at December 31, 2021, 2020, and 2019, was $8.6 million, $185.7 million, and $305.0 million, respectively. In 2021, 2020, and 2019, 234,216, 616,585, and 707,849 options were exercised, respectively. The total intrinsic value of options exercised was $21.2 million, $68.6 million and $79.4 million for the years ended December 31, 2021, 2020 and 2019, respectively. For the year ended December 31, 2021 we received $9.1 million in cash from stock option exercises.

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		
	2021	2020	2019
Dividend yield	— %	— %	— %
Volatility	69.71%	73.46%	73.73%
Risk-free interest rate	0.69%	1.44%	2.18%
Expected term of options (in years)	5.65	5.86	6.23
Weighted average grant date fair value	$120.97	$196.96	$69.76

Expected volatility is based on the Company's own historical volatility since its IPO and benchmarked public companies during fiscal years 2021, 2020 and 2019. The risk-free interest rate, ranging from 0.09% to 1.31% during the year ended December 31, 2021, 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.

14. Employee Benefit Plans

In 2010, we adopted an Employee Investment Plan, qualified under Section 401(k) of the Code, which is a retirement savings plan covering substantially all of our U.S. employees (the Plan). The Plan is administered under the "safe harbor" provision of ERISA. Under the Plan, an eligible employee may elect to contribute a percentage of their salary on a pre-tax basis, subject to federal statutory limitations. Beginning in January 2019, the Company implemented a discretionary employer matching contribution of $1.00 for every $1.00 contributed by a participating employee up to $6,000 and $5,000 annually in 2021 and 2020, respectively, which such matching contributions become fully vested after four years of service. The Company recorded expense of $1.7 million, $1.1 million and $0.4 million for the twelve months ended December 31, 2021, 2020, and 2019 respectively, which includes the Company's contributions and administrative costs.

15. Commitments and Contingencies

Litigation

From time to time, the Company is a party to legal proceedings in the course of its business, including the matters described below. The outcome of any such legal proceedings, regardless of the merits, is inherently uncertain. In addition, litigation and related matters are costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities. If the Company were unable to prevail in any such legal proceedings, its business, results of operations, liquidity and financial condition could be adversely affected. The Company recognizes accruals for litigations to the extent that it can conclude that a loss is both probable and reasonably estimable and recognizes legal expenses as incurred.

Patel Litigation

On October 15, 2020, Toshif Patel filed a complaint for alleged violation of federal securities laws against the Company, its Chief Executive Officer and its Chief Financial Officer in the United States District Court for the Eastern District of Texas. The complaint purported to bring a federal securities class action on behalf of a class of persons who acquired the Company's common stock between October 15, 2019 and August 7, 2020. The complaint alleged, among other things, that the defendants made false and misleading statements regarding the sufficiency of its MOXIe Part 2 study results to support a single study marketing approval of omaveloxolone for the treatment of FA in the United States. On September 27, 2021, the plaintiff voluntarily dismissed the case.

Bardoxolone Securities Litigation

Four putative stockholders of the Company have filed complaints for alleged violations of the federal securities laws against the Company and certain of its executives, including its Chief Executive Officer, its Chief Operating Officer and Chief Financial Officer, and its Chief Innovation Officer (in one of the suits). The complaints, three of which were filed in the United States District Court for the Eastern District of Texas, and one of which was filed the District of New Jersey, allege, among other things, that the defendants made false and misleading statements regarding the sufficiency of the Phase 3 CARDINAL study to support an NDA for bardoxolone as treatment for chronic kidney disease caused by Alport syndrome, and the Company's interactions with the FDA concerning the study. The complaints filed in the United States District Court for the Eastern District of Texas, were filed on December 20, 2021, January 7, 2022, and January 20, 2022, and the complaint filed in the District of New Jersey was filed on February 18, 2022. The plaintiffs seek, among other things, a class action designation, an award of damages, and costs and expenses, including counsel fees and expert fees. The Company currently expects all of the cases to be consolidated and for a single, consolidated, amended complaint to be filed in the future.

The Company believes that the allegations contained in the complaints are without merit and intends to defend the cases. The Company cannot predict at this point the length of time that these actions will be ongoing or the liability, if any, which may arise therefrom.

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, 2021.

The Company has certain agreements with licensors, licensees, collaborators, and vendors that contain indemnification provisions. In such provisions, the Company typically agrees to indemnify the licensor, licensee, collaborator, or vendor 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.

16. Net Loss 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:

	Years Ended December 31		
	2021	**2020**	**2019**
Numerator			
Net loss (in thousands)	$ (297,386)	$ (247,752)	$ (290,170)
Denominator			
Weighted-average number of common shares used in net loss per share—basic	36,321,351	33,709,480	30,414,203
Dilutive potential common shares	—	—	—
Weighted-average number of common shares used in net loss per share—diluted	36,321,351	33,709,480	30,414,203
Net loss per share—basic	$ (8.19)	$ (7.35)	$ (9.54)
Net loss per share—diluted	$ (8.19)	$ (7.35)	$ (9.54)

The number of weighted average options and RSUs that were not included in the diluted earnings per share calculation because the effect would have been anti-dilutive represented 5,552,325, 4,414,820, and 4,088,949 shares for the years ended 2021, 2020, and 2019, respectively.

17. Subsequent Events

On January 3, 2022, the Company awarded 985,531 options to purchase shares of common stock which are time-based awards, vesting over four years. In addition, the Company awarded 493,003 RSUs, vesting over four years and 30,000 performance-based stock options and 15,000 performance-based RSU awards, vesting over approximately four years, upon meeting performance conditions.

On January 7, 2022, January 20, 2022 and February 18, 2022, three putative stockholders of the Company filed complaints for alleged violation of the federal securities laws against the Company. See Note 15, *Commitments and Contingencies* of Notes to Consolidated Financial Statements for a description of these litigations.

On February 4, 2022, the Company extended the lease for the office and laboratory space in Irving, Texas, to extend until October 31, 2024, with an option to extend for a fixed twelve-month period.

We received a complete response letter (CRL) from the FDA in February 2022 with respect to its review of our NDA for bardoxolone in the treatment of patients with CKD caused by Alport syndrome. We will continue to work with the FDA to confirm our next steps on our Alport syndrome program.

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Management Leadership

J. Warren Huff
Founding Chief Executive Officer

Manmeet S. Soni
Chief Operating Officer, Chief Financial Officer and President

Dawn C. Bir
Chief Commercial Officer and Executive Vice President

Colin J. Meyer, M.D.
Chief Innovation Officer and Executive Vice President

Michael D. Wortley
Chief Legal Officer and Executive Vice President

Samina Khan, M.D.
Chief Medical Officer and Senior Vice President

Andrea Loewen
Senior Vice President, Global Regulatory Affairs

Board of Directors

J. Warren Huff
Founding Chief Executive Officer

Martin W. Edwards, M.D.
Retired

William D. McClellan, Jr.
Aerin Medical Inc.

R. Kent McGaughy, Jr.
CPMG, Inc.

Jack B. Nielsen
Vivo Capital, LLC

Christy J. Oliger
Retired

William E. Rose
Montrose Capital, Inc.

Shamin Ruff
Stoke Therapeutics

MOXIe FALCON EAGLE

Stockholder Information

Annual Stockholders Meeting

The annual meeting of stockholders will be held on June 8, 2022, at 8:00 a.m. Central Daylight Time in a virtual-meeting format only via live webcast as detailed in the proxy statement for the annual meeting.

Investor Inquiries

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www.reatapharma.com/contact-us

Stock Listing

NASDAQ: RETA

Transfer Agent

American Stock Transfer & Trust Company
6201 15th Avenue
Brooklyn, New York 11219

Annual Report on Form 10-K

The company's Annual Report on Form 10-K and other information may be obtained without charge in writing at Reata Pharmaceuticals, Inc., Attention: Secretary, 5320 Legacy Drive, Plano, Texas 75024; or by telephone at (469) 442-4772; or by going to Investors on our website at www.reatapharma.com.

2021 Annual Report

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REATA PHARMACEUTICALS