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

FORM 10-K

(Mark One)

x **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

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

FOR THE TRANSITION PERIOD FROM TO

COMMISSION FILE NUMBER 001-36485

ARDELYX, INC.
(EXACT NAME OF REGISTRANT AS SPECIFIED IN ITS CHARTER)

DELAWARE	**26-1303944**
(STATE OR OTHER JURISDICTION OF INCORPORATION OR ORGANIZATION)	**(I.R.S. EMPLOYER IDENTIFICATION NO.)**

400 FIFTH AVE., SUITE 210, WALTHAM, MASSACHUSETTS 02451
(ADDRESS OF PRINCIPAL EXECUTIVE OFFICES, INCLUDING ZIP CODE)

(510) 745-1700
(REGISTRANT'S TELEPHONE NUMBER, INCLUDING AREA CODE)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Trading Symbol(s)	Name of Each Exchange on Which Registered
Common Stock, par value $0.0001 per share	**ARDX**	**The Nasdaq Global Market**

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

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No x

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes o No x

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 x No o

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 x No o

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	x	Accelerated filer	o
Non-accelerated filer	o	Small reporting company	o
		Emerging growth company	o

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. o

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. x

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No x

The aggregate market value of the Registrant's common stock held by non-affiliates of the Registrant as of the last business day of the Registrant's most recently completed second fiscal quarter, June 30, 2021, based on the last reported sales price of the Registrant's common stock on the Nasdaq Global Market of $7.58 per share was $768,831,274.

The number of shares of Registrant's Common Stock outstanding as of February 23, 2022, was 130,294,254.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the Registrant's Definitive Proxy Statement for its 2022 Annual Meeting of Stockholders, which will be filed with the Commission within 120 days of December 31, 2021, the close of the Registrant's 2021 fiscal year, are incorporated by reference into Part III of this Report.

ARDELYX, INC.
FORM 10-K FOR THE FISCAL YEAR ENDED December 31, 2021
TABLE OF CONTENTS

NOTE REGARDING FORWARD-LOOKING STATEMENTS

Unless the context requires otherwise, in this Annual Report on Form 10-K the terms "Ardelyx", "we," "us," "our" and "the Company" refer to Ardelyx, Inc.

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "continue," "could," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "predict," "potential," "positioned," "seek," "should," "target," "will," "would," and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our expectations regarding our plans to commence the commercialization of IBSRELA® (tenapanor) in the U.S. for the treatment of irritable bowel syndrome with constipation ("IBS-C") in April 2022;

- our expectations regarding the timing of our receipt of a decision from the Office of New Drugs (“OND”) with respect to our appeal of the Appeal Denied Letter (“ADL”) received from the Office of Cardiology, Hematology, Endocrinology and Nephrology (“OCHEN”) of the United States ("U.S.) Food and Drug Administration (“FDA”) relating to our New Drug Application (“NDA”) for tenapanor for the control of serum phosphorus in adult patients with chronic kidney disease (“CKD”) on dialysis (the “Hyperphosphatemia Indication”);

- our expectations regarding our plans for our participation in the commercialization of XPHOZAH® (tenapanor) for the control of serum phosphorus in adult patients with CKD on dialysis in the U.S., if approved;

- our expectations regarding our Japanese collaboration partner’s plans to file a marketing authorization application with the Japanese Pharmaceuticals and Medical Devices Agency (“PMDA”) in the second half of 2022;

- our expectations regarding the potential market size and the size of the patient populations for IBSRELA and XPHOZAH;

- our plans with respect to RDX013 and RDX020;

- the implementation of our business model and strategic plans for our business, product candidates and technology;

- estimates of our expenses, future revenue, capital requirements, our needs for additional financing and our ability to obtain additional capital;

- our financial performance; and

- developments and projections relating to our competitors and our industry.

Factors that could cause actual results or conditions to differ from those anticipated by these and other forward-looking statements include those more fully described in the “ITEM 1A. RISK FACTORS” section and elsewhere in this Annual Report on Form 10-K. Except as required by law, we assume no obligation to update any forward-looking statement publicly, or to revise any forward-looking statement to reflect events or developments occurring after the date of this Annual Report on Form 10-K, even if new information becomes available in the future. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in any such forward-looking statement.

SUMMARY OF PRINCIPAL RISKS ASSOCIATED WITH OUR BUSINESS

- We have a limited operating history, have incurred significant losses since our inception and will incur losses in the future, which makes it difficult for us to assess our future viability.

- Although our financial statements have been prepared on a going concern basis, our current level of cash and investments alone is not sufficient to meet our operating plans for the next twelve months, raising substantial doubt regarding our ability to continue as a going concern.

- We will require substantial additional financing to achieve our goals, including our goals of commercializing IBSRELA beginning in April 2022 and pursuing a formal dispute resolution (“FDR”) process in response to the CRL received from the FDA relating to our NDA for tenapanor for the Hyperphosphatemia Indication and the inability to access necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our efforts to commercialize IBSRELA or to seek and obtain tenapanor for the Hyperphosphatemia Indication.
- Our failure to meet the continued listing requirements of The Nasdaq Global Market ("Nasdaq") could result in a de-listing of our common stock. On February 28, 2022, we received a letter from Nasdaq indicating that we have failed to comply with the minimum bid price requirement of Nasdaq Listing Rule 5550(a)(2). Nasdaq Listing Rule 5550(a)(2) requires that companies listed on the Nasdaq Capital Market maintain a minimum closing bid price of at least $1.00 per share. Under Nasdaq Listing Rule 5810(c)(3)(A), we have a 180 calendar day grace period to regain compliance by meeting the continued listing standard. To regain compliance, the closing bid price of the Company’s common stock must meet or exceed $1.00 per share for a minimum of ten consecutive business days during this grace period. We are monitoring the bid price of our common stock and will consider options available to us to achieve compliance. There can be no assurances that we will be successful in restoring our compliance with the Nasdaq listing requirements.

- We have never generated any revenue from product sales and may never be profitable.

- We are substantially dependent on the successful launch and commercialization of IBSRELA for IBS-C, and there is no guarantee that we will achieve sufficient market acceptance for IBSRELA; secure adequate coverage and reimbursement for IBSRELA; or generate sufficient revenue from product sales of IBSRELA .

- Our success is also dependent upon our ability to obtain regulatory approval for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis, and there can be no assurances that we will be successful in obtaining such regulatory approval.

- Even if we are successful in obtaining regulatory approval for tenapanor for control of serum phosphorus in adult patients with CKD on dialysis, the expense and time required to do so could adversely impact our ability to successfully commercialize XPHOZAH for the Hyperphosphatemia Indication.

- IBSRELA, and/or XPHOZAH, if approved and commercialized, may cause undesirable side effects or have other properties that could limit the commercial success of the product.

- We have no prior experience in the marketing, sale and distribution of pharmaceutical products; and there are significant risks in building and managing a sales organization.

- Third-party payor coverage and reimbursement status of newly-commercialized products are uncertain. Failure to obtain or maintain adequate coverage and reimbursement for IBSRELA and XPHOZAH, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

- We rely completely on third parties to manufacture IBSRELA, XPHOZAH and RDX013. If they are unable to comply with applicable regulatory requirements, unable to source sufficient raw materials, experience manufacturing or distribution difficulties or are otherwise unable to manufacture sufficient quantities to meet demand, our commercialization of IBSRELA, and XPHOZAH, if approved and commercialized, and our development efforts for tenapanor or RDX013 may be materially harmed.

- Our operating activities may be restricted as a result of covenants related to the indebtedness under our loan and security agreement and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.

NOTE REGARDING TRADEMARKS

ARDELYX®, IBSRELA®, and XPHOZAH® are trademarks of Ardelyx. All other trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners.

ITEM 1. BUSINESS

Company Overview

We are a biopharmaceutical company founded with a mission to discover, develop and commercialize innovative first-in-class medicines that meet significant unmet medical needs. This includes adult patients with irritable bowel syndrome with constipation (“IBS-C”), adult patients with chronic kidney disease (“CKD”) on dialysis suffering from elevated serum phosphorus, or hyperphosphatemia; and adult patients with CKD and/or heart failure with elevated serum potassium, or hyperkalemia.

Since commencing operations in October 2007, substantially all our efforts have been dedicated to our research and development (“R&D”) activities, including developing tenapanor and developing our proprietary drug discovery and design platform. We have not generated any revenues from product sales. As of December 31, 2021, we had an accumulated deficit of $712.9 million.

We expect to continue to incur substantial operating losses for the foreseeable future as we prepare for commercialization of IBSRELA® (tenapanor) in April of this year, seek to gain approval for XPHOZAH® (tenapanor) for the control of serum phosphorus in adult patients with CKD on dialysis; prepare for the potential commercialization of XPHOZAH, if approved; incur manufacturing and development cost for, tenapanor; and incur development costs for RDX013. To date, we have funded our operations from the sale and issuance of common stock and convertible preferred stock, funds from our collaboration partnerships, which includes license fees, milestones and product supply revenue, as well as funds from our loan agreements with our lenders.

Our Product Pipeline

IBSRELA for IBS-C

Our unique discovery platform and deep understanding of the primary mechanism of sodium transport in the intestine resulted in our discovery and development of IBSRELA, a first-in-class, FDA approved, sodium hydrogen exchanger 3 ("NHE3") inhibitor for the treatment of IBS-C in adults. IBSRELA acts locally in the gut and is minimally absorbed. By inhibiting NHE3, IBSRELA exerts a triple action mechanism. First, it blocks dietary sodium absorption, leading to increased intestinal transit time and softer stool to address constipation. Second, it decreases intestinal permeability to reduce abdominal pain, and, third, it decreases visceral hypersensitivity to reduce abdominal pain. The triple action mechanism of IBSRELA is differentiated from existing therapies and has been shown to provide significant improvement in abdominal pain, bloating, and constipation – with a quick onset of action and sustained efficacy. In clinical trials, treatment with IBSRELA has been demonstrated to result in improved quality of life versus placebo and patient treatment satisfaction.

We plan to launch IBSRELA in the U.S. in April 2022.

IBS-C is a gastrointestinal disorder characterized by both abdominal pain and altered bowel movements, estimated to affect 11 million people in the U.S. IBS-C is associated with significantly impaired quality of life, reduced productivity, and substantial economic burden. The introduction of new agents over the last decade has led to an established prescription ("RX") treated market with 9,000 writers accounting for 50% of the RXs. Despite the active use of GCC agonist therapies, 83% of Health Care Providers ("HCPs") report a significant unmet need for new therapies, and report that approximately 35% of the patients currently under their care do not adequately respond to the available treatments. When presented with the IBSRELA product profile, 75% of HCPs respond favorably, with the efficacy profile and novel method of action rated as the most compelling aspects of the product profile.

In preparation for our commercial launch of IBSRELA, we have built a commercial organization highly experienced in launching novel therapies into specialty areas. The established nature of the market, limited number of players, concentration of prescribers, recognized unmet need, and favorable response to the novel mechanism IBSRELA product profile enable a targeted promotional effort centered on the 9,000 health care providers that account for 50% of IBS-C prescriptions. Central to the go to market strategy is a highly experienced specialty sales force, many with existing relationships across their GI target base, full company engagement, and innovative peer-to-peer and digital initiatives leveraging the rapidly evolving market dynamics in how HCPs receive information and interact with industry.

With a concentrated promotional focus on patients currently being managed for IBS-C by high writing HCPs - in contrast to the DTC centered, market building approach taken by the existing GCC agonists - competition for IBSRELA will come largely from the four prescription products indicated for IBS-C: Linzess (linaclotide); Amitiza (lubiprostone); Trulance (plecanatide) and Zelnorm (tegaserod). Additionally, over the counter products are commonly used to treat the constipation component of IBS-C, both alone, and in combination with the IBS-C indicated RX therapies.

We have established commercial agreements with Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd. (“Fosun Pharma”) in China and Knight Therapeutics, Inc. (“Knight”) in Canada for IBSRELA for IBS-C. Knight is currently marketing IBSRELA in Canada.

Development Candidate XPHOZAH: A New Approach for The Control of Serum Phosphorus in Adult Patients with CKD on Dialysis

XPHOZAH is a first-in-class medicine being developed for the control of serum phosphorus in adult patients with CKD on dialysis. XPHOZAH has a unique mechanism of action and acts locally in the gut to inhibit NHE3. This results in the tightening of the epithelial cell junctions, thereby significantly reducing paracellular uptake of phosphate, the primary pathway of phosphate absorption. If approved, XPHOZAH would be the first therapy for phosphate management that blocks phosphorus absorption at the primary site of uptake. It is not a phosphate binder.

In June 2020, we submitted a new drug application ("NDA") to the U.S. Food and Drug Administration (“FDA”) for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. The NDA was supported by three Phase 3 trials involving over 1,000 adult patients that evaluated the use of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis, with two trials evaluating tenapanor as monotherapy and one trial evaluating tenapanor as part of a dual mechanism approach with phosphate binders. All three Phase 3 trials met their primary and key secondary endpoints.

On July 28, 2021, we received a Complete Response Letter ("CRL") from the FDA’s Division of Cardiology and Nephrology (the “Division”) regarding our NDA for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. According to the CRL, while the Division agrees “that the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in adult patients with CKD on dialysis,” the Division characterizes the magnitude of the treatment effect as “small and of unclear clinical significance.” Following an End-of-Review Type A meeting (“End of Review Meeting”) in October 2021, with the Division, we submitted a Formal Dispute Resolution Request (“FDRR”) in December 2021 to the Office of Cardiology, Hematology, Endocrinology and Nephrology (“OCHEN”). The FDRR was focused on demonstrating that the data submitted in the NDA supported the clinical significance of the treatment effect of tenapanor.

On February 4, 2022, we received an Appeal Denied Letter (“ADL”) from OCHEN. On February 18, 2022, we submitted an appeal of the ADL to the FDA’s Center for Drug Evaluation and Research, Office of New Drugs (“OND”). If accepted, we expect a decision on the appeal to the OND in April 2022. While the CRL noted that in order for the NDA to be approved, we need to conduct an additional adequate and well-controlled trial demonstrating a clinically relevant treatment effect on serum phosphorus or an effect on the clinical outcome thought to be caused by hyperphosphatemia in adult patients with CKD on dialysis, the ADL provided a potential additional path forward involving the resubmission of the NDA (without conducting an additional trial) with a number of new analyses of each of our Phase 3 clinical trials; an assessment of tenapanor’s benefits and risks; and a proposal of how to label tenapanor for prescribers. There can be no assurances that the Formal Dispute Resolution (“FDR”) process will result in approval of our NDA, or in a clear path to resubmission of our NDA that is achievable in terms of clinical endpoints, time and cost.

RDX013 Program: Small Molecule for Treating Hyperkalemia

We are also advancing a small molecule potassium secretagogue program, RDX013, for the potential treatment of hyperkalemia. Hyperkalemia is a common problem in patients with heart and kidney disease, particularly in patients taking customary blood pressure medications known as renin-angiotensin-aldosterone system (“RAAS”) inhibitors. RDX013 is a novel mechanism agent designed to target the underlying biological mechanisms of potassium secretion to lower elevated potassium. While currently available therapies are all ion exchange agents, RDX013 is a first in class secretagogue with demonstrated proof of concept in a Phase 2 dose ranging study evaluating the safety and pharmacodynamics of RDX013 in adult patients with hyperkalemia. The next steps for RDX013 will be determined based on final analyses of the Phase 2 results, continued formulation development, and sufficient financial resources.

RDX020 Program: Small molecule for Treating Metabolic Acidosis

We have an ongoing discovery program targeting the inhibition of bicarbonate exchange inhibitor for the treatment of metabolic acidosis, a highly prevalent comorbidity in CKD patients that is strongly correlated with disease progression and adverse outcomes. We have identified lead compounds that are potent, selective and proprietary inhibitors of bicarbonate secretion. Our research organization was eliminated as part of our October 2021 restructuring, and therefore, we currently expect to continue to advance this discovery program utilizing third-party resources managed by internal non-clinical expertise.

Our Commercial Strategy

We have developed a portfolio of novel products to address unmet medical needs across gastrointestinal and cardiorenal therapeutic areas and intend to commercialize our products in the United States. We have established a high-quality commercial organization highly experienced in bringing novel products to our customers, including patients, payors and healthcare providers. Our commercial capabilities, including marketing, access, patient services and sales are designed to support our commercialization of IBSRELA, and will enable the commercialization of XPHOZAH, if approved. We have executed ex-U.S. collaborations with established industry leaders to efficiently bring XPHOZAH for hyperphosphatemia and IBSRELA for IBS-C to adult patients in specific territories outside of the Unites States.

We continue to evaluate our strategy for the commercialization of IBSRELA and XPHOZAH in other ex-U.S. territories.

Collaboration Partners

We have exclusive rights to tenapanor in the U.S. and we have established agreements with Kyowa Kirin Co., Ltd. ("KKC") in Japan, Fosun Pharma in China and Knight in Canada for the development and commercialization of tenapanor for certain indications in their respective territories.

Knight has exclusive rights for the development, commercialization and distribution of tenapanor in Canada for hyperphosphatemia and IBS-C. In March 2021, Knight announced the commercial availability of IBSRELA in Canada, following its approval by Health Canada in April 2020. Under the terms of the agreement with Knight, we received a $2.3 million nonrefundable, one-time upfront payment in March 2018 and are eligible to receive additional development and commercialization milestone payments worth up to $17.4 million. We are also eligible to receive royalties throughout the term of the agreement, and a transfer price for manufacturing services.

KKC has exclusive rights for the development, commercialization and distribution of tenapanor in Japan for cardiorenal indications. In April 2021, we announced that KKC had commenced four phase 3 clinical trials in Japan evaluating tenapanor for hyperphosphatemia. The phase 3 clinical trials consist of a multi-center, randomized, double-blind, placebo-controlled, parallel-group comparative study; a phosphate binder-combination parallel-group comparative study; an open-label, single-arm study evaluating adult hyperphosphatemia patients on peritoneal dialysis; and a long-term study evaluating serum phosphorus in adult patients who switch from one or more phosphate binders to tenapanor. KKC has publicly announced its plans to file a marketing authorization application with the Japanese Pharmaceuticals and Medical Devices Agency (“PMDA”) in the second half of 2022. Under the terms of the agreement with KKC, we received a $30.0 million upfront payment from KKC, and we may be entitled to receive up to $55.0 million in total development milestones, of which $10.0 million has been received and recognized as revenue as of December 31, 2021, and approximately ¥8.5 billion for commercialization milestones, or approximately $73.9 million at the currency exchange rate on December 31, 2021, as well as high-teen royalties on net sales throughout the term of the agreement.

Fosun Pharma has exclusive rights for the development and commercialization for the development, commercialization and distribution of tenapanor in China for both hyperphosphatemia and IBS-C. Under the terms of the Fosun Agreement, we received $12.0 million in upfront license, and we may be entitled to additional development and commercialization milestones of up to $110.0 million, as well as reimbursement of cost plus a reasonable overhead for the supply of product and tiered royalties on net sales ranging from the mid-teens to 20%.

Corporate Restructurings

On July 29, 2021, our Board of Directors approved, and on August 2, 2021, we began implementing a restructuring plan to better align our workforce and anticipated commercial and development spend with our capital resources and the needs of our business following the receipt of the CRL for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. Under the restructuring plan, we reduced our workforce by 83 employees (approximately 33%). Impacted employees

received cash payments equal to their base pay for a notice period of sixty (60) days and Company funded COBRA premiums through such notice period.

Following the conclusion of our End of Review Meeting with the FDA, in October 2021, we began to implement an additional restructuring plan to further reduce operating costs and better align our workforce with the needs of our business. Under the restructuring plan, we planned to reduce our workforce by approximately 100 of our remaining employees (approximately 60%). The impacted employees received notice that their positions would be eliminated on December 15, 2021.

On November 30, 2021, we announced plans to launch IBSRELA, our approved treatment for IBS-C in adults. In connection with the planned launch of IBSRELA, which we currently expect to occur in April 2022, we retained 28 of the employees whose positions were originally planned to be eliminated as part of the restructuring plan, thereby reducing the number of employees impacted by the restructuring plan to 72. The restructuring plan, which resulted in the elimination of our research organization was substantially completed in December 2021.

Employees who were impacted by the restructurings were eligible to receive severance benefits and Company funded COBRA premiums, contingent upon an impacted employee's execution (and non-revocation, where applicable) of a separation agreement, which included a general release of claims against us. In connection with the restructurings, we have incurred restructuring charges of $6.2 million, which were recorded during the twelve months ended December 31, 2021, related to one-time employee termination benefits, including severance payments and other employee-related costs. Of these charges, $2.7 million was recorded in research and development expenses, and $3.5 million was recorded in general and administrative expense in the accompanying statements of operations and comprehensive loss. Most of the cash payments related to the reduction in workforce were disbursed during the twelve months ended December 31, 2021. We have reported the remaining estimated liability of $0.5 million as accrued compensation and benefits in our Balance Sheet as of December 31, 2021.

CORPORATE DEVELOPMENT

In July 2020, we filed a Form S-3 registration statement, which became effective in August 2020, containing (i) a base prospectus for the offering, issuance and sale by us of up to a maximum aggregate offering price of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units, from time to time in one or more offerings; and (ii) a prospectus supplement for the offering, issuance and sale by us of up to a maximum aggregate offering price of $100.0 million of our common stock that may be issued and sold, from time to time, under an Open Market Sales Agreement with Jefferies LLC, as sales agent, deemed to be "at-the-market offerings" (the "2020 Open Market Sales Agreement"). Pursuant to the 2020 Open Market Sales Agreement, Jefferies, as sales agent, received a commission of up to 3.0% of the gross sales price for shares of common stock sold under the 2020 Open Market Sales Agreement. We sold a cumulative total of 23.3 million shares and received gross proceeds of $100.0 million at a weighted average sales price of approximately $4.30 per share under the 2020 Open Market Sales Agreement.

In August 2021, we filed an additional prospectus supplement under the Registration Statement for the offering, issuance and sale by us of up to a maximum aggregate offering price of $150.0 million of our common stock that may be issued and sold, from time to time, under an additional sales agreement we entered into with Jefferies (the "2021 Open Market Sales Agreement"), pursuant to which we may, from time to time, sell up to $150.0 million in shares of our common stock through Jefferies. We are not required to sell shares under the 2021 Open Market Sales Agreement. Pursuant to the 2021 Open Market Sales Agreement, Jefferies, as our sales agent, receives a commission of up to 3.0% of the gross sales price for shares of common stock sold under the 2021 Open Market Sales Agreement. As of December 31, 2021, we have sold 15.7 million shares and received gross proceeds of $25.0 million at a weighted average sales price of approximately $1.60 per share under the 2021 Open Market Sales Agreement.

In December 2019, we completed an underwritten public offering of 23.0 million shares of common stock, resulting in the receipt of aggregate gross proceeds of approximately $143.8 million, less underwriting discounts, commissions and offering expenses totaling approximately $8.9 million, which resulted in net proceeds of approximately $134.9 million.

In November 2019, we enhanced our strategic partnership with KKC by entering into a Stock Purchase Agreement, pursuant to which we sold to KKC an aggregate of 2.9 million shares of our common stock for aggregate gross proceeds of approximately $20.0 million.

As of December 31, 2021, we had cash, cash equivalents and investments totaling $116.7 million.

INTELLECTUAL PROPERTY

Our commercial success depends in part on our ability to obtain and maintain proprietary protection for our drug candidates, manufacturing and process discoveries, and other know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our intellectual property by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology and inventions that are important to the development and operation of our business. We also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of our issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the U.S. Patent and Trademark Office (the "USPTO") to determine priority of invention, which would result in substantial costs to us even if the eventual outcome is favorable to us.

The term of individual patents depends upon the legal term of the patents in countries in which they are obtained. In most countries, including the United States, the patent term is generally 20 years from the earliest date of filing a non-provisional patent application in the applicable country. In the U.S., a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over a commonly owned patent or a patent naming a common inventor and having an earlier expiration date.

In addition, in the United States, the Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of a U.S. patent as partial compensation for the patent term lost during the FDA regulatory review process occurring while the patent is in force. A patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one patent applicable to each regulatory review period may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. Similar provisions are available in the European Union and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug.

We may rely, in some circumstances, on trade secrets to protect our technology. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaboration partners, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning the business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during the normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

Tenapanor Patents

Our tenapanor patent portfolio is wholly owned by us. This portfolio includes five issued U.S. patents, three issued Israeli patents, two issued patents in each of European Patent Organization, Japan, Korea, Hong Kong and Mexico and one issued patent in each of the following territories: Australia, Brazil, India, and China. These issued patents cover the composition and certain methods of using tenapanor and are predicted, without extension or adjustment, to expire in December 2029. The portfolio further includes patents covering the use of tenapanor for the control of serum phosphorus that have been issued in the U.S., Europe, Japan, China, Australia, Gulf Co-op countries, Hong Kong, Israel, Korea, Mexico, New Zealand, Russia and Taiwan and is pending in other countries. These patents are predicted, without extension or adjustment, to expire in April 2034.

Additional U.S. and international patent applications are pending covering additional methods of treatment with tenapanor, and composition of matter and methods of using compounds that we believe may be follow on compounds to tenapanor.

Other Program Patents

We have patent applications pending in the U.S. and internationally that cover the compositions and methods of using compounds in our RDX013 program.

MANUFACTURING

To date, we have relied upon third-party contract manufacturing organizations (“CMOs”) to manufacture both the active pharmaceutical ingredient and final drug product dosage forms of our potential drug candidates used as clinical trial material. We expect that we will continue to rely upon CMOs for the manufacture of commercial product for IBSRELA, our clinical trial materials and for our commercial product requirements for XPHOZAH, when and if regulatory approval is received. Our license agreements with Knight, and Fosun Pharma require us to supply final drug product dosage forms of tenapanor for their use in the development and commercialization of tenapanor in each of their respective territories. We are further obligated to supply active pharmaceutical ingredient to KKC to support their development and commercialization of tenapanor in Japan. We expect that we will use CMOs to satisfy our supply obligations to our collaboration partners.

GOVERNMENT REGULATION

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of drugs. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling, and export and import of our product candidates.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act (the “FFDCA”) and the FDA’s implementing regulations. If we fail to comply with applicable FDA or other requirements at any time during the drug development process, the approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA’s refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us. FDA approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States.

The process required by the FDA before a drug may be marketed in the United States generally involves:

- completion of extensive preclinical laboratory tests, preclinical animal studies and formulation studies, some performed in accordance with the FDA’s current Good Laboratory Practice (“GLP”) regulations;
- submission to the FDA of an Investigational New Drug (“IND”) application which must become effective before human clinical trials in the United States may begin;
- approval by an independent institutional review board, (“IRB”) or ethics committee at each clinical trial site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with Good Clinical Practice ("GCP") regulations to establish the safety and efficacy of the drug candidate for each proposed indication;
- submission to the FDA of a new drug application (“NDA”);
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current Good Manufacturing Practice (“cGMP”) regulations;
- satisfactory completion of a potential review by an FDA advisory committee, if applicable; and
- FDA review and approval of the NDA prior to any commercial marketing, sale or commercial shipment of the drug.

The preclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Nonclinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The results of preclinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol and other information, are submitted as part of an IND to the FDA. Additional preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day period, raises concerns or questions relating to the IND and places the clinical trial on a clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development.

Clinical trials involve the administration of the investigational drug to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be used. Each protocol must be submitted to the FDA as part of the IND.

An independent IRB or ethics committee for each medical center proposing to conduct a clinical trial must also review and approve a plan for any clinical trial before it can begin at that center and the IRB must monitor the clinical trial until it is completed. The FDA, the IRB, or the sponsor may suspend or discontinue a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP requirements, including the requirements for informed consent.

All clinical research performed in the United States in support of an NDA must be submitted in advance by the FDA under the IND regulations and procedures described above. However, a sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA so long as the clinical trial is conducted in compliance with GCP and if the FDA is able to validate the data from the study through an onsite inspection, if necessary. GCP includes review and approval by an independent ethics committee, such as an IRB, and obtaining and documenting the freely given informed consent of each subject before study initiation. If the applicant seeks approval of an NDA solely on the basis of foreign data, the FDA will only accept such data if they are applicable to the U.S. population and U.S. medical practice, the studies have been performed by clinical investigators of recognized competence, and the data may be considered valid without the need for an on-site inspection by the FDA, or if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or through other appropriate means.

Clinical Trials

The clinical investigation of a new drug is typically conducted in three or four phases, which may overlap or be combined, and generally proceed as follows.

- *Phase 1*: Clinical trials are initially conducted in a limited population of subjects to test the drug candidate for safety, dose tolerance, absorption, metabolism, distribution and excretion in healthy humans or, on occasion, in patients with severe problems or life-threatening diseases to gain an early indication of its effectiveness.

- *Phase 2*: Clinical trials are generally conducted in a limited patient population to evaluate dosage tolerance and appropriate dosage, identify possible adverse effects and safety risks, and evaluate preliminarily the efficacy of the drug for specific targeted indications in patients with the disease or condition under study.

- *Phase 3*: Clinical trials are typically conducted when Phase 2 clinical trials demonstrate that a dose range of the product candidate is effective and has an acceptable safety profile. Phase 3 clinical trials are commonly referred to as “pivotal” studies, which typically denotes a study which presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug. Phase 3 clinical trials are generally undertaken with large numbers of patients, such as groups of several hundred to several thousand, to further evaluate dosage, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse patient population at multiple, geographically-dispersed clinical trial sites.

- *Phase 4*: In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor’s agreement to conduct additional clinical trials after NDA approval. In other cases, a sponsor may voluntarily conduct

additional clinical trials post approval to gain more information about the drug. Such post approval trials are typically referred to as Phase 4 clinical trials.

Concurrent with clinical trials, companies usually complete additional nonclinical studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the drug in commercial quantities in accordance with GMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

The FDA, the IRB or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate.

New Drug Applications

The results of preclinical studies and of the clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the drug, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use.

Under the Prescription Drug User Fee Act, the FDA has a goal of responding to standard review NDAs for new molecular entities within ten months after the 60-day filing review period, or six months after the 60-day filing review period for priority review NDAs and for non-new molecular entities, within ten months of receipt of standard review NDAs and six month of receipt for priority review NDAs, but this timeframe is often extended by FDA requests for additional information or clarification. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an application, the FDA may inspect the facility or the facilities at which the finished drug product, and sometimes the active pharmaceutical ingredient (“API”) is manufactured, and will not approve the drug unless cGMP compliance is satisfactory. The FDA may also inspect the sites at which the clinical trials were conducted to assess their compliance and will not approve the drug unless compliance with GCP requirements is satisfactory.

After the FDA evaluates the NDA and conducts inspections of manufacturing facilities where the drug product and/or its API will be produced, if deemed necessary, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete, and the application is not ready for approval. A Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. The FDA could also approve the NDA with a Risk Evaluation and Mitigation Strategy (“REMS”) if it is determined that a REMS is necessary to ensure that the drug’s benefits outweigh its risks and a REMS to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post-market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product’s safety and effectiveness after commercialization. The FDA has the authority to prevent or limit further marketing of a drug based on the results of these post-marketing programs. Once the FDA approves an NDA, or supplement thereto, the FDA may withdraw the approval if ongoing regulatory requirements are not met or if safety problems are identified after the drug reaches the market.

Drugs may be marketed only for the FDA approved indications and in accordance with the provisions of the approved labeling. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing

processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the applicant to develop additional data or conduct additional preclinical studies and clinical trials.

The testing and approval processes require substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. Even if we believe a clinical trial has demonstrated safety and efficacy of one of our drug candidates for the proposed indication, the results may not be satisfactory to the FDA. Nonclinical and clinical data may be interpreted by the FDA in different ways, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals which could delay or preclude us from marketing drugs. The FDA may limit the indications for use or place other conditions on any approvals that could restrict the commercial application of the drugs. After approval, certain changes to the approved drug, such as adding new indications, manufacturing changes, or additional labeling claims are subject to further FDA review and approval. Depending on the nature of the change proposed, an NDA supplement must be filed and approved before the change may be implemented.

Other Regulatory Requirements

Any drugs manufactured or distributed by us or our collaboration partners pursuant to FDA approvals would be subject to continuing regulation by the FDA, including recordkeeping requirements and reporting of adverse experiences associated with the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic announced and unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as warning or untitled letters, suspension of manufacturing, seizure of product, injunctive action or possible civil penalties. We cannot be certain that we or our present or future third-party manufacturers or suppliers will be able to comply with the cGMP regulations and other ongoing FDA regulatory requirements. If we or our present or future third-party manufacturers or suppliers are not able to comply with these requirements, the FDA may, among other things, halt our clinical trials, require us to recall a drug from distribution or withdraw approval of the NDA for that drug.

The FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet. A company can make only those claims relating to safety and efficacy that are in the final label or consistent with the final label. Failure to comply with these requirements can result in, among other things, adverse publicity, warning or untitled letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available drugs for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use.

Hatch-Waxman Act

Under the Price Competition and Patent Term Restoration Act, or Hatch-Waxman Act, Section 505 of the FFDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A Section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A Section 505(b)(2) NDA is an application that contains full reports of investigations of safety and efficacy but where at least some of the information required for approval comes from investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. This regulatory pathway enables the applicant to rely, in part, on the FDA's prior findings of safety and efficacy for an existing product, or published literature, in support of its application. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application ("ANDA"). An ANDA provides for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics and intended use, among other things, to a previously approved product. ANDAs are termed "abbreviated" because they are generally not required to include nonclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through in vitro, in vivo, or other testing. The generic version must deliver the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovator drug and can often be substituted by pharmacists under prescriptions written for the reference listed drug. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the

applicant's drug or a method of using the drug. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA or 505(b)(2) NDA.

Upon submission of an ANDA or a 505(b)(2) NDA, an applicant must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through the last type of certification, also known as a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all of the listed patents claiming the referenced product have expired.

If the ANDA or 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must send notice of the Paragraph IV certification to the NDA holder and patent owners once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. If the Paragraph IV certification is challenged by an NDA holder or the patent owner(s), the FDA may not approve that application until the earlier of 30 months from the receipt of the notice of the Paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent was favorably decided in the applicant's favor or settled, or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay. In instances where an ANDA or 505(b)(2) NDA applicant files a Paragraph IV certification, the NDA holder or patent owner(s) regularly take action to trigger the 30-month stay, recognizing that the related patent litigation may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) NDA could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation.

The Hatch-Waxman Act establishes periods of regulatory exclusivity for certain approved drug products, during which the FDA cannot approve (or in some cases accept) an ANDA or 505(b)(2) application that relies on the branded reference drug. For example, the holder of an NDA, including a 505(b)(2) NDA, may obtain five years of exclusivity upon approval of a new drug containing a new chemical entity ("NCE") that has not been previously approved by the FDA. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the therapeutic activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a Paragraph IV certification of patent invalidity or non-infringement.

The Hatch-Waxman Act also provides three years of marketing exclusivity to the holder of an NDA (including a 505(b)(2) NDA) for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant. This three-year exclusivity period protects against FDA approval of ANDAs and 505(b)(2) NDAs for the specific condition of the new drug's approval. As a general matter, the three-year exclusivity does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy.

Fraud and Abuse Laws

In the U.S. the research, manufacturing, distribution, sale and promotion of drug products and medical devices are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare & Medicaid Services ("CMS") other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, state Attorneys General, and other state and local government agencies. These laws include but are not limited to, the Anti-Kickback Statute, the federal False Claims Act, the federal Physician Payments Sunshine Act, and other state and federal laws and regulations.

The Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchase, order, or prescription of a particular drug, for which payment may be made under a federal

healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

The federal False Claims Act prohibits anyone from knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Moreover, the government may assert 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 False Claims Act. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties for each separate false claim, the potential for exclusion from participation in federal healthcare programs. As well, although the federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. If the government were to allege that we were, or convict us of, violating these false claims laws, we could be subject to a substantial fine and may suffer a decline in our stock price. In addition, private individuals have the ability to bring actions under the federal False Claims Act.

In addition to the laws described above, the Physician Payments Sunshine Act requires certain drug manufacturers to report payments and other transfer of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants and certified nurse midwives) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties, and additional penalties for knowing failures, for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Manufacturers must submit reports by the 90th day of each subsequent calendar year.

Many states have also adopted laws similar to the federal laws discussed above. Some of these state prohibitions apply to the referral of patients for healthcare services reimbursed by any insurer, not just federal healthcare programs such as Medicare and Medicaid. There has also been a recent trend of increased regulation of payments made to physicians and other healthcare providers. Certain states mandate implementation of compliance programs, impose restrictions on drug manufacturers' marketing practices and/or require the tracking and reporting of pricing and marketing information as well as gifts, compensation and other remuneration to physicians. Many of these laws contain ambiguities as to what is required to comply with such laws, which may affect our sales, marketing, and other promotional activities by imposing administrative and compliance burdens on us. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state and perhaps federal, authorities.

Violations of any of such laws or any other governmental regulations that apply may result in penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of operations, reporting obligations and integrity oversight, exclusion from participation in federal and state healthcare programs and imprisonment.

Third-Party Coverage and Reimbursement

Sales of pharmaceutical products depend in significant part on the availability of coverage and adequate reimbursement by third-party payors, such as state and federal governments, including Medicare and Medicaid, and commercial managed care providers. In the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for our product candidates, if approved, will be made on a payor by payor basis. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. A decision by a third-party payor not to cover our product candidates could reduce physician utilization of our products once approved and have a material adverse effect on our future sales, results of operations and financial condition. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate

reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

There is increased uncertainty related to insurance coverage and reimbursement for certain drugs, like XPHOZAH, which, if approved, will be marketed for the control of serum phosphorus in adult patients with CKD on dialysis. In January 2011, CMS implemented a new prospective payment system for dialysis treatment. Under the ESRD prospective payment system, CMS generally makes a single bundled payment to the dialysis facility for each dialysis treatment that covers all items and services routinely required for dialysis treatments furnished to Medicare beneficiaries in Medicare-certified ESRD facilities or at their home, including the cost of certain routine drugs. The inclusion of oral medications without injectable or intravenous equivalents in the bundled payment was initially delayed until January 1, 2014 and through several subsequent legislative actions was delayed until January 1, 2025. As a result, absent further legislation or regulation on this matter, beginning in 2025, oral ESRD-related drugs without injectable or intravenous equivalents may be included in the ESRD bundle and separate Medicare payment for these drugs will no longer be available, as is the case today under Medicare Part D. While it is too early to project the full impact that bundling may have on XPHOZAH and our business should XPHOZAH be brought into the bundle in 2025, or at any time, we may be unable to sell XPHOZAH, if approved, to dialysis providers on a profitable basis if third-party payors reduce their current levels of payment, or if our costs of production are higher than levels necessary for an appropriate gross margin after payment of all discounts, rebates and chargebacks.

Healthcare Reform

In March 2010, Congress passed the Patient Protection and Affordable Care Act, a healthcare reform measure (the “ACA”). The ACA was signed into law and substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacted the pharmaceutical industry.

The ACA contained a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement changes and fraud and abuse measures, which have impacted existing government healthcare programs and have resulted in the development of new programs, including Medicare payment for performance initiatives and improvements to the physician quality reporting system and feedback program.

Additionally, the ACA:

- increased the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1% of the average manufacturer price;
- required collection of rebates for drugs paid by Medicaid managed care organizations;
- expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer’s Medicaid rebate liability;
- expanded access to commercial health insurance coverage through new state-based health insurance marketplaces, or exchanges;
- required manufacturers to participate in a coverage gap discount program, under which they must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D; and
- imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell “branded prescription drugs” to specified federal government programs.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the “individual mandate” was repealed by Congress. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace from February 15, 2021 through August 15, 2021. The executive order instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and, due to subsequent legislative amendments, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 and a 1% reduction from April 1, 2022 through June 30, 2022, unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, beginning January 1, 2024.

Recently, there has also been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. By way of example, the Build Back Better Act, if enacted, would introduce substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, and the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D. If the Build Back Better Act is not enacted, similar or other drug pricing proposals could appear in future legislation. Additionally, individual states have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and to encourage importation from other countries and bulk purchasing. These new laws and the regulations and policies implementing them, as well as other healthcare reform measures that may be adopted in the future, may have a material adverse effect on our industry generally and on our ability to successfully develop and commercialize our products.

Government Price Reporting

Medicaid is a joint federal and state program for low-income and disabled beneficiaries. Medicare is a federal program covering individuals age 65 and over as well as those with certain disabilities. As a condition of having federal funds being made available for our covered drugs under Medicaid, we intend to enroll in the Medicaid Drug Rebate Program ("MDRP"), which would require us to pay a rebate to state Medicaid programs for each unit of our covered drugs dispensed to a Medicaid beneficiary and paid for by a state Medicaid program. Medicaid drug rebates are based on pricing data that we must report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services ("CMS"), the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the average manufacturer price ("AMP") and the best price ("BP") for each drug. If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. Manufacturers who fail to provide information timely or are found to have knowingly submitted false information to the government may be subject to civil monetary penalties and other sanctions, including termination from the MDRP.

Federal law requires that a manufacturer that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program (the "340B program") in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. We intend to participate in the 340B program, which is administered by the Health Resources and Services Administration ("HRSA"), and requires us to charge statutorily defined covered entities no more than the 340B "ceiling price" for the our covered outpatient drugs used in an outpatient setting. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price calculated using a statutory formula, which is based on the AMP and rebate amount for the covered outpatient drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B-eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have drug products paid for with federal funds under Medicaid and purchased by certain federal agencies and grantees, manufacturers must also participate in the U.S. Department of Veterans Affairs ("VA") Federal Supply Schedule ("FSS") pricing program. Under the VA/FSS program, manufacturers must report the Non-Federal Average Manufacturer Price ("Non-FAMP") for their covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non-FAMP using a statutory formula. These four agencies are the VA, the U.S. Department of Defense, the U.S. Coast Guard, and the U.S. Public Health Service (including the Indian Health Service). Manufacturers must also pay rebates on products purchased by military personnel and dependents through the TRICARE retail pharmacy program. Manufacturers who fail to provide timely information or are found to have knowingly submitted false information may be subject to civil monetary penalties.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information.

Data Privacy and Security Laws

Numerous state, federal and foreign laws, including consumer protection laws and regulations, govern the collection, dissemination, use, access to, confidentiality and security of personal information, including health-related information. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws, including the Health Insurance Portability and Accountability Act of 1996, as amended, and regulations promulgated thereunder (collectively "HIPAA"), and federal and state consumer protection laws and regulations (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure, and protection of health-related and other personal information could apply to our operations or the operations of our partners. In addition, certain state laws, such as the California Consumer Privacy Act ("CCPA") and the California Privacy Rights Act ("CPRA") govern the privacy and security of personal data, including health-related data in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Further, certain foreign laws govern the privacy and security of personal data, including health-related data. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing.

Other Regulations

We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control, and disposal of hazardous or potentially hazardous substances. We may incur significant costs to comply with such laws and regulations now or in the future.

Impact of COVID-19

The global COVID-19 pandemic has impacted the operational decisions of companies worldwide. It also has created and may continue to create significant uncertainty in the global economy. We have undertaken measures to protect our employees, partners, collaborators, and vendors, some of which impact our normal operations. To date, we have been able to continue our operations with our workforce, most of whom are working remotely, and our pre-existing infrastructure that supports secure access to our internal systems. If, however, the COVID-19 pandemic has a substantial impact on the productivity of our employees, our ability to successfully prepare for and execute the commercial launch of IBSRELA, including our ability to hire and successfully integrate into the company the new personnel required to prepare for such launch, or our ability to pursue our appeal of the ADL issued by OHCEN following the issuance of a CRL for our NDA for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis, the results of our operations and overall financial performance may be adversely impacted. The extent of the impact from the COVID-19 pandemic on our business will depend largely on future developments that are highly uncertain and cannot be predicted. For a discussion of risks of COVID-19 relating to our business, see "Item 1A. - Risk Factors- Risks Related to Our Business- The ongoing COVID-19 pandemic, or any other outbreak of epidemic diseases, or the perception of their effects, could have a material adverse effect on our business, financial condition,

results of operations or cash flows." As of the date of issuance of this financial report, we are not aware of any specific event or circumstance that would require updates to our estimates and judgments or revisions to the carrying value of our assets or liabilities. These estimates may change as new events occur and additional information is obtained.

Human Capital

The future success of our company depends on our ability to attract, retain, and further develop top talent. We plan to launch IBSRELA in April 2022 and, as a result, we are building an experienced commercial team and expanding our internal resources to support a commercial organization. During this ongoing transition and expansion of our workforce, we remain steadfastly committed to our core values, including our goal to develop and maintain an inclusive, diverse, and safe workplace with opportunities for our employees to grow and develop in their careers, supported by strong compensation and benefits.

At December 31, 2021, we had approximately 86 full-time employees, 55 of whom were engaged directly in development and manufacturing, and 31 in marketing, sales and administrative activities. During 2021 our employee base decreased by approximately 43, or 33%, primarily as a result of our restructurings in August 2021 and October 2021.

Inclusion and Diversity

Our culture is supported by an unwavering commitment to inclusion and diversity. As of December 31, 2021, approximately 63% of our workforce was female; 43% of our executive leadership team was female and 56% of our employees in managerial roles were female. As of December 31, 2021, minorities represented approximately 39% of our workforce, of which 41% of our employees in managerial roles were minorities. We strive to foster a culture where mutual respect, inclusive behavior, and dignity are core to our individual expectations.

We believe that our success will be significantly impacted by our ability to create and maintain a safe inclusive environment where everyone is empowered to do their best work—regardless of race, color, national origin, religion, sex, sexual orientation, gender identity and expression, age, or disability. We are united by our desire to serve our patients, and we are proud financial sponsors of the California Life Sciences Association Racial and Social Equity Initiative, a first step in a unified effort for the life sciences industry in California to do more for the under-served and under-represented, focusing on the most critical need to address the inequality for Black, Hispanic, Native American and Pacific Islander populations in California.

Core Values

Fostering and maintaining a strong, healthy culture is a key strategic focus. Our core values reflect who we are and the way our employees interact with one another, our partners and our stockholders. We are dedicated to our core values, recognizing that this dedication will foster an environment where we will be able to realize our vision of advancing patient care. We are Passionate, aware that with integrity and determination, we make a difference for patients. We are Fearless, aware that by challenging convention, we truly innovate. We are Dedicated, aware that working tirelessly together, we are greater than the sum of our parts. We are Inclusive, aware that with respect, grace and humor, we are family. We encourage our employees to live out our core values and to discuss our core values with potential candidates looking to join our team. We believe that this is an important step in helping our culture stay strong and unique.

Health, Safety, and Wellness

The health, safety, and wellness of our employees is a priority in which we have always invested, and will continue to do so. These investments and the prioritization of employee health, safety, and wellness took on particular significance in light of COVID-19. In response to the COVID-19 pandemic, we implemented significant changes that we determined were in the best interest of our employees, as well as the communities in which we operate, in compliance with government regulations. This included having the vast majority of our employees work from home. We have reopened our facilities and are currently inviting our employees to return to our facilities in the manner in which they are comfortable. We will continue to monitor infection rates and severity of disease in those communities in which are facilities are located and will continue to adopt and align our policies to focus on the health, safety and wellness of our employees, and the needs of our business.

Compensation and Benefits

We recognize that we operate within an industry where there is significant competition for top talent, and we endeavor to provide not only a strong healthy culture, but also important compensation and benefits programs to help meet the needs of our employees. In addition to base compensation, these programs, include annual bonuses, stock awards, an Employee Stock Purchase Plan, 401(k), healthcare and insurance benefits, health savings (funded by the Company) and flexible spending

accounts, family leave, family care resources, and flexible work schedules, among many others. As a response to the COVID-19 pandemic, we implemented payments to assist employees in paying for expenses incurred in working from home.

Ensuring fair and equitable pay is integral to our commitment to our employees. Our executive team and Board of Directors strongly support this commitment. We conduct pay equity reviews annually to help us understand whether our compensation structure is appropriate and to identify what improvements can be made.

Corporate Information

We were incorporated in Delaware on October 17, 2007, under the name Nteryx and changed our name to Ardelyx, Inc. in June 2008. We operate in one business segment, which is the development and planned commercialization of biopharmaceutical products. Our principal office is located at 400 Fifth Avenue, Suite 210, Waltham, Massachusetts 02415. Our telephone number is (510) 745-1700 and our website address is www.ardelyx.com.

We file electronically with the Securities and Exchange Commission ("SEC") our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended. We make available on our website at www.ardelyx.com, free of charge, copies of these reports, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that website is www.sec.gov.

ITEM 1A. RISK FACTORS

Our business involves significant risks, some of which are described below. You should carefully consider these risks, as well as other information in this Annual Report on Form 10-K, including our financial statements and the notes thereto and "Management's Discussion and Analysis of Financial Condition and Results of Operations." The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations, cash flows, the trading price of our common stock and our growth prospects. Many of the following risks and uncertainties are, and will be, exacerbated by the COVID-19 pandemic and any worsening of the global business and economic environment as a result. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

Risks Related to our Financial Condition and Capital Requirements

We have a limited operating history, have incurred significant losses since our inception and we will incur losses in the future, which makes it difficult to assess our future viability; although our financial statements have been prepared on a going concern basis, our current level of cash and investments alone is not sufficient to meet our operating plans for the next twelve months, raising substantial doubt regarding our ability to continue as a going concern.

We are a clinical-stage biopharmaceutical company with a limited operating history. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. To date, we have focused substantially all of our efforts on our research and development activities, including developing tenapanor and developing our proprietary drug discovery and design platform. To date, we have not commercialized any products or generated any revenue from the sale of products.

We are not profitable and have incurred losses in each year since our inception in October 2007, and we do not know whether or when we will become profitable. We continue to incur significant research, development and other expenses related to our ongoing operations. As of December 31, 2021, we had an accumulated deficit of $712.9 million.

We expect to continue to incur substantial operating losses for the foreseeable future as we prepare for commercialization of IBSRELA® (tenapanor) for the treatment of irritable bowel syndrome with constipation ("IBS-C") in April of this year, seek to gain approval for XPHOZAH® (tenapanor) for the control of serum phosphorus in adult patients with chronic kidney disease ("CKD") on dialysis (the "Hyperphosphatemia Indication"); prepare for the potential commercialization of XPHOZAH, if approved; incur manufacturing and development cost for, tenapanor; and incur development costs for RDX013.

Ernst & Young LLP, our independent registered public accounting firm for the fiscal year ended December 31, 2021, has included an explanatory paragraph in their opinion that accompanies our audited financial statements as of the year ended December 31, 2021, indicating our current liquidity position raises substantial doubt about our ability to continue as a going

concern. We plan to address our operating cash flow requirements with our current cash and investments, cash generated from the product launch of IBSRELA, our potential receipt of anticipated milestone payments from our collaboration partners, our ability to access the capital markets, as well as through the implementation of cash preservation activities to reduce or defer discretionary spending.

There are no assurances that our efforts to meet our operating cash flow requirements will be successful. If our current cash and investments as well as our plans to meet our operating cash flow requirements are not sufficient to fund necessary expenditures and meet our obligations for at least the next twelve months, our liquidity, financial condition and business prospects will be materially affected.

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. Further, the net losses we incur may fluctuate significantly from quarter-to-quarter and year-to-year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

We have substantial net operating loss and tax credit carryforwards for Federal and California income tax purposes. Such net operating losses and tax credits carryforwards may be reduced as a result of certain intercompany restructuring transactions. In addition, the future utilization of such net operating loss and tax credit carryforwards and credits will be subject to limitations, pursuant to Internal Revenue Code Sections 382 and 383, as a result of ownership changes that have occurred previously and additional limitations may be applicable as a result of ownership changes that could occur in the future.

We will require substantial additional financing to achieve our goals, including our goals of commercializing IBSRELA beginning in April 2022 and pursuing a formal dispute resolution ("FDR") process in response to the Complete Response Letter ("CRL") received from the U.S. Food and Drug Administration ("FDA") relating to our New Drug Application ("NDA") for tenapanor for the Hyperphosphatemia Indication and the inability to access necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our efforts to commercialize IBSRELA or to seek and obtain approval for tenapanor for the Hyperphosphatemia Indication.

Since our inception, most of our resources have been dedicated to our research and development activities, including developing tenapanor and developing our proprietary drug discovery and design platform. Following the receipt of the CRL, we implemented two restructuring plans in order to reduce operating costs and to better align our workforce with the needs of our business. Notwithstanding the restructurings, we believe that we will continue to expend substantial resources for the foreseeable future, including, costs associated with our efforts to commercialize IBSRELA commencing in April 2022, cost associated with our efforts to pursue approval for our NDA for tenapanor for the Hyperphosphatemia Indication through the FDR process; conducting pediatric clinical trials for IBSRELA and XPHOZAH, if approved, development of RDX013; and manufacturing for IBSRELA and RDX013. Our future funding requirements will depend on many factors, including, but not limited to:

- the extent to which we are able to generate product revenue from sales of IBSRELA;
- whether we are successful in our efforts under the FDR process to secure approval for our NDA for tenapanor for the Hyperphosphatemia Indication, or to reach resolution with the FDA regarding a path to address the deficiencies in the NDA noted in the CRL and ADL, and the time and cost associated with such path;
- the sales price and the availability of adequate third-party reimbursement for IBSRELA and XPHOZAH, if approved;
- the manufacturing costs of IBSRELA and XPHOZAH;
- the selling and marketing costs associated with IBSRELA and XPHOZAH, if approved;
- our ability to maintain our existing collaboration partnerships and to establish additional collaboration partnerships, in-license/out-license, joint ventures or other similar arrangements and the financial terms of such agreements;
- the timing, receipt, and amount of sales of, or royalties on, tenapanor, if any;
- the cash requirements of any future acquisitions or discovery of product candidates;
- any clinical trials we are required to or decide to pursue for tenapanor or RDX013;

- the time and cost necessary to respond to technological and market developments;
- the costs of filing, prosecuting, maintaining, defending and enforcing any patent claims and other intellectual property rights, including litigation costs and the outcome of such litigation, including costs of defending any claims of infringement brought by others in connection with the development, manufacture or commercialization of tenapanor or any of our product candidates; and
- the payment of interest and principal related to our loan and security agreement entered into with SLR Investment Corp. in February 2022.

Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate our commercialization of IBSRELA, our efforts to secure approval for XPHOZAH for the hyperphosphatemia indication, or clinical trials for tenapanor or RDX013. Additionally, our inability to access capital on a timely basis and on terms that are acceptable to us may force us to restructure certain aspects of our business or identify and complete one or more strategic collaborations or other transactions in order to fund the development or commercialization of IBSRELA or XPHOZAH through the use of alternative structures.

Our failure to meet the continued listing requirements of The Nasdaq Global Market could result in a de-listing of our common stock.
If we fail to satisfy the continued listing requirements of The Nasdaq Global Market ("Nasdaq") such as the minimum stockholders' equity requirement or the minimum closing bid price requirement, Nasdaq may take steps to de-list our common stock. For example, on February 28, 2022 we received a letter from Nasdaq indicating that Nasdaq had determined that we had failed to comply with the minimum bid price requirement of Nasdaq Listing Rule 5550(a)(2). Nasdaq Listing Rule 5550(a)(2) requires that companies listed on the Nasdaq Global Market maintain a minimum closing bid price of at least $1.00 per share. In accordance with Nasdaq Listing Rule 5810(c)(3)(A), we have been provided with a period of 180 calendar days, or until August 29, 2022, to regain compliance with the minimum bid price requirement. We are monitoring the bid price of our common stock and will consider options available to us to achieve compliance. If we fail to maintain compliance with this requirement, or any other of the continued listing requirements of The Nasdaq Global Market, Nasdaq may take steps to de-list our common stock.

If Nasdaq de-lists our securities for trading on the Nasdaq or takes other actions with respect to our Nasdaq listing, we could face significant adverse consequences, including:

- a limited availability of market quotations for our common stock;
- reduced liquidity with respect to our common stock;
- reduced trading volume in and market price of our common stock;
- a limited amount of news and analyst coverage for our company; and
- a decreased ability to issue additional securities or obtain additional financing in the future.

Such a de-listing would likely have an adverse effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. We may take actions to avoid such a de-listing or in the event of a de-listing, we may take actions to restore our compliance with Nasdaq's listing requirements, but we can provide no assurance that any such action taken by us would allow our common stock to remain listed or to become listed again, stabilize the market price or improve the liquidity or trading volume of our common stock, prevent our common capitalization and stockholder's equity from dropping below the Nasdaq minimum requirements, or prevent other future non-compliance with Nasdaq's continued listing requirements.

We have never generated any revenue from product sales and may never be profitable.

We received FDA approval for our NDA for tenapanor for the treatment of IBS-C in adults in September 2019, and we currently expect to launch IBSRELA in April 2022. We have no other products approved for sale and have received a CRL from the FDA for our NDA for the Hyperphosphatemia Indication and an Appeal Denied Letter ("ADL") in response to our appeal of the CRL to the FDA Office of Cardiology, Hematology, Endocrinology and Nephrology ("OCHEN"). There can be no assurances that our NDA for tenapanor for the Hyperphosphatemia Indication will be approved for such indication or any other related indication. We have never generated any revenue from product sales. Our ability to generate revenue from product sales and achieve profitability depends on our ability to successfully commercialize IBSRELA; obtain approval by the FDA for the Hyperphosphatemia Indication, and subsequently successfully commercialize XPHOZAH for the Hyperphosphatemia Indication; and the ability of our collaboration partners to obtain regulatory approval to market tenapanor in their respective territories. There can be no assurances that we will generate sufficient product revenue from sales of IBSRELA and, if approved, XPHOZAH, to cover our expenses. Our ability to generate product revenue from sales or pursuant to milestone payments depends heavily on many factors, including but not limited to:

- our ability to successfully commercialize IBSRELA;
- obtaining market acceptance of IBSRELA as a viable treatment option for IBS-C;
- our ability to obtain and sustain an adequate level of coverage and reimbursement for IBSRELA by third-party payors;
- whether we are successful in our efforts under the FDR process to secure approval for our NDA for tenapanor for the Hyperphosphatemia Indication, or whether we are able during the FDR to reach resolution with the FDA regarding a path to addressing the deficiencies in our NDA noted in the CRL and ADL that is achievable in terms of clinical study design, time and cost;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide an adequate (in amount and quality) supply of product to support the market demand for IBSRELA, and, if approved, XPHOZAH;
- addressing any competing technological and market developments;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how, and our ability to develop, manufacture and commercialize our product candidates and products without infringing intellectual property rights of others; and
- attracting, hiring, and retaining qualified personnel.

With respect to our commercialization of IBSRELA, and if we are successful in obtaining regulatory approval to market XPHOZAH, our revenue will be dependent, in part, upon the size of the markets in the U.S. and the label for which approval is or was granted, accepted price for the product, the ability to get reimbursement at any price. While there is significant uncertainty related to the insurance coverage and reimbursement of newly approved products in general in the United States, there is additional uncertainty related to insurance coverage and reimbursement for drugs, like XPHOZAH, which, if approved, will be marketed for the control of serum phosphorus in adult patients with CKD on dialysis or for another other related indication. If we are successful in obtaining regulatory approval to market XPHOZAH for such indication, our ability to generate and sustain future revenues from sales of tenapanor for such indication, may be dependent upon whether and when XPHOZAH, along with other oral ESRD related drugs without an injectable or intravenous equivalent, are bundled into the ESRD prospective payment system, and the manner in which such introduction into the ESRD prospective payment system may occur. See "Third-party payor coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for IBSRELA or XPHOZAH, if approved, could limit our ability to market those products and decrease our ability to generate revenue" below. Additionally, if the number of adult patients for IBSRELA or XPHOZAH, if approved, is not as significant as we estimate, the indication approved by regulatory authorities for XPHOZAH is narrower than we expect, coverage and reimbursement for either IBSRELA or XPHOZAH, if approved, are not available in the manner and to the extent we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from the sale of IBSRELA or XPHOZAH, if approved. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our failure to generate adequate revenue from product sales would likely depress our market value and could impair our ability to raise capital, expand our business, discover or develop other product candidates or continue our operations. A decline in the value of our common stock could cause our stockholders to lose all or part of their investment.

Principal Risks Related to Our Business

We are substantially dependent on the successful launch and commercialization of IBSRELA for IBS-C, and there is no guarantee that we will achieve sufficient market acceptance for IBSRELA; secure adequate coverage and reimbursement for IBSRELA; or generate sufficient revenue from product sales of IBSRELA.

In November 2021, we announced plans to launch IBSRELA, our approved treatment for IBS-C in adults. We are investing a significant portion of our efforts and financial resources to prepare for and fund the commercialization of IBSRELA, which we currently expect to commence in April 2022. Our ability to successfully launch IBSRELA, and the overall commercial success of IBSRELA will depend on a number of factors, including the following:

- the ability of the third-party manufacturers we contract with to provide an adequate (in amount and quality) supply of product to support the launch and market demand for IBSRELA;
- our ability to obtain and sustain an adequate level of coverage and reimbursement for IBSRELA by third-party payors;
- the effectiveness of IBSRELA as a treatment for adult patients with IBS-C;
- the size of the treatable patient population;
- the effectiveness of our sales, market access and marketing efforts;
- the adoption of IBSRELA by physicians for the treatment of IBS-C, depends upon whether physicians view IBSRELA as a safe and effective treatment for adult patients with IBS-C;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of IBSRELA compared to alternative and competing treatments; and
- the prevalence and severity of adverse side effects of IBSRELA;
- our potential involvement in lawsuits in connection with enforcing intellectual property rights in and to IBSRELA;
- our potential involvement in third-party interference, opposition, derivation or similar proceedings with respect to our patent rights directed to IBSRELA, and avoiding other challenges to our patent rights and patent infringement claims; and
- a continued acceptable safety and tolerability profile of IBSRELA following approval.

Our potential to achieve revenue from the commercialization of IBSRELA and the amount of such potential revenue is subject to these and other factors, and may be unpredictable from quarter-to-quarter. If the number of patients in the market for IBSRELA or the price that the market can bear is not as significant as we estimate, or if we are not able to secure adequate physician and patient acceptance of IBSRELA or adequate coverage and reimbursement for IBSRELA, we may not generate sufficient revenue from sales of IBSRELA. Any failure of IBSRELA to achieve market acceptance, sufficient third-party coverage or reimbursement, or commercial success for would adversely affect our results of operations.

Our success is also dependent upon our ability to obtain regulatory approval for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis, and there can be no assurances that we will be successful in obtaining such regulatory approval.

Our success is also dependent upon our ability to obtain regulatory approval for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. To date, we have invested a significant amount of our efforts and financial resources in the research and development of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. On July 28, 2021, we received a CRL from the'FDA's Division of Cardiology and Nephrology (the "Division") regarding our NDA for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. According to the CRL, the FDA has determined that the magnitude of the treatment effect observed in our Phase 3 clinical trials was small and of unclear of clinical significance. Following an End-of-Review Type A meeting ("End of Review Meeting") in October 2021, with the Division, we submitted a Formal Dispute Resolution Request ("FDRR") in December 2021. The FDRR was focused on demonstrating that the data submitted in the NDA supported the clinical significance of the treatment effect of tenapanor. On February 4, 2022, we received an ADL from OCHEN. On February 18, 2022, we submitted an appeal of the ADL to the FDA's

Center for Drug Evaluation and Research, Office of New Drugs ("OND"). If accepted, we expect a decision on the appeal to the OND in April 2022. There can be no assurances that the Formal Dispute Resolution ("FDR") process will result in approval of our NDA, or in a clear path to resubmission of our NDA that is achievable in terms of clinical study design, time and cost. As a result, the regulatory approval process for our NDA is highly uncertain. We may not obtain approval at all, and if we are able to obtain approval, the expense and time to do so could adversely impact our ability to successfully commercialize XPHOZAH, our business and our results of operations.

Even if we are successful in obtaining regulatory approval for tenapanor for control of serum phosphorus in adult patients with CKD on dialysis, the expense and time required to do so could adversely impact our ability to successfully commercialize XPHOZAH for the Hyperphosphatemia Indication.

We may not be successful in obtaining approval for tenapanor for the Hyperphosphatemia Indication, and if we are able to obtain approval, the expense and time to do so could adversely impact our ability to successfully commercialize XPHOZAH for the Hyperphosphatemia Indication, our business and our results of operations. If we are successful in obtaining approval for XPHOZAH for the Hyperphosphatemia Indication, the commercial success of XPHOZAH will depend on a number of factors, including the following:

- the ability of the third-party manufacturers we contract with to provide an adequate (in amount and quality) supply of product to support the market demand for both IBSRELA and XPHOZAH;
- whether or not the content and breadth of the label approved by the FDA for XPHOZAH may materially and adversely impact our ability to commercialize the product for the approved indication;
- whether or when XPHOZAH, along with other oral end-stage renal disease ("ESRD") related drugs without an injectable or intravenous equivalent, are bundled into the ESRD prospective payment system, and the manner in which such introduction into the ESRD prospective payment system may occur;
- the prevalence and severity of adverse side effects of XPHOZAH;
- acceptance of XPHOZAH as safe, effective and well-tolerated by patients and the medical community, and, the extent to which the issuance of a CRL by the FDA has impacted the potential acceptance of XPHOZAH as safe, effective and well-tolerated;
- our ability to manage the commercialization of IBSRELA and XPHOZAH and the complex pricing and reimbursement negotiations that may arise with marketing the same product at different doses for separate indications;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of XPHOZAH compared to alternative and competing treatments;
- obtaining and sustaining an adequate level of coverage and reimbursement for XPHOZAH by third-party payors;
- our potential involvement in lawsuits in connection with enforcing intellectual property rights in and to XPHOZAH;
- our potential involvement in third-party interference, opposition, derivation or similar proceedings with respect to our patent rights, and avoiding other challenges to our patent rights and patent infringement claims; and
- a continued acceptable safety and tolerability profile of XPHOZAH following approval.

IBSRELA, and/or XPHOZAH, if approved and commercialized, may cause undesirable side effects or have other properties that could limit the commercial success of the product.

Undesirable side effects caused by IBSRELA, and/or XPHOZAH, if approved, could cause us or regulatory authorities to interrupt, delay or halt the commercialization of the product. To date, the most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo in the two Phase 3 trials include: diarrhea, abdominal distension, flatulence and dizziness. Despite our receipt of marketing approval for IBSRELA and the completion of our Phase 3 clinical program for XPHOZAH, the prevalence and/or severity of these or other side effects could result in a number of potentially significant negative consequences could occur, including:

- regulatory authorities may withdraw their approval of the product or seize the product;

- we or a collaboration partner may be required to recall the product;
- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof, including the imposition of a Risk Evaluation and Mitigation Strategy ("REMS") which could require creation of a Medication Guide or patient package insert outlining the risks of such side effects for distribution to patients, a communication plan to educate healthcare providers of the drugs' risks, as well as other elements to assure safe use of the product, such as a patient registry and training and certification of prescribers;
- we or a collaboration partner may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of new labeling statements, such as a "black box" warning or a contraindication;
- we could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

Any of the foregoing events could prevent us, or a collaboration partner, from achieving or maintaining market acceptance of IBSRELA, and/or XPHOZAH, if approved, and could result in the loss of significant revenue to us, which would materially and adversely affect our results of operations and business.

We have no prior experience in the marketing, sale and distribution of pharmaceutical products; and there are significant risks in building and managing a commercial organization.

Prior to the receipt of the CRL for our NDA for the Hyperphosphatemia Indication, we had made significant progress in the establishment of our sales, marketing, and access organizations. Many members of those teams had their positions eliminated by our restructuring plans adopted in August and October 2021. In November 2021, we announced our plans to commercialize IBSRELA and commenced our efforts to rebuild the critical components of the sales, marketing and access teams aligned to the IBSRELA commercial opportunity. As a company, we have no prior experience in building and managing a commercial organization, or in the marketing, sale and distribution of pharmaceutical products. There can be no assurances that we will be successful in our efforts to hire, retain, and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, comply with regulatory requirements applicable to the marketing and sale of drug products and effectively manage a geographically dispersed sales and marketing team.

If we fail or are delayed in the development of our internal sales, marketing and distribution capabilities, we may need to delay the commercialization of IBSRELA, or commercialization could be adversely impacted.

Our operating activities may be restricted as a result of covenants related to the indebtedness under our loan and security agreement and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.

On February 23, 2022, we entered into a loan and security agreement with SLR Investment Corp. (the "Lender") pursuant to which the Lender agreed to provide us a $50.0 million term loan facility with a maturity date of March 1, 2027. The loan was funded in the amount of $27.5 million on February 23, 2022 and the remaining $22.5 million may be funded upon the satisfaction of both of the following conditions precedent to funding (i) receipt from the FDA of approval of the NDA for tenapanor for the Hyperphosphatemia Indication on or prior to December 31, 2022 and (ii) our achievement of a minimum of $30.0 million in net product revenue calculated on a trailing six month basis. Until we have repaid all funded indebtedness, the loan and security agreement subjects us to various customary covenants, including requirements as to financial reporting and insurance and restrictions on our ability to dispose of our business or property, to change our line of business, to liquidate or dissolve, to enter into any change in control transaction, to merge or consolidate with any other entity or to acquire all or substantially all the capital stock or property of another entity, to incur additional indebtedness, to incur liens on our property, to pay any dividends or other distributions on capital stock other than dividends payable solely in capital stock, to redeem capital stock, to enter into licensing agreements, to engage in transactions with affiliates, and to encumber our intellectual property. Our business may be adversely affected by these restrictions on our ability to operate our business.

We are permitted to make interest only payments on the loan facility through March 2024, with principal repayments commencing on April 1, 2024, however, we may be required to repay the outstanding indebtedness under the loan facility if an

event of default occurs under the loan and security agreement. An event of default will occur if, among other things, we fail to make payments under the loan and security agreement; we breach any of our covenants under the loan and security agreement, subject to specified cure periods with respect to certain breaches; the Lender determines that a material adverse change has occurred; we or our assets become subject to certain legal proceedings, such as bankruptcy proceedings; we are unable to pay our debts as they become due; or we default on contracts with third parties which would permit the Lender to accelerate the maturity of such indebtedness or that could have a material adverse change on us. We may not have enough available cash or be able to raise additional funds through equity or debt financings to repay such indebtedness at the time any such event of default occurs. In this case, we may be required to delay, limit, reduce or terminate our activities necessary to commercialize IBSRELA, and/or if approved, XPHOZAH, clinical trials for tenapanor or RDX013, the Lender could also exercise its rights as collateral agent to take possession of and to dispose of the collateral securing the term loans, which collateral includes substantially all of our property (excluding intellectual property, which is subject to a negative pledge). Our business, financial condition and results of operations could be materially adversely affected as a result of any of these events.

Third-party payor coverage and reimbursement status of newly commercialized products are uncertain. Failure to obtain or maintain adequate coverage and reimbursement for IBSRELA and XPHOZAH, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

The pricing, coverage and reimbursement of IBSRELA and XPHOZAH, if approved, must be adequate to support a commercial infrastructure. The availability and adequacy of coverage and reimbursement by governmental and private payors are essential for most patients to be able to afford treatments. Sales of IBSRELA, and XPHOZAH, if approved and commercialized, will depend substantially, both domestically and abroad, on the extent to which the costs of the product will be paid for by health maintenance, managed care, pharmacy benefit, and similar healthcare management organizations, or reimbursed by government authorities, private health insurers, and other third-party payors. If coverage and reimbursement are not available, or are available only to limited levels, we, or our collaboration partners, may not be able to successfully commercialize IBSRELA, or XPHOZAH, if approved. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about coverage and reimbursement for new drugs are typically made by the Centers for Medicare & Medicaid Services (“CMS”), an agency within the United States Department of Health and Human Services responsible for administering the Medicare program, as CMS decides whether and to what extent a new drug will be covered and reimbursed under Medicare. Private payors tend to follow the coverage reimbursement policies established by CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for products such as ours.

There is increased uncertainty related to insurance coverage and reimbursement for drugs, like XPHOZAH for the Hyperphosphatemia Indication, which, if approved, will be marketed for the control of serum phosphorus in adult patients with CKD on dialysis or for another other related indication. In January 2011, CMS implemented a new prospective payment system for dialysis treatment. Under the ESRD prospective payment system, CMS generally makes a single bundled payment to the dialysis facility for each dialysis treatment that covers all items and services routinely required for dialysis treatments furnished to Medicare beneficiaries in Medicare-certified ESRD facilities or at their home, including the cost of certain routine drugs. The inclusion of oral medications without injectable or intravenous equivalents in the bundled payment was initially delayed until January 1, 2014, and through several subsequent legislative actions was delayed until January 1, 2025. As a result, absent further legislation or regulation on this matter, beginning in 2025, oral ESRD-related drugs without injectable or intravenous equivalents may be included in the ESRD bundle and separate Medicare payment for these drugs will no longer be available, as is the case today under Medicare Part D. While it is too early to project the full impact that bundling may have on sales of XPHOZAH, if approved and commercialized, and on our business should XPHOZAH be brought into the bundle in 2025, or at any time, we may be unable to sell XPHOZAH for the Hyperphosphatemia Indication, if approved, to dialysis providers on a profitable basis if third-party payors reduce their current levels of payment, or if our costs of production are higher than levels necessary for an appropriate gross margin after payment of all discounts, rebates and chargebacks.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, Japan, China and other countries has and will continue to put pressure on the pricing and usage of IBSRELA and XPHOZAH, even if regulatory approval is received in such countries. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medicinal products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, these caps may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of IBSRELA, and if approved and commercialized, XPHOZAH, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

We rely completely on third parties to manufacture IBSRELA, XPHOZAH and RDX013. If they are unable to comply with applicable regulatory requirements, unable to source sufficient raw materials, experience manufacturing or distribution difficulties or are otherwise unable to manufacture sufficient quantities to meet demand, our commercialization of IBSRELA, and XPHOZAH, if approved and commercialized, and our development efforts for tenapanor and RDX013 may be materially harmed.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture IBSRELA, or any of other our product candidates on a commercial scale, or to manufacture our drug supplies for use in the conduct of our nonclinical and clinical studies. The facilities used by our contract manufacturers to manufacture our drug supply are subject to inspection by the FDA. Our ability to control the manufacturing process of our product candidates is limited to the contractual requirements and obligations we impose on our contract manufacturer. Although they are contractually required to so do, we are completely dependent on our contract manufacturing partners for compliance with the regulatory requirements, known as current Good Manufacturing Practice requirements (“cGMPs”), for manufacture of both active drug substances and finished drug products.

The manufacture of pharmaceutical products requires significant expertise and capital investment. Manufacturers of pharmaceutical products often encounter difficulties in commercial production. These problems may include difficulties with production costs and yields, quality control, including stability of the product and quality assurance testing, and shortages of qualified personnel, as well as compliance with federal, state and foreign regulations and the challenges associated with complex supply chain management. Even if our contract manufacturers do not experience problems and commercial manufacturing is achieved, their maximum or available manufacturing capacities may be insufficient to meet commercial demand. Finding alternative manufacturers or adding additional manufacturers requires a significant amount of time and involves significant expense. New manufacturers would need to develop and implement the necessary production techniques and processes, which along with their facilities, would need to be inspected and approved by the regulatory authorities in each applicable territory. In addition, the raw materials necessary to make API for our products are acquired from a limited number of sources. Any delay or disruption in the availability of these raw materials could result in production disruptions, delays or higher costs with consequent adverse effects on us.

If our contract manufacturers fail to adhere to applicable GMP or other regulatory requirements, experience delays or disruptions in the availability of raw materials or experience manufacturing or distribution problems, we may suffer significant consequences, including the inability to meet our product requirements for our clinical development programs, and if tenapanor is commercialized for any indication, such events could result in product seizures or recalls, loss of product approval, fines and sanctions, reputational damage, shipment delays, inventory shortages, inventory write-offs and other product-related charges and increased manufacturing costs. As a result, or if maximum or available manufacturing capacities are insufficient to meet demand, our development or our commercialization efforts for IBSRELA, and/or XPHOZAH, if approved, may be materially harmed.

Additional Risks Related to Our Business and Industry

Clinical drug development involves a lengthy and expensive process with an uncertain outcome and the results of earlier studies and trials may not be predictive of future trial results.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing 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. The results of preclinical and clinical studies of our product candidates, including RDX013, may not be predictive of the results of later-stage clinical trials. An unexpected adverse event profile, or the results of drug-drug interaction studies, may present challenges for the future development and commercialization of a product candidate for a particular condition despite receipt of positive efficacy data in a clinical study. A number of companies in the pharmaceutical, biopharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials for similar

indications that we are pursuing due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier studies, and we cannot be certain that we will not face similar setbacks.

We could encounter delays in our future development of RDX013 if any clinical trials are suspended or terminated by us, by the IRBs of the institutions in which the trial is being conducted, or by the FDA or other regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a 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 resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

In addition, identifying and qualifying patients to participate in our RDX013 clinical trials is critical to the success of the clinical trials. The timing of our clinical trials depends, in part, on the speed at which we can recruit patients to participate in testing our product candidates. Patients may be unwilling to participate in our clinical studies because of concerns about adverse events observed with the current standard of care, competitor products and/or other investigational agents, in each case for the same indications and/or similar patient populations. In addition, patients currently receiving treatment with the current standard of care or a competitor product may be reluctant to participate in a clinical trial with an investigational drug, or our inclusion and exclusion criteria for our clinical trials may present challenges in identifying acceptable patients. As a result, the timeline for recruiting patients and conducting RDX013 clinical trials may be delayed. These delays could result in increased costs, delays in advancing our development of RDX013, or termination of the clinical studies altogether. Any of these occurrences may significantly harm our business, financial condition and prospects.

We will rely on third parties to conduct all of our nonclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may be unable to obtain regulatory approval for additional products or commercialize our product candidates.

We do not have the ability to independently conduct nonclinical studies or clinical trials. We rely on medical institutions, clinical investigators, contract laboratories, and other third parties, such as CROs, to conduct clinical trials on our product candidates. The third parties with whom we contract for execution of the clinical trials play a significant role in the conduct of these trials and the subsequent collection and analysis of data. However, these third parties are not our employees, and except for contractual duties and obligations, we control only certain aspects of their activities and have limited ability to control the amount or timing of resources that they devote to our programs. Although we rely, and will continue to rely, on these third parties to conduct our nonclinical studies and our clinical trials, we remain responsible for ensuring that each of our studies and clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on third parties does not relieve us of our regulatory responsibilities. We, and these third parties are required to comply with current GLPs for nonclinical studies, and good clinical practices (“GCPs”) for clinical studies. GLPs and GCPs are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area (“EEA”) and comparable foreign regulatory authorities for all of our products in nonclinical and clinical development, respectively. Regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our third-party contractors fail to comply with applicable regulatory requirements, including GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the European Medicines Agency (“EMA”), or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. There can be no assurance that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

We face substantial competition, and our competitors may discover, develop or commercialize products faster or more successfully than us.

The biotechnology and pharmaceutical industries are highly competitive, and we face significant competition from companies in the biotechnology, pharmaceutical and other related markets that are researching and marketing products designed to address diseases that we are currently developing products to treat. If approved for marketing by the FDA or other regulatory agencies, tenapanor, as well as our other product candidates, would compete against existing treatments.

For example, numerous treatments exist for constipation and the constipation component of IBS-C, many of which are over-the-counter. These include psyllium husk (such as Metamucil), methylcellulose (such as Citrucel), calcium polycarbophil (such as FiberCon), lactulose (such as Cephulac), polyethylene glycol (such as MiraLax), sennosides (such as Exlax), bisacodyl

(such as Ducolax), docusate sodium (such as Colace), magnesium hydroxide (such as Milk of Magnesia), saline enemas (such as Fleet), and sorbitol. These agents are generally inexpensive and work well to temporarily relieve constipation.

We are aware of four prescription products marketed for certain patients with IBS-C, including Linzess (linaclotide), Amitiza (lubiprostone), Trulance (plecanatide) and Zelnorm (tegaserod maleate).

Additionally, XPHOZAH, if approved for the Hyperphosphatemia Indication will compete with phosphate binders used for the same or similar indication`. If approved, our label for XPHOZAH may include data comparing the effectiveness of tenapanor to phosphate binders used for the same indication. The various types of phosphate binders commercialized in the United States include the following:

- Calcium carbonate (many over-the-counter brands including Tums and Caltrate);
- Calcium acetate (several prescription brands including PhosLo and Phoslyra);
- Lanthanum carbonate (Fosrenol);
- Sevelamer hydrochloride (Renagel);
- Sevelamer carbonate (Renvela);
- Sucroferric oxyhydroxide (Velphoro); and
- Ferric citrate (Auryxia).

All of the phosphate binders listed above are available as generics in the U.S., with the exception of Velphoro and Auryxia. In addition to the currently available phosphate binders, we are aware of at least two other binders in development, including fermagate (Alpharen), an iron-based binder in Phase 3 being developed by Opko Health, Inc., and PT20, an iron-based binder in Phase 3 being developed by Shield Therapeutics.

It is possible that our competitors' drugs may be less expensive and more effective than our product candidates, or that will render our product candidates obsolete. It is also possible that our competitors will commercialize competing drugs or treatments before we or our collaboration partners can launch any products developed from our product candidates. We also anticipate that we will face increased competition in the future as new companies enter into our target markets.

Many of our competitors have materially greater name recognition and financial, manufacturing, marketing, research and drug development resources than we do. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Large pharmaceutical companies in particular have extensive expertise in preclinical and clinical testing and in obtaining regulatory approvals for drugs. In addition, academic institutions, government agencies, and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaboration partnerships or licensing relationships with our competitors.

We may experience difficulties in managing our current activities and growth given our level of managerial, operational, financial and other resources.

While we have continued to work to optimize our management composition, personnel and systems to support our current activities for future growth, these resources may not be adequate for this purpose. Our need to effectively execute our business strategy requires that we:

- manage any commercialization activities in which we may engage effectively;
- manage our clinical trials effectively;
- manage our internal development efforts effectively while carrying out our contractual obligations to licensors, contractors, collaborators, government agencies and other third parties;
- continue to improve our operational, financial and management controls, reporting systems and procedures; and

- retain and motivate our remaining employees and potentially identify, recruit, and integrate additional employees.

If we are unable to maintain or expand our managerial, operational, financial and other resources to the extent required to manage our development and commercialization activities, our business will be materially adversely affected.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of IBSRELA, and/or XPHOZAH, if approved.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk following the commercial launch of IBSRELA in April 2022. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for the product;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- regulatory investigations, product recalls or withdrawals, or labeling, marketing or promotional restrictions;
- loss of revenue; and
- the inability to commercialize or co-promote our IBSRELA, and/or XPHOZAH, if approved.

Our inability to obtain and maintain sufficient product liability insurance at an acceptable cost and scope of coverage to protect against potential product liability claims could prevent or inhibit the commercialization of any products we develop. Although we maintain product liability insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions and deductibles, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses.

If we fail to attract, retain and motivate our executives, senior management and key personnel, our business will suffer.

Recruiting and retaining qualified scientific, clinical, medical, manufacturing, and sales and marketing personnel is critical to our success. We are highly dependent on our executives, senior management and certain other key employees. The loss of the services of our executives, senior management or other key employee could impede the achievement of our development and commercial objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executives, senior management and other 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 marketing approval of and commercialize products. We may be unable to hire, train or motivate these key personnel on acceptable terms given the intense competition among numerous biopharmaceutical companies for similar personnel, particularly in our geographic regions. If we are unable to continue to attract and retain high quality personnel, our ability to grow and pursue our business strategy will be limited.

Actual or perceived failures to comply with applicable data protection, privacy and security laws, regulations, standards and other requirements could adversely affect our business, results of operations, and financial condition.

The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention, and security of personal data, such as information that we may collect in connection with clinical trials in the U.S. and abroad. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot yet determine the impact future laws, regulations, standards, or perception of their requirements may have on our business. This evolution may create uncertainty in our business, affect our ability to operate in certain jurisdictions or to collect, store, transfer use and share personal information, necessitate the acceptance of more onerous obligations in our contracts, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state or foreign laws or regulation, our internal policies and procedures or our contracts governing our processing of personal information could result in negative publicity, government investigations and enforcement actions, claims by third parties and damage to our reputation, any of which could have a material adverse effect on our operations, financial performance and business.

As our operations and business grow, we may become subject to or affected by new or additional data protection laws and regulations and face increased scrutiny or attention from regulatory authorities. In the U.S., HIPAA imposes, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information. We may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA. Depending on the facts and circumstances, we could be subject to significant penalties if we violate HIPAA.

Certain states have also adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. Such laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. For example, the California Consumer Privacy Act ("CCPA") went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. Further, the California Privacy Rights Act (CPRA) recently passed in California. The CPRA will impose additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It will also create a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. The majority of the provisions will go into effect on January 1, 2023, and additional compliance investment and potential business process changes may be required. Similar laws have passed in Virginia and Colorado, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

Furthermore, the Federal Trade Commission (FTC) and many state Attorneys General continue to enforce federal and state consumer protection laws against companies for online collection, use, dissemination and security practices that appear to be unfair or deceptive. For example, according to the FTC, failing to take appropriate steps to keep consumers' personal information secure can constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act. The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities.

We are also or may become subject to rapidly evolving data protection laws, rules and regulations in foreign jurisdictions. For example, in Europe, the European Union General Data Protection Regulation (GDPR) went into effect in May 2018 and imposes strict requirements for processing the personal data of individuals within the European Economic Area (EEA). Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July 2020, the Court of Justice of the EU (CJEU) limited how organizations could lawfully transfer personal data from the EU/EEA to the United States by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions on the use of standard contractual clauses. Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. Relatedly, following the United

Kingdom's withdrawal from the European Economic Area and the European Union, and the expiry of the transition period, companies have to comply with both the GDPR and the GDPR as incorporated into United Kingdom national law, the latter regime having the ability to separately fine up to the greater of £17.5 million or 4% of global turnover. The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, for example around how data can lawfully be transferred between each jurisdiction, which may expose us to further compliance risk.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. Any failure or perceived failure by us or our employees, representatives, contractors, consultants, CROs, collaborators, or other third parties to comply with such requirements or adequately address privacy and security concerns, even if unfounded, could result in additional cost and liability to us, damage our reputation, and adversely affect our business and results of operations.

We and our collaborators, CROs and other contractors and consultants depend on information technology systems, and any failure of these systems could harm our business. Security breaches, loss of data, and other disruptions could compromise sensitive information related to our business or prevent us from accessing critical information and expose us to liability, which could adversely affect our business, results of operations and financial condition.

We and our collaborators, CROs, and other contractors and consultants collect and maintain information in digital form that is necessary to conduct our business, and we are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we and our collaborators, CROs and other contractors and consultants collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. It is critical that we and our collaborators, CROs and other contractors and consultants do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We have established physical, electronic and organizational measures designed to safeguard and secure our systems to prevent a data compromise, and rely on commercially available systems, software, tools, and monitoring to provide security for our information technology systems and the processing, transmission and storage of digital information. We have also outsourced elements of our information technology infrastructure, and as a result a number of third-party vendors may or could have access to our confidential information. Our internal information technology systems and infrastructure, and those of our current and any future collaborators, CROs, contractors and consultants and other third parties on which we rely, are vulnerable to damage from computer viruses, malware, natural disasters, terrorism, war, telecommunication and electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization.

The risk of a security breach or disruption or data loss, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. In addition, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information or other intellectual property. As a result of the COVID-19 pandemic, we may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. The costs to us to mitigate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service and other harm to our business and our competitive position. We and certain of our service providers are from time to time subject to cyberattacks and security incidents. While we do not believe that we have experienced any significant system failure, accident or security breach to date. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product development programs, and/or of our efforts to commercialize tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis or for another other related indication, if approved. For example, the loss of clinical trial data from completed or 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. In addition, such a breach may require notification to governmental agencies, the media or individuals pursuant to various federal and state privacy and security laws, if applicable. Moreover, if a computer security breach affects our systems or those of our collaborators, CROs or other contractors, or results in the unauthorized release of personally identifiable information, our reputation could be materially damaged. We would also

be exposed to a risk of loss or litigation and potential liability, which could materially adversely affect our business, results of operations and financial condition.

We have previously identified a material weakness in our internal control over financial reporting. If we fail to maintain proper and effective internal controls, our ability to produce accurate and timely financial statements could be impaired, which could harm our operating results, our ability to operate our business and investors' views of us and could have a material adverse effect on the price of our common stock.

In 2019, management and our independent registered public accounting firm identified a control deficiency that constituted a material weakness in our internal control over financial reporting. The material weakness was due to a failure in the design and implementation of controls over the evaluation of the terms of our clinical trial contracts for inclusion into our clinical financial model which estimates clinical trial expenses. Specifically, we had failed to properly interpret an expense in our clinical trial contracts which resulted in the over accrual of our clinical trial expenses during 2018 and the first quarter of 2019.

We developed and implemented a remediation plan for this material weakness which included modifications to the design and implementation of certain internal controls, and the material weakness was remediated as of December 31, 2019. Although we have remediated this material weakness, as attested by our independent registered public accounting firm, we can give no assurance that an additional material weakness or significant deficiency in our internal controls over financial reporting will not be identified in the future. Our failure to implement and maintain effective internal controls over financial reporting could result in errors in our financial statements that could result in a restatement of our financial statements and cause us to fail to meet our reporting obligations. If we cannot in the future favorably assess the effectiveness of our internal controls over financial reporting, investor confidence in the reliability of our financial reports may be adversely affected, which could have a material adverse effect on the trading price of our common stock.

We have formed in the past, and may form in the future, collaboration partnerships, joint ventures and/or licensing arrangements, and we may not realize the benefits of such collaborations.

We have current collaboration partnerships for the commercialization of tenapanor in certain foreign countries, and we may form additional collaboration partnerships, create joint ventures or enter into additional licensing arrangements with third parties in the United States and abroad that we believe will complement or augment our existing business. In particular, we have formed collaboration partnerships with KKC for commercialization of tenapanor for hyperphosphatemia in Japan; with Fosun Pharma for commercialization of tenapanor for hyperphosphatemia and IBS-C in China and related territories; and in Canada with Knight for commercialization of tenapanor for IBS-C and hyperphosphatemia. We face significant competition in seeking appropriate collaboration partners, and the process to identify an appropriate partner and negotiate appropriate terms is time-consuming and complex. Any delays in identifying suitable additional collaboration partners and entering into agreements to develop our product candidates could also delay the commercialization of our product candidates, which may reduce their competitiveness even if they reach the market. There is no guarantee that our current collaboration partnerships or any such arrangements we enter into in the future will be successful, or that any collaboration partner will commit sufficient resources to the development, regulatory approval, and commercialization effort for such products, or that such alliances will result in us achieving revenues that justify such transactions. We have received a CRL from the FDA regarding our NDA for the Hyperphosphatemia Indication. While we are pursuing an appeal through the FDR process, there can be no assurances that we will be successful in obtaining approval for tenapanor for the Hyperphosphatemia Indication. Even if we are successful in obtaining approval for the NDA, the delay in obtaining such approval may result in delay in the regulatory process for our partners, which could have a material adverse effect on our business and results of operations.

The ongoing COVID-19 pandemic, or any other outbreak of epidemic diseases, or the perception of their effects, could have a material adverse effect on our business, financial condition, results of operations or cash flows.

Outbreaks of epidemic, pandemic, or contagious diseases, such as the current novel coronavirus ("COVID-19") pandemic or, historically, the Ebola virus, Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome or the H1N1 virus, could disrupt our business. Business disruptions could include disruptions or restrictions on our ability to conduct our clinical trials, as planned, travel, as well as temporary closures of the facilities of our collaboration partners, suppliers or contract manufacturers. Any disruption of our clinical trial operations, collaboration partners, suppliers or contract manufacturers could adversely impact our operating results.

Economic and health conditions related to the COVID-19 pandemic in the United States and across most of the globe remain uncertain and continue to evolve. While at this point, the extent to which the coronavirus outbreak may impact our results is uncertain, it could result in delays in the manufacture of tenapanor, or in the delivery of key intermediates or raw materials required to manufacture tenapanor or delays in clinical development activities by us, or our collaboration partners. It

could also materially and negatively impact our ability to successfully commercialize IBSRELA, and/or XPHOZAH, if approved, or the ability of our collaboration partners to successfully commercialize such products, if approved for marketing and sale by the foreign regulatory authorities, including our ability, and that of our collaboration partners to educate physicians and patients about the benefits, administration and use of the product.

- Although we have reopened our offices and invited our personnel to return to the office, we continue to permit our personnel to work remotely, which could negatively impact productivity, or disrupt, delay, or otherwise adversely impact our business. In addition, this could increase our cyber-security risk, create data accessibility concerns, and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with local and federal regulators, ethics committees, manufacturing sites, research or clinical trial sites and important agencies and contractors.

- The FDA and comparable foreign regulatory agencies may continue to experience operational interruptions or delays, which may impact timelines for regulatory submission, trial initiation and regulatory approval.

The full effects of the COVID-19 remain unknown. The extent to which the outbreak may continue to impact our business, including, our commercialization and manufacturing will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as access to physician offices for our commercial and medical teams, business closures or business disruptions.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

We may consider strategic transactions, such as acquisitions of companies, asset purchases, and/or in-licensing of products, product candidates or technologies. In addition, if we are unable to access capital on a timely basis and on terms that are acceptable to us, we may be forced to further restructure certain aspects of our business or identify and complete one or more strategic collaborations or other transactions in order to fund the commercialization of IBSRELA, our continued efforts to seek approval for our NDA for tenapanor for the Hyperphosphatemia Indication and/or the development of RDX013 through the use of alternative structures. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, spin outs, collaboration partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near- and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including:

- up-front, milestone and royalty payments, equity investments and financial support of new research and development candidates including increase of personnel, all of which may be substantial;

- exposure to unknown liabilities;

- disruption of our business and diversion of our management’s time and attention in order to develop acquired products, product candidates or technologies;

- incurrence of substantial debt or dilutive issuances of equity securities;

- higher-than-expected acquisition and integration costs;

- write-downs of assets or goodwill or impairment charges;

- increased amortization expenses;

- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;

- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and

- inability to retain key employees of any acquired businesses.

Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and could have a material adverse effect on our business, results of operations, financial condition and prospects.

If we seek and obtain approval to commercialize our product candidates outside of the United States, manufacture our product candidates outside of the United States, or otherwise engage in business outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

We or our collaboration partners may decide to seek marketing approval for certain of our product candidates outside the United States or otherwise engage in business outside the United States, including entering into contractual agreements with third-parties. We currently utilize contract manufacturing organizations located outside of the United States to manufacture our active drug substance for tenapanor. We are subject to additional risks related to entering these international business markets and relationships, including:

- different regulatory requirements for drug approvals in foreign countries;
- differing United States and foreign drug import and export rules;
- reduced protection for intellectual property rights in foreign countries;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- different reimbursement systems, and different competitive drugs;
- 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;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, 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 these distributors; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters.

Our business involves the use of hazardous materials and we and third-parties with whom we contract must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our development activities involve the controlled storage, use and disposal of hazardous materials, including the components of our product candidates and other hazardous compounds. We and manufacturers and suppliers with whom we may contract are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. We cannot guarantee that the safety procedures utilized by third-party manufacturers and suppliers with whom we may contract will comply with the standards prescribed by laws and regulations or will eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. We do not currently carry biological or hazardous waste insurance coverage.

We may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

We currently occupy a leased facility located in the San Francisco Bay Area, which in the past has experienced severe earthquakes. We do not carry earthquake insurance. Earthquakes or other 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 California facility, that damaged critical infrastructure, such as our enterprise financial systems or manufacturing resource planning and enterprise quality systems, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Risks Related to Government Regulation

Despite having received regulatory approval for IBSRELA, and even if we receive regulatory approval for XPHOZAH, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, IBSRELA, and XPHOZAH, if approved, could be subject to other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Even if a drug is approved by the FDA or foreign regulatory authorities, the manufacturing processes, labeling, packaging, distribution, pharmacovigilance, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and GCP regulations for any clinical trials that we conduct post-approval. As such, we and our third-party contract manufacturers will be subject to continual review and periodic inspections to assess compliance with regulatory requirements. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control. Regulatory authorities may also impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-marketing studies. Furthermore, any new legislation addressing drug safety issues could result in delays or increased costs to assure compliance.

We will also be required to report certain adverse reactions and production problems, if any, to the FDA, and to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may not promote our products for indications or uses for which they do not have FDA approval.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- warning or untitled letters, fines or holds on clinical trials;
- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market or voluntary or mandatory product recalls;
- injunctions or the imposition of civil or criminal penalties;
- suspension or revocation of existing regulatory approvals;
- suspension of any of our ongoing clinical trials;
- refusal to approve pending applications or supplements to approved applications submitted by us;
- restrictions on our or our contract manufacturers' operations; or

- product seizure or detention, or refusal to permit the import or export of products.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize IBSRELA and XPHOZAH, if approved. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

In addition, the FDA's policies may change, and additional government regulations may be enacted. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, or otherwise review and process regulatory submissions in a timely manner, which could negatively impact our business.

The ability of the FDA to review and process regulatory submissions can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Separately, in response to the global COVID-19 pandemic, on March 10, 2020, the FDA announced its intention to postpone most foreign inspections of manufacturing facilities and products through April 2020, and subsequently, on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, on July 10, 2020, the FDA announced its intention to resume certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA utilized this risk-based assessment system to assist in determining when and where it was safest to conduct prioritized domestic inspections. Additionally, on April 15, 2021, the FDA issued a guidance document in which the FDA described its plans to conduct voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites, among other facilities. According to the guidance, the FDA may request such remote interactive evaluations where the FDA determines that remote evaluation would be appropriate based on mission needs and travel limitations. In May 2021, the FDA outlined a detailed plan to move toward a more consistent state of inspectional operations, and in July 2021, the FDA resumed standard inspectional operations of domestic facilities. More recently, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our IBSRELA and XPHOZAH. The manufacturing facilities on which we rely may not continue to meet regulatory requirements or may not be able to meet supply demands.

All entities involved in the preparation of product for commercial sale, or product candidates for clinical trials, including our existing contract manufacturers are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with cGMP regulations. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our

product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of an NDA or comparable regulatory filing on a timely basis and must adhere to cGMP regulations enforced by the FDA and other regulatory agencies through their facilities inspection programs. The facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the manufacture of our product or the associated quality systems for compliance with the regulations applicable to the activities being conducted. Although we oversee the contract manufacturers, we cannot control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with the regulatory requirements. If these facilities do not pass a pre-approval plant inspection, regulatory approval of the products may not be granted or may be substantially delayed until any violations are corrected to the satisfaction of the regulatory authority, if ever. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time consuming for us or a third party to implement, and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent suspension of production or closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other applicable regulatory authority can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product, withdrawal of an approval, or suspension of production. As a result, our business, financial condition, and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, an alternative manufacturer would need to be qualified through an NDA, a supplemental NDA or equivalent foreign regulatory filing, which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause us to incur higher costs and could cause the delay or termination of clinical studies, regulatory submissions, required approvals, or commercialization of our product candidates. Furthermore, if our suppliers fail to meet contractual requirements and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed, or we could lose potential revenue.

If we fail to comply or are found to have failed to comply with FDA and other regulations related to the promotion of our products for unapproved uses, we could be subject to criminal penalties, substantial fines or other sanctions and damage awards.

The regulations relating to the promotion of products for unapproved uses are complex and subject to substantial interpretation by the FDA and other government agencies. With respect to the commercialization of IBSRELA and/or XPHOZAH, if approved, we will be restricted from marketing the product outside of its approved labeling, also referred to as off-label promotion. However, physicians may nevertheless prescribe an approved product to their patients in a manner that is inconsistent with the approved label, which is an off-label use. In preparation for the commercial launch of IBSRELA, we have implemented compliance and training programs designed to ensure that our sales and marketing practices comply with applicable regulations regarding off-label promotion. Notwithstanding these programs, the FDA or other government agencies may allege or find that our practices constitute prohibited promotion of our product candidates for unapproved uses. We also cannot be sure that our employees will comply with company policies and applicable regulations regarding the promotion of products for unapproved uses.

Over the past several years, a significant number of pharmaceutical and biotechnology companies have been the target of inquiries and investigations by various federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U.S. Attorneys' Offices, the Office of Inspector General of the Department of Health and Human Services, the FDA, the Federal Trade Commission and various state Attorneys General offices. These investigations have alleged violations of various federal and state laws and regulations, including claims asserting antitrust violations, violations of the FFDCA, the False Claims Act, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the

promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. Many of these investigations originate as "qui tam" actions under the False Claims Act. Under the False Claims Act, any individual can bring a claim on behalf of the government alleging that a person or entity has presented a false claim, or caused a false claim to be submitted, to the government for payment. The person bringing a qui tam suit is entitled to a share of any recovery or settlement. Qui tam suits, also commonly referred to as "whistleblower suits," are often brought by current or former employees. In a qui tam suit, the government must decide whether to intervene and prosecute the case. If it declines, the individual may pursue the case alone.

If the FDA or any other governmental agency initiates an enforcement action against us or if we are the subject of a qui tam suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects and reputation.

IBSRELA and/or XPHOZAH, if approved, may cause or contribute to adverse medical events that we are required to report to regulatory agencies and if we fail to do so we could be subject to sanctions that would materially harm our business.

Some participants in clinical studies of tenapanor have reported adverse effects after being treated with tenapanor, including diarrhea, abdominal distension, flatulence and dizziness. If we are successful in commercializing any products, FDA and foreign regulatory agency regulations require that we report certain information about adverse medical events if those products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We may fail to report adverse events we become aware of within the prescribed timeframe. We may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. If we fail to comply with our reporting obligations, the FDA or a foreign regulatory agency could take action, including criminal prosecution, the imposition of civil monetary penalties, seizure of our products or delay in approval or clearance of future products.

Our employees, independent contractors, principal investigators, CROs, collaboration partners, consultants and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, collaboration partners, consultants and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate any of the following: FDA regulations, including those laws that require the reporting of true, complete and accurate financial and other information to the FDA; manufacturing standards; or federal and state healthcare fraud and abuse laws and regulations. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. These activities also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and 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 comply with such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Failure to obtain regulatory approvals in foreign jurisdictions would prevent us from marketing our products internationally.

In order to market any product in the EEA (which is composed of the 27 Member States of the European Union plus Norway, Iceland and Liechtenstein), and many other foreign jurisdictions, separate regulatory approvals are required. In the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization ("MA"). Before the MA is

granted, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

The approval procedures vary among countries and can involve additional clinical testing, and the time required to obtain approval may differ from that required to obtain FDA approval. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one or more foreign regulatory authorities does not ensure approval by regulatory authorities in other foreign countries or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not be able to file for regulatory approvals or to do so on a timely basis, and even if we do file, we may not receive necessary approvals to commercialize our products in any market.

We and our collaboration partners may be subject to healthcare laws, regulation and enforcement; our failure or the failure of any such collaboration partners to comply with these laws could have a material adverse effect on our results of operations and financial conditions.

Following our commercial introduction of IBSRELA, and the regulatory approval by a foreign government and the commercial introduction of any either IBSRELA or XPHOZAH by our collaboration partner in such jurisdiction, we and our collaboration partners may be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. The laws that may affect our ability to operate as a commercial organization include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation;

- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent. In addition, the government may assert 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 false claims statutes;

- the federal Civil Monetary Penalties law, which prohibits, among other things, offering or transferring remuneration to a federal healthcare beneficiary that a person knows or should know is likely to influence the beneficiary’s decision to order or receive items or services reimbursable by the government from a particular provider or supplier;

- federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation;

- the federal physician sunshine requirements under the ACA, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to CMS information related to payments and other transfers of value to physicians, (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants and certified nurse midwives), and teaching hospitals, and ownership and investment interests held by physicians (as defined by the statute) and their immediate family members;

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which 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 otherwise restrict payments that may be made to healthcare providers and other potential referral sources;

- state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or pricing information and marketing expenditures; and

- European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. If our operations are found to be in violation of any of the laws described above or any other governmental laws and 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 and imprisonment, any of which could adversely affect our ability to market our products and adversely impact our financial results.

Legislative or regulatory healthcare reforms in the United States may make it more difficult and costly for us to obtain regulatory clearance or approval of our product candidates and to produce, market and distribute our products after clearance or approval is obtained.

From time to time, legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the regulatory clearance or approval, manufacture, and marketing of regulated products or the reimbursement thereof. In addition, FDA regulations and guidance are often revised or reinterpreted by the FDA in ways that may significantly affect our business and our products. Any new regulations or revisions or reinterpretations of existing regulations may impose additional costs or lengthen review times of our product candidates. We cannot determine what effect changes in regulations, statutes, legal interpretation or policies, when and if promulgated, enacted or adopted may have on our business in the future. Such changes could, among other things, require:

- additional clinical trials to be conducted prior to obtaining approval;
- changes to manufacturing methods;
- recall, replacement, or discontinuance of one or more of our products; and
- additional record keeping.

Each of these would likely entail substantial time and cost and could materially harm our business and our financial results. In addition, delays in receipt of or failure to receive regulatory clearances or approvals for any future products would harm our business, financial condition and results of operations.

In addition, the full impact of recent healthcare reform and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model. In the United States, the ACA was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The ACA, among other things, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace from February 15, 2021 through August 15, 2021. The executive order instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. These new laws, among other things, included aggregate reductions of Medicare payments of 2% per fiscal year to providers that will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 and a 1% reduction from April 1, 2022 through June 30, 2022, unless additional action is taken by Congress, additional specific reductions in Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and an increase in the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, beginning January 1, 2024. Recently, there has also been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. By way of example, the Build Back Better Act, if enacted, would introduce substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, and the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D. If the Build Back Better Act is not enacted, similar or other drug pricing proposals could appear in future legislation. Additionally, individual states have become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and to encourage importation from other countries and bulk purchasing.

We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect the demand for any drug products for which we may obtain regulatory approval, our ability to set a price that we believe is fair for our products, our ability to obtain coverage and reimbursement approval for a product, our ability to generate revenues and achieve or maintain profitability, and the level of taxes that we are required to pay.

Following the commercial launch of IBSRELA, if we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.

Following the commercial launch of IBSRELA, we intend to participate in the Medicaid Drug Rebate Program ("MDRP") and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require manufacturers to pay rebates or otherwise provide discounts to government payors in connection with drugs that are dispensed to beneficiaries of these programs. Medicaid drug rebates are based on pricing data that we will be obligated to report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services ("CMS"), the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the average manufacturer price ("AMP") and the best price ("BP") for each drug. If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. In addition, there is increased focus by the Office of Inspector General within the U.S. Department of Health and Human Services on the methodologies used by manufacturers to calculate AMP, and BP, to assess manufacturer compliance with MDRP reporting requirements. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP, which would result in payment not being available for our covered drugs under Medicaid. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations.

Federal law requires that a manufacturer that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program (the "340B program") in order for federal funds to be available for the manufacturer's drugs under Medicaid. We intend to participate in the 340B program, which is administered by the Health Resources and Services Administration ("HRSA"), and requires us to charge statutorily defined covered entities no more than the 340B "ceiling price" for the our covered drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and rebate amount for the covered drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We will be obligated to report 340B ceiling

prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B-eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have drug products paid for with federal funds under Medicaid and purchased by certain federal agencies and grantees, we also must participate in the U.S. Department of Veterans Affairs ("VA") Federal Supply Schedule ("FSS") pricing program. Under the VA/FSS program, we will become obligated to report the Non-Federal Average Manufacturer Price ("Non-FAMP") for our covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non-FAMP using a statutory formula. These four agencies are the VA, the U.S. Department of Defense, the U.S. Coast Guard, and the U.S. Public Health Service (including the Indian Health Service). We will also be required to pay rebates on products purchased by military personnel and dependents through the TRICARE retail pharmacy program. If we fail to provide timely information or are found to have knowingly submitted false information, we may be subject to civil monetary penalties.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation that may prevent or limit our ability to take price increases at certain rates or frequencies. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for IBSRELA, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information. If we are found to have violated state law requirements, we may become subject to penalties or other enforcement mechanisms, which could have a material adverse effect on our business.

Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by us, governmental or regulatory agencies, and the courts. The terms, scope and complexity of these government pricing programs change frequently, as do interpretations of applicable requirements for pricing and rebate calculations. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming. Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. Price recalculations under the MDRP also may affect the ceiling price at which we are required to offer products under the 340B program. Civil monetary penalties can be applied if we are found to have knowingly submitted any false price or product information to the government, if we fail to submit the required price data on a timely basis, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. In the event that CMS were to terminate our Medicaid rebate agreement, no federal payments would be available under Medicaid or Medicare for IBSRELA. We cannot assure you that our submissions will not be found to be incomplete or incorrect.

Risks Related to Intellectual Property

Our success will depend on our ability to obtain, maintain and protect our intellectual property rights

Our success and ability to compete depend in part on our ability to obtain, maintain and enforce issued patents, trademarks and other intellectual property rights and proprietary technology in the United States and elsewhere. If we cannot adequately obtain, maintain and enforce our intellectual property rights and proprietary technology, competitors may be able to use our technologies or the goodwill we have acquired in the marketplace and erode or negate any competitive advantage we may have and our ability to compete, which could harm our business and ability to achieve profitability and/or cause us to incur significant expenses.

We rely on a combination of contractual provisions, confidentiality procedures and patent, trademark, copyright, trade secret and other intellectual property laws to protect the proprietary aspects of our products, product candidates, brands, technologies, trade secrets, know-how and data. These legal measures afford only limited protection, and competitors or others may gain access to or use our intellectual property rights and proprietary information. Our success will depend, in part, on preserving our trade secrets, maintaining the security of our data and know-how and obtaining, maintaining and enforcing other

intellectual property rights. We may not be able to obtain, maintain and/or enforce our intellectual property or other proprietary rights necessary to our business or in a form that provides us with a competitive advantage.

Failure to obtain, maintain and/or enforce intellectual property rights necessary to our business and failure to protect, monitor and control the use of our intellectual property rights could negatively impact our ability to compete and cause us to incur significant expenses. The intellectual property laws and other statutory and contractual arrangements in the United States and other jurisdictions we depend upon may not provide sufficient protection in the future to prevent the infringement, use, violation or misappropriation of our patents, trademarks, data, technology and other intellectual property rights and products by others, and may not provide an adequate remedy if our intellectual property rights are infringed, misappropriated or otherwise violated by others.

We rely in part on our portfolio of issued and pending patent applications in the United States and other countries to protect our intellectual property and competitive position. However, it is also possible that we may fail to identify patentable aspects of inventions made in the course of our development, manufacture and commercialization activities before it is too late to obtain patent protection on them. If we fail to timely file for patent protection in any jurisdiction, we may be precluded from doing so at a later date. Although we enter into non-disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, suppliers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in any of our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Moreover, should we become a licensee of a third party's patents or patent applications, depending on the terms of any future in-licenses to which we may become a party, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering technology in-licensed from third parties. Therefore, these patents and patent applications may not be prosecuted, maintained and/or enforced in a manner consistent with the best interests of our business. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The patent positions of companies, including our patent position, may involve complex legal and factual questions that have been the subject of much litigation in recent years, and, therefore, the scope of any patent claims that we have or may obtain cannot be predicted with certainty. Accordingly, we cannot provide any assurances about which of our patent applications will issue, the breadth of any resulting patent, whether any of the issued patents will be found to be infringed, invalid or unenforceable or will be threatened or challenged by third parties, that any of our issued patents have, or that any of our currently pending or future patent applications that mature into issued patents will include, claims with a scope sufficient to protect our products and services. Our pending and future patent applications may not result in the issuance of patents or, if issued, may not issue in a form that will be advantageous to us. The coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. We cannot offer any assurances that the breadth of our granted patents will be sufficient to stop a competitor from developing, manufacturing and commercializing a product or technologies in a non-infringing manner that would be competitive with one or more of our products or technologies, or otherwise provide us with any competitive advantage. Furthermore, any successful challenge to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for our commercial success. Further, there can be no assurance that we will have adequate resources to enforce our patents.

Patents have a limited lifespan. In the United States, the natural expiration of a utility patent is generally 20 years from the earliest effective non-provisional filing date. Though an issued patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products or services. Patents, if issued, may be challenged, deemed unenforceable, invalidated, narrowed or circumvented. Proceedings challenging our patents or patent applications could result in either loss of the patent, or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. Any successful challenge to our patents and patent applications could deprive us of exclusive rights necessary for our commercial success. In addition, defending such challenges in such proceedings may be costly. Thus, any patents that we may own may not provide the anticipated level of, or any, protection against competitors. Furthermore, an adverse decision may result in a third party receiving a patent right sought by us, which in turn could affect our ability to develop, manufacture or commercialize our products or technologies.

Some of our patents and patent applications may in the future be co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products,

services and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- Any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect our products or product candidates;
- Any of our pending patent applications will issue as patents;
- We were the first to make the inventions covered by each of our patents and pending patent applications;
- We were the first to file patent applications for these inventions;
- Others will not develop, manufacture and/or commercialize similar or alternative products or technologies that do not infringe our patents;
- Any of our challenged patents will be found to ultimately be valid and enforceable;
- Any patents issued to us will provide a basis for an exclusive market for our commercially viable products or technologies will provide us with any competitive advantages or will not be challenged by third parties;
- We will develop additional proprietary technologies or products that are separately patentable; or
- Our commercial activities or products will not infringe upon the patents of others.

We may become subject to third party claims alleging infringement, misappropriation or violation of such third parties' patents or other intellectual property rights and/or third party claims seeking to invalidate our patents, which would be costly, time consuming and, if successfully asserted against us, delay or prevent the development, manufacture or commercialization of our products or product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture or commercialize our products and product candidates without infringing, misappropriating or otherwise violating the intellectual property rights of third parties. There have been many lawsuits and other proceedings asserting infringement or misappropriation of patents and other intellectual property rights in the pharmaceutical and biotechnology industries, and companies in the industry have used intellectual property litigation to gain a competitive advantage. While we take steps to ensure that we do not infringe upon, misappropriate or otherwise violate the intellectual property rights of others, there can be no assurances that we will not be subject to claims alleging that the manufacture, use or sale of IBSRELA or XPHOZAH or of any other product candidates infringes existing or future third-party patents, or that such claims, if any, will not be successful. Because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of IBSRELA or XPHOZAH or other product candidates. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our own patent portfolio may thus have no deterrent effect. We may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of IBSRELA or XPHOZAH or our other product candidates.

Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights. These proceedings could cause us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing a third party's patents. We may be required to indemnify future collaboration partners against such claims. We are not aware of any threatened or pending claims related to these matters, but in the future litigation may be necessary to defend against such claims. If a patent infringement suit were brought against us, we could be forced to stop or delay development, manufacturing or sales of the product or product candidate that is the subject of the suit. As a result of patent infringement claims, or in order to avoid potential claims, we may choose to seek, or be required to seek, a license from the third party and would most likely be required to pay license fees or royalties or both. These licenses may not be available on acceptable terms, or at all. Even if we were able to obtain a license, we may be unable to maintain such licenses and the rights may be nonexclusive, which would give our competitors access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or forced to redesign it if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms, or unable to maintain such licenses when granted. Even if we are successful in defending against such claims, such litigation can be expensive and time consuming to

litigate and would divert management's attention from our core business. Any of these events could harm our business significantly.

We also could be ordered to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing a third party's patents or other intellectual property right. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third party patents are valid and enforceable, and infringed by the use of our products and/or technologies, which could have a negative impact on the commercial success of our current and any future products or technologies. If we were to challenge the validity of any such third party U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. We will have similar burdens to overcome in foreign courts in order to successfully challenge a third party claim of patent infringement. Even if we are successful in defending against such claims, such litigation can be expensive and time consuming to litigate and would divert management's attention from our core business. Any of these events could harm our business significantly.

In addition to infringement claims against us, third parties may also raise similar claims before administrative bodies in the United States or abroad. Such mechanisms include reexamination, post grant review, inter parties review, derivation or opposition proceedings before the United States Patent and Trademark Office (the "USPTO") or other jurisdictional body relating to our intellectual property rights or the intellectual property rights of others. If third parties prepare and file patent applications in the United States that also claim technology similar or identical to ours, we may have to participate in interference or derivation proceedings in the USPTO to determine which party is entitled to a patent on the disputed invention. We may also become involved in similar opposition proceedings in the European Patent Office or similar offices in other jurisdictions regarding our intellectual property rights with respect to our products and technology. Since patent applications are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Such administrative proceedings could result in revocation of or amendment to our patents in such a way that they no longer cover our products or product candidates. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity and/or unenforceability, we may lose at least part, and perhaps all, of the patent protection on our products or technologies. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations, and prospects.

If our intellectual property related to IBSRELA, XPHOZAH, RDX013 or any future product candidates is not adequate or if we are not able to successfully enforce our intellectual property right, the commercial value of IBSRELA, or our product candidates may be adversely affected and we may not be able to compete effectively in our market.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or license may fail to result in issued patents in the United States or in foreign countries. Additionally, our research and development efforts may result in product candidates for which patent protection is limited or not available. Even if patents do successfully issue, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. For example, U.S. patents can be challenged by any person before the new USPTO Patent Trial and Appeals Board at any time before one year after that person is served an infringement complaint based on the patents. Patents granted by the European Patent Office may be similarly opposed by any person within nine months from the publication of the grant. Similar proceedings are available in other jurisdictions, and in the United States, Europe and other jurisdictions third parties can raise questions of validity with a patent office even before a patent has granted. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. For example, a third party may develop a competitive product that provides therapeutic benefits similar to one or more of our product candidates but has a sufficiently different composition to fall outside the scope of our patent protection. If the breadth or strength of protection provided by the patents and patent applications we hold or pursue with respect to IBSRELA, XPHOZAH, RDX013 or any future product candidates is successfully challenged, then our ability to commercialize such product could be negatively affected, and we may face unexpected competition that could have a material adverse impact on our business. Further, if we encounter delays in our clinical trials, the period of time during which we or our collaboration partners could market RDX013 or any future product candidates under patent protection would be reduced.

Even where laws provide protection, costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and the outcome of such litigation would be uncertain. If we or one of our collaboration partners were to initiate legal proceedings against a third party to enforce a patent covering a product or product candidate, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an

alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability against our intellectual property related to a product or a product candidate, we would lose at least part, and perhaps all, of the patent protection on such product or product candidate. Such a loss of patent protection would have a material adverse impact on our business. Moreover, our competitors could counterclaim that we infringe their intellectual property, and some of our competitors have substantially greater intellectual property portfolios than we do.

We also rely on trade secret protection and confidentiality agreements to protect proprietary know-how that may not be patentable, processes for which patents may be difficult to obtain and/or enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology, to assign their inventions to us, and endeavor to execute confidentiality agreements with all such parties, we cannot be certain that we have executed such agreements with all parties who may have helped to develop our intellectual property or who had access to our proprietary information, nor can we be certain that our agreements will not be breached by such consultants, advisors or third parties, or by our former employees. The breach of such agreements by individuals or entities who were actively involved in the discovery and design of our products or potential drug candidates, or in the development of our discovery and design platform, including APECCS, could require us to pursue legal action to protect our trade secrets and confidential information, which would be expensive, and the outcome of which would be unpredictable. If we are not successful in prohibiting the continued breach of such agreements, our business could be negatively impacted. We cannot guarantee that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Further, 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 both in the United States and abroad. If we are unable to prevent material disclosure of the intellectual property related to our technologies to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of marketing exclusivity for IBSRELA or our product candidates, our business may be materially harmed.

Following the approval by the FDA for our NDA to market tenapanor for IBS-C, we became eligible to seek and sought patent term restoration under the Hatch-Waxman Act for one of the U.S. patents covering our approved product or the use thereof. The Hatch-Waxman Act allows a maximum of one patent to be extended per FDA approved product. Patent term extension also may be available in certain foreign countries upon regulatory approval of our product candidates. Despite seeking patent term extension for tenapanor or other product candidates, we may not be granted patent term extension either in the United States or in any foreign country 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 term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority 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 and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions to maintain patent applications and issued patents. Noncompliance with these requirements can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the

relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

We may not be able to enforce our intellectual property rights throughout the world.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. In addition, changes in the law and legal decisions by courts in the United States and foreign countries may affect our ability to obtain and enforce adequate intellectual property protection for our technology.

We may be subject to claims that we or our employees have misappropriated the intellectual property, including know-how or trade secrets, of a third party, or claiming ownership of what we regard as our own intellectual property.

Many of our employees, consultants and contractors were previously employed at or engaged by other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Some of these employees, consultants and contractors, executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment. Although we try to ensure that our employees, consultants and contractors do not use the intellectual property and other proprietary information or know-how or trade secrets of others in their work for us, and do not perform work for us that is in conflict with their obligations to another employer or any other entity, we may be subject to claims that we or these employees, consultants and contractors have used or disclosed such intellectual property, including know-how, trade secrets or other proprietary information. In addition, an employee, advisor or consultant who performs work for us may have obligations to a third party that are in conflict with their obligations to us, and as a result such third party may claim an ownership interest in the intellectual property arising out of work performed for us. We are not aware of any threatened or pending claims related to these matters, but in the future litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, or access to consultants and contractors. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the 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 develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and scientific personnel.

Risks Related to Our Common Stock

Our stock price may be volatile and our stockholders may not be able to resell shares of our common stock at or above the price they paid.

The trading price of our common stock is highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. These factors include those discussed in this “Risk Factors” section and others such as:

- the success or lack of success with regards to our commercial launch of IBSRELA in April 2022;
- announcements of regulatory decisions regarding our NDA seeking marketing approval for tenapanor for the Hyperphosphatemia Indication;

- announcements regarding any potential receipt from Nasdaq of notice regarding a de-listing of our common stock;
- results of regulatory inspections of our facilities or those of our contract manufacturing organizations, or specific label restrictions or patient populations for XPHOZAH's use, if approved, or changes or delays in the regulatory review process;
- announcements regarding whether XPHOZAH, if approved, alone or with other oral only medications, will be included in the bundled prospective payment system for the treatment of ESRD patients, and the time and manner in which such transition is achieved;
- announcements regarding results from our RDX013 Phase 2 clinical trial;
- announcements relating to our current or future collaboration partnerships;
- announcements of therapeutic innovations or new products by us or our competitors;
- adverse actions taken by regulatory agencies with respect to our product label, our clinical trials, manufacturing supply chain or sales and marketing activities;
- changes or developments in laws or regulations applicable to our approved products or our product candidates;
- the success of our testing and clinical trials;
- failure to meet any of our projected timelines or goals with regard to the commercial launch of IBSRELA, or the clinical development and commercialization of any of our product candidates;
- the success of our efforts to acquire or license or discover additional product candidates;
- any intellectual property infringement actions in which we may become involved;
- the success of our efforts to obtain adequate intellectual property protection for our product candidates;
- announcements concerning our competitors or the pharmaceutical industry in general;
- achievement of expected product sales and profitability;
- manufacture, supply or distribution shortages;
- actual or anticipated fluctuations in our operating results;
- FDA or other U.S. or foreign regulatory actions affecting us or our industry or other healthcare reform measures in the United States;
- changes in financial estimates or recommendations by securities analysts;
- trading volume of our common stock;
- sales of our common stock by us, our executive officers and directors or our stockholders in the future;
- sales of debt securities and sales or licensing of assets;
- general economic and market conditions and overall fluctuations in the United States equity markets; and
- the loss of any of our key scientific or management personnel.

In addition, the stock markets in general, and the markets for pharmaceutical, biopharmaceutical and biotechnology stocks in particular, have experienced extreme volatility that may have been unrelated to the operating performance of the issuer. These broad market fluctuations may adversely affect the trading price or liquidity of our common stock. In the past, when the market price of a stock has been volatile, holders of that stock have sometimes instituted securities class action litigation against the issuer. If any of our stockholders were to bring such a lawsuit against us, we could incur substantial costs defending the

lawsuit and the attention of our management would be diverted from the operation of our business, which could seriously harm our financial position. Any adverse determination in litigation could also subject us to significant liabilities.

Our principal stockholders own a significant percentage of our stock and, together with our management, will be able to exert significant control over matters subject to stockholder approval.

Based on the number of shares outstanding as of December 31, 2021, our officers, directors and stockholders who hold at least 5% of our stock together beneficially own approximately 17.6% of our outstanding common stock. If these officers, directors, and principal stockholders or a group of our principal stockholders act together, they will be able to exert a significant degree of influence over our management and affairs and control matters requiring stockholder approval, including the election of directors, amendments to our organizational documents, and approval of any merger, sale of assets or other business combination transactions. The interests of this concentration of ownership may not always coincide with our interests or the interests of other stockholders. For instance, officers, directors and principal stockholders, acting together, could cause us to enter into transactions or agreements that we would not otherwise consider. Similarly, this concentration of ownership may have the effect of delaying or preventing a change in control of our company otherwise favored by our other stockholders.

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. As of December 31, 2021, we had approximately 130.2 million shares of common stock outstanding. Of those shares, approximately 18.7 million were held by current directors, executive officers and stockholders owning 5% or more of our outstanding common stock.

As of December 31, 2021, 3.5 million shares of common stock issuable upon vesting of outstanding restricted stock units and approximately 10.4 million shares of common stock issuable upon exercise of outstanding options were eligible for sale in the public market to the extent permitted by the provisions of the applicable vesting schedules, and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are issued and sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

If we sell shares of our common stock in future financings, stockholders may experience immediate dilution and, as a result, our stock price may decline.

We may from time to time issue additional shares of common stock at a discount from the current trading price of our common stock. As a result, our stockholders would experience immediate dilution upon the purchase of any shares of our common stock sold at such discount. In addition, as opportunities present themselves, we may enter into financing or similar arrangements in the future, including the issuance of debt securities, preferred stock or common stock. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

General Risk Factors

We incur significant costs as a result of operating as a public company, and our management will devote substantial time to new compliance initiatives. We may fail to comply with the rules that apply to public companies, including Section 404 of the Sarbanes-Oxley Act of 2002, which could result in sanctions or other penalties that would harm our business.

We incur significant legal, accounting and other expenses as a public company, including costs resulting from public company reporting obligations under the Securities Exchange Act of 1934, as amended (the “Exchange Act”) and regulations regarding corporate governance practices. The listing requirements of The Nasdaq Global Market require that we satisfy certain corporate governance requirements relating to director independence, distributing annual and interim reports, stockholder meetings, approvals and voting, soliciting proxies, conflicts of interest and a code of conduct. Our management and other personnel will need to devote a substantial amount of time to ensure that we comply with all of these requirements. Moreover, the reporting requirements, rules and regulations will increase our legal and financial compliance costs and will make some activities more time consuming and costly. Any changes we make to comply with these obligations may not be sufficient to allow us to satisfy our obligations as a public company on a timely basis, or at all. These reporting requirements, rules and regulations, coupled with the increase in potential litigation exposure associated with being a public company, could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or board committees or to serve as executive officers, or to obtain certain types of insurance, including directors’ and officers’ insurance, on acceptable terms.

We are subject to Section 404 of The Sarbanes-Oxley Act of 2002 ("Section 404") and the related rules of the Securities and Exchange Commission ("SEC") which require, among other things, our management and independent registered public accounting firm to report on the effectiveness of our internal control over financial reporting. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts.

During the course of our review and testing of our internal controls, we may identify deficiencies and be unable to remediate them before we must provide the required reports. Furthermore, if we have a material weakness in our internal controls over financial reporting, we may not detect errors on a timely basis and our financial statements may be materially misstated. We or our independent registered public accounting firm may not be able to conclude on an ongoing basis that we have effective internal control over financial reporting, which could harm our operating results, cause investors to lose confidence in our reported financial information and cause the trading price of our stock to fall. In addition, as a public company we are required to file accurate and timely quarterly and annual reports with the SEC under the Exchange Act. Any failure to report our financial results on an accurate and timely basis could result in sanctions, lawsuits, delisting of our shares from The Nasdaq Global Market or other adverse consequences that would materially harm our business.

We may be adversely affected by the global economic environment.

Our ability to attract and retain collaboration partners or customers, invest in and grow our business and meet our financial obligations depends on our operating and financial performance, which, in turn, is subject to numerous factors, including the prevailing economic conditions and financial, business and other factors beyond our control, such as the rate of unemployment, the number of uninsured persons in the United States, presidential elections, other political influences and inflationary pressures. Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The 2008 global financial crisis caused extreme volatility and disruptions in the capital and credit markets. We cannot anticipate all the ways in which the global economic climate and global financial market conditions could adversely impact our business in the future.

We are exposed to risks associated with reduced profitability and the potential financial instability of our collaboration partners or customers, many of which may be adversely affected by volatile conditions in the financial markets. For example, unemployment and underemployment, and the resultant loss of insurance, may decrease the demand for healthcare services and pharmaceuticals. If fewer patients are seeking medical care because they do not have insurance coverage, our collaboration partners or customers may experience reductions in revenues, profitability and/or cash flow that could lead them to reduce their support of our programs or financing activities. If collaboration partners or customers are not successful in generating sufficient revenue or are precluded from securing financing, they may not be able to pay, or may delay payment of, accounts receivable that are owed to us. In addition, volatility in the financial markets could cause significant fluctuations in the interest rate and currency markets. We currently do not hedge for these risks. The foregoing events, in turn, could adversely affect our financial condition and liquidity. In addition, if economic challenges in the United States result in widespread and prolonged unemployment, either regionally or on a national basis, or if certain provisions of the Patient Protection and ACA, as amended by the Health Care and Education Reconciliation Act, collectively known as the ACA, are repealed, a substantial number of people may become uninsured or underinsured. To the extent economic challenges result in fewer individuals pursuing or being able to afford our product candidates once commercialized, our business, results of operations, financial condition and cash flows could be adversely affected.

Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could significantly reduce the value of our shares to a potential acquirer or delay or prevent changes in control or changes in our management without the consent of our board of directors. The provisions in our charter documents include the following:

- a classified board of directors with three-year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors;
- no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates;
- the exclusive right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors;

- the required approval of at least two-thirds of the shares entitled to vote to remove a director for cause, and the prohibition on removal of directors without cause;

- the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquirer;

- the ability of our board of directors to alter our bylaws without obtaining stockholder approval;

- the required approval of at least two-thirds of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws or repeal the provisions of our amended and restated certificate of incorporation regarding the election and removal of directors;

- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;

- the requirement that a special meeting of stockholders may be called only by the chairman of the board of directors, the chief executive officer, the president or the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and

- advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of us.

In addition, these provisions would apply even if we were to receive an offer that some stockholders may consider beneficial.

We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction.

Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful third-party claims against us and may reduce the amount of money available to us.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that we will indemnify our directors and officers, in each case to the fullest extent permitted by Delaware law.

In addition, as permitted by Section 145 of the Delaware General Corporation Law, our amended and restated bylaws and our indemnification agreements that we have entered into with our directors and officers provide that:

- We will indemnify our directors and officers for serving us in those capacities or for serving other business enterprises at our request, to the fullest extent permitted by Delaware law. Delaware law provides that a corporation may indemnify such person if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the registrant and, with respect to any criminal proceeding, had no reasonable cause to believe such person's conduct was unlawful.

- We may, in our discretion, indemnify employees and agents in those circumstances where indemnification is permitted by applicable law.

- We are required to advance expenses, as incurred, to our directors and officers in connection with defending a proceeding, except that such directors or officers shall undertake to repay such advances if it is ultimately determined that such person is not entitled to indemnification.

- We will not be obligated pursuant to our amended and restated bylaws to indemnify a person with respect to proceedings initiated by that person against us or our other indemnities, except with respect to proceedings authorized by our board of directors or brought to enforce a right to indemnification.

- The rights conferred in our amended and restated bylaws are not exclusive, and we are authorized to enter into indemnification agreements with our directors, officers, employees and agents and to obtain insurance to indemnify such persons.

- We may not retroactively amend our amended and restated bylaw provisions to reduce our indemnification obligations to directors, officers, employees and agents.

We do not currently intend to pay dividends on our common stock, and, consequently, our stockholders' ability to achieve a return on their investment will depend on appreciation in the price of our common stock.

We do not currently intend to pay any cash dividends on our common stock for the foreseeable future. We currently intend to invest our future earnings, if any, to fund our growth. Additionally, the terms of our loan and security agreements could restrict our ability to pay dividends. Therefore, our stockholders are not likely to receive any dividends on our common stock for the foreseeable future. Since we do not intend to pay dividends, our stockholders' ability to receive a return on their investment will depend on any future appreciation in the market value of our common stock. There is no guarantee that our common stock will appreciate or even maintain the price at which our holders have purchased it.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business.

Following a national referendum and enactment of legislation by the government of the United Kingdom, the United Kingdom formally withdrew from the European Union and ratified a trade and cooperation agreement governing its future relationship with the European Union. The agreement, which is being applied provisionally from January 1, 2021, until it is ratified by the European Parliament and the Council of the European Union, addresses trade, economic arrangements, law enforcement, judicial cooperation and a governance framework including procedures for dispute resolution, among other things. Because the agreement merely sets forth a framework in many respects and will require complex additional bilateral negotiations between the United Kingdom and the European Union as both parties continue to work on the rules for implementation, significant political and economic uncertainty remains about how the precise terms of the relationship between the parties will differ from the terms before withdrawal.

These developments, or the perception that any related developments could occur, have had and may continue to have a material adverse effect on global economic conditions and financial markets, and may significantly reduce global market liquidity, restrict the ability of key market participants to operate in certain financial markets or restrict our access to capital. Any of these factors could have a material adverse effect on our business, financial condition and results of operations and reduce the price of our common stock.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our headquarters is currently located in Waltham, Massachusetts consisting of 12,864 square feet of leased office space under a lease agreement that expires in June 2026. In addition, we lease 72,500 square feet of office and laboratory space in Fremont, California under a lease agreement that expires in March 2025 and 4,768 square feet of office space in Milwaukee, Wisconsin under a lease agreement that expires in February 2026. Prior to October 2021, our headquarters were co-located in Fremont, California and Waltham, Massachusetts.

ITEM 3. LEGAL PROCEEDINGS

On July 30, 2021, a putative securities class action lawsuit was commenced in the U.S. District Court for the Northern District of California naming as defendants Ardelyx and two current officers. The complaint alleges that the defendants violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended, and Rule 10b-5 thereunder, by making false and misleading statements and omissions of material fact related to tenapanor. The plaintiff seeks to represent all persons who purchased or otherwise acquired Ardelyx securities between August 6, 2020, and July 19, 2021. The plaintiff seeks damages and interest, and an award of costs, including attorneys' fees. We believe the plaintiff's claims are without merit and we have not recorded any accrual for a contingent liability associated with these legal proceedings.

From time to time, we may be involved in legal proceedings arising in the ordinary course of business. We believe that as of December 31, 2021, there is no litigation pending that would reasonably be expected to have a material adverse effect on our results of operations and financial condition, and no contingent liabilities were accrued as of December 31, 2021.

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

Common Stock

On June 19, 2014, our common stock commenced trading on The Nasdaq Global Market under the symbol "ARDX". Prior to that date, there was no public trading market for our common stock. As of December 31, 2021, there were 30 holders of record of our common stock.

Dividends

We have never declared or paid cash dividends on our capital stock. We currently intend to retain any future earnings to finance the growth and development of our business.

Securities Authorized for Issuance under Equity Compensation Plans

The information required by this item regarding executive compensation will be incorporated by reference to the information set forth in the sections titled "Executive Compensation" in our Proxy Statement.

Recent Sales of Unregistered Securities

None.

Use of Proceeds

Not applicable.

Issuer Purchases of Equity Securities

Not applicable.

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 in conjunction with our financial statements and related notes included elsewhere in this report. This discussion and other parts of this report contain forward-looking statements that involve risk and uncertainties, such as statements of our plans, objectives, expectations and intentions. Our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section of this report entitled "Risk Factors." These forward-looking statements speak only as of the date hereof. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason. Unless the context requires otherwise, the terms "Ardelyx", "Company", "we", "us", and "our" refer to Ardelyx, Inc.

OVERVIEW

We are a biopharmaceutical company founded with a mission to discover, develop and commercialize innovative first-in-class medicines that meet significant unmet medical needs. This includes adult patients with irritable bowel syndrome with constipation ("IBS-C"), adult patients with chronic kidney disease ("CKD") on dialysis suffering from elevated serum phosphorus, or hyperphosphatemia; and adult patients with CKD and/or heart failure with elevated serum potassium, or hyperkalemia.

Since commencing operations in October 2007, substantially all our efforts have been dedicated to our research and development ("R&D") activities, including developing tenapanor and developing our proprietary drug discovery and design

platform. We have not generated any revenues from product sales. As of December 31, 2021, we had an accumulated deficit of $712.9 million.

We expect to continue to incur substantial operating losses for the foreseeable future as we prepare for commercialization of IBSRELA® (tenapanor) in April of this year, seek to gain approval for XPHOZAH® (tenapanor) for the control of serum phosphorus in adult patients with CKD on dialysis; prepare for the potential commercialization of XPHOZAH, if approved; incur manufacturing and development cost for, tenapanor; and incur development costs for RDX013. To date, we have funded our operations from the sale and issuance of common stock and convertible preferred stock, funds from our collaboration partnerships, which includes license fees, milestones and product supply revenue, as well as funds from our loan agreements with our lenders.

On February 28, 2022, we received a letter from Nasdaq indicating that we have failed to comply with the minimum bid price requirement of Nasdaq Listing Rule 5550(a)(2). Nasdaq Listing Rule 5550(a)(2) requires that companies listed on the Nasdaq Capital Market maintain a minimum closing bid price of at least $1.00 per share. Under Nasdaq Listing Rule 5810(c)(3)(A), we have a 180 calendar day grace period to regain compliance by meeting the continued listing standard. To regain compliance, the closing bid price of the Company's common stock must meet or exceed $1.00 per share for a minimum of ten consecutive business days during this grace period. We are monitoring the bid price of our common stock and will consider options available to us to achieve compliance. There can be no assurances that we will be successful in restoring our compliance with the Nasdaq listing requirements.

OUR PRODUCT PIPELINE

IBSRELA for IBS-C

Our unique discovery platform and deep understanding of the primary mechanism of sodium transport in the intestine resulted in our discovery and development of IBSRELA, a first-in-class, FDA approved, sodium hydrogen exchanger 3 ("NHE3") inhibitor for the treatment of IBS-C in adults. IBSRELA acts locally in the gut and is minimally absorbed. By inhibiting NHE3, IBSRELA exerts a triple action mechanism. First, it blocks dietary sodium absorption, leading to increased intestinal transit time and softer stool to address constipation. Second, it decreases intestinal permeability to reduce abdominal pain, and, third, it decreases visceral hypersensitivity to reduce abdominal pain. The triple action mechanism of IBSRELA is differentiated from existing therapies and has been shown to provide significant improvement in abdominal pain, bloating, and constipation – with a quick onset of action and sustained efficacy. Treatment with IBSRELA has been demonstrated to result in improved quality of life versus placebo and patient treatment satisfaction.

We plan to launch IBSRELA in the U.S. in April 2022.

IBS-C is a gastrointestinal disorder characterized by both abdominal pain and altered bowel movements, estimated to affect 11 million people in the U.S. IBS-C is associated with significantly impaired quality of life, reduced productivity, and substantial economic burden. The introduction of new agents over the last decade has led to an established prescription ("RX") treated market with 9,000 writers accounting for 50% of the RXs. Despite the active use of GCC agonist therapies, 83% of Health Care Providers ("HCPs") report a significant unmet need for new therapies, and report that approximately 35% of the patients currently under their care do not adequately respond to the available treatments. When presented with the IBSRELA product profile, 75% of HCPs respond favorably, with the efficacy profile and novel method of action rated as the most compelling aspects of the product profile.

In preparation for our commercial launch of IBSRELA, we have built a commercial organization highly experienced in launching novel therapies into specialty areas. The established nature of the market, limited number of players, concentration of prescribers, recognized unmet need, and favorable response to the novel mechanism IBSRELA product profile enable a targeted promotional effort centered on the 9,000 health care providers that account for 50% of IBS-C prescriptions. Central to the go to market strategy is a highly experienced specialty sales force, many with existing relationships across their GI target base, full company engagement, and innovative peer-to-peer and digital initiatives leveraging the rapidly evolving market dynamics in how HCPs receive information and interact with industry.

With a concentrated promotional focus on patients currently being managed for IBS-C by high writing HCPs - in contrast to the DTC centered, market building approach taken by the existing GCC agonists - competition for IBSRELA will come largely from the four prescription products indicated for IBS-C: Linzess (linaclotide); Amitiza (lubiprostone); Trulance (plecanatide) and Zelnorm (tegaserod). Additionally, over the counter products are commonly used to treat the constipation component of IBS-C, both alone, and in combination with the IBS-C indicated RX therapies.

We have established commercial agreements with Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd. (“Fosun Pharma”) in China and Knight Therapuetics, Inc. (“Knight”) in Canada for IBSRELA for IBS-C. Knight is currently marketing IBSRELA in Canada.

Development Candidate XPHOZAH: A New Approach for The Control of Serum Phosphorus in Adult Patients with CKD on Dialysis

XPHOZAH is a first-in-class medicine being developed for the control of serum phosphorus in adult patients with CKD on dialysis. XPHOZAH has a unique mechanism of action and acts locally in the gut to inhibit NHE3. This results in the tightening of the epithelial cell junctions, thereby significantly reducing paracellular uptake of phosphate, the primary pathway of phosphate absorption. If approved, XPHOZAH would be the first therapy for phosphate management that blocks phosphorus absorption at the primary site of uptake. It is not a phosphate binder.

In June 2020, we submitted a new drug application ("NDA") to the U.S. Food and Drug Administration (“FDA”) for tenapanor the control of serum phosphorus in adult patients with CKD on dialysis. The NDA was supported by three Phase 3 trials involving over 1,000 adult patients that evaluated the use of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis, with two trials evaluating tenapanor as monotherapy and one trial evaluating tenapanor as part of a dual mechanism approach with phosphate binders. All three Phase 3 trials met their primary and key secondary endpoints.

On July 28, 2021, we received a Complete Response Letter ("CRL") from the FDA regarding our NDA for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. According to the CRL, while the FDA agrees “that the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in adult patients with CKD on dialysis,” the FDA characterizes the magnitude of the treatment effect as “small and of unclear clinical significance.” Following an End-of-Review Type A meeting (“End of Review Meeting”) in October 2021, with the FDA’s Division of Cardiology and Nephrology (the “Division”), we submitted a Formal Dispute Resolution Request (“FDRR”) in December 2021. The FDRR was focused on demonstrating that the data submitted in the NDA supported the clinical significance of the treatment effect of tenapanor.

On February 4, 2022, we received an Appeal Denied Letter (“ADL”) from the FDA’s Office of Cardiology, Hematology, Endocrinology and Nephrology (“OCHEN”). On February 18, 2022, we submitted an appeal of the ADL to the FDA’s Center for Drug Evaluation and Research, Office of New Drugs (“OND”). If accepted, we expect a decision on the appeal to the OND in April 2022. While the CRL noted that in order for the NDA to be approved, we need to conduct an additional adequate and well-controlled trial demonstrating a clinically relevant treatment effect on serum phosphorus or an effect on the clinical outcome thought to be caused by hyperphosphatemia in adult patients with CKD on dialysis, the ADL provided a potential additional path forward involving the resubmission of the NDA (without conducting an additional trial) with a number of new analyses of each of our Phase 3 clinical trials; an assessment of tenapanor’s benefits and risks; and a proposal of how to label tenapanor for prescribers. There can be no assurances that the Formal Dispute Resolution (“FDR”) process will result in approval of our NDA, or in a clear path to resubmission of our NDA that is achievable in terms of clinical endpoints, time and cost.

RDX013 Program: Small Molecule for Treating Hyperkalemia

We are also advancing a small molecule potassium secretagogue program, RDX013, for the potential treatment of hyperkalemia. Hyperkalemia is a common problem in patients with heart and kidney disease, particularly in patients taking customary blood pressure medications known as renin-angiotensin-aldosterone system (“RAAS”) inhibitors. RDX013 is a novel mechanism agent designed to target the underlying biological mechanisms of potassium secretion to lower elevated potassium. While currently available therapies are all ion exchange agents, RDX013 is a first in class secretagogue with demonstrated proof of concept in a Phase 2 dose ranging study evaluating the safety and pharmacodynamics of RDX013 in adult patients with hyperkalemia. The next steps for RDX013 will be determined based on final analyses of the Phase 2 results, continued formulation development, and sufficient financial resources.

RDX020 Program: Small molecule for Treating Metabolic Acidosis

We have an ongoing discovery program targeting the inhibition of bicarbonate exchange inhibitor for the treatment of metabolic acidosis, a highly prevalent comorbidity in CKD patients that is strongly correlated with disease progression and adverse outcomes. We have identified lead compounds that are potent, selective and proprietary inhibitors of bicarbonate secretion. Our research organization was eliminated as part of our October 2021 restructuring, and therefore, we currently expect to continue to advance this discovery program utilizing third-party resources managed by internal non-clinical expertise.

FINANCIAL OPERATIONS OVERVIEW

Revenue

Our revenue to date has been generated primarily through license, research and development collaborative agreements with various collaboration partners. We have not generated any revenue from commercial product sales. We currently expect to commence commercialization of IBSRELA in April 2022. In the future, we may generate revenue from a combination of our own product sales and payments in connection with our current or future collaborative partnerships, including license fees, other upfront payments, milestone payments, royalties and payments for drug product and/or drug substance. We expect that any revenue we generate will fluctuate in future periods as a result of, among other factors: the extent to which we are successful in our efforts to commercialize IBSRELA; whether we receive regulatory approval for tenapanor for the control of serum phosphorous in adult patients with CKD on dialysis (the "Hyperphosphatemia Indication"), and if such approval is received, the timing of such approval and the extent to which we are successful in our efforts to commercialize XPHOZAH for such indication; the timing and progress of goods and services provided pursuant to our current or future collaborative partnerships; our or our collaborators' achievement of preclinical, clinical, regulatory or commercialization milestones, to the extent achieved; the timing and amount of any payments to us relating to the aforementioned milestones; and the extent to which any of our product candidates are approved and successfully commercialized by a collaboration partner. If we are not able to obtain market acceptance for IBSRELA; if we are not successful in our efforts to obtain and sustain an adequate level of coverage and reimbursement for IBSRELA by third-party payors; if we fail to obtain regulatory approval for tenapanor for the Hyperphosphatemia indication and/or our current collaboration partners or any future collaboration partners fail to obtain regulatory approval for tenapanor in their respective territories, our ability to generate future revenue from our product sales or from our collaborative arrangements, and our results of operations and financial position, would be materially and adversely affected. Our past revenue performance is not necessarily indicative of results to be expected in future periods. See Note 2, Summary of Significant Accounting Policies, in the notes to our financial statements, included in Part II, Item 8, of this Annual Report on Form 10-K, for further details.

Cost of Revenue

Cost of revenue represents payments due to AstraZeneca AB ("AstraZeneca"), which under the terms of a termination agreement entered into in 2015 (the "AZ Termination Agreement") is entitled to (i) future royalties at a rate of 10% of net sales of tenapanor or other NHE3 products by us or our licensees, and (ii) 20% of non-royalty revenue received from our collaboration partners as a result of the development and commercialization of tenapanor or certain other NHE3 inhibitors. We have agreed to pay AstraZeneca up to a maximum of $75.0 million in the aggregate for (i) and (ii). We recognize these expenses as cost of revenue when we recognize the corresponding revenue that gives rise to payments due to AstraZeneca. To date, we recognized an aggregate of $11.6 million as cost of revenue under the AZ Termination Agreement since 2017. See details in *Note 5, Collaboration and Licensing Agreements*, under AstraZeneca, in the notes to our financial statements, included in Part II, Item 8, of this Annual Report on Form 10-K.

Research and Development

Pursuant to the October 2021 restructuring plan, we have eliminated our internal research organization and expect to continue our discovery efforts with respect to RDX020 through the use of third-parties managed internally by non-clinical expertise. We recognized all research and development expenses as they were incurred to support the discovery, research, development and manufacturing of our product candidates. Research and development expenses include, but are not limited to, the following:

- external research and development expenses incurred under agreements with consultants, third-party contract research organizations ("CROs") and investigative sites where a substantial portion of our clinical studies are conducted, and with contract manufacturing organizations where our clinical supplies are produced;
- expenses associated with supplies and materials consumed in connection with our research operations;
- expenses associated with producing tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis prior to FDA approval;
- other costs associated with research, clinical development and regulatory activities;
- employee-related expenses, which include salaries, bonuses, benefits, travel and stock-based compensation; and

- facilities and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation and amortization expense, information technology expense and other supplies.

General and Administrative

General and administrative expenses consist primarily of salaries and related benefits, including stock-based compensation, for certain of our executives, our board members, and our finance, legal, business development, market development, commercial and support staff. Other general and administrative expenses include facility related costs and professional fees for legal, accounting and audit, investor relations, other consulting services and allocated facility related costs not otherwise included in research and development expenses.

Interest Expense

Interest expense represents the interest paid on our loan payable.

Other Income, net

Other income, net consists of interest income earned on our cash and cash equivalents and held-to-maturity investments, the periodic revaluation of the exit fee related to our loan and currency exchange gains and losses.

Provision for Income Taxes

Our provision for income taxes includes current and deferred tax, including foreign withholding taxes paid on payments received from certain collaboration partners. Deferred income taxes reflect the tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Our deferred tax assets continue to be fully offset by a valuation allowance, including deferred tax assets related to our net operating loss carryforwards, which may be subject to annual limitations as a result of ownership changes that may have occurred or could occur in the future.

CRITICAL ACCOUNTING POLICES AND ESTIMATES

A detailed discussion of our significant accounting policies can be found in *Note 2, Summary of Significant Accounting Policies*, in the notes to our financial statements, included in Part II, Item 8, of this Annual Report on Form 10-K. Critical accounting policies are those that require significant judgment and/or estimates by management at the time that financial statements are prepared such that materially different results might have been reported if other assumptions had been made. These estimates form the basis for making judgments about the carrying values of assets and liabilities. We base our estimates and judgments on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. Actual results could differ materially from these estimates.

We consider certain accounting policies related to revenue recognition, accrued research and development expenses and stock-based compensation to be critical policies to understanding the judgments and estimates applied in our reported financial results.

Revenue Recognition

We generate revenue primarily from research and collaboration and license agreements with customers. Goods and services in the agreements may include the grant of licenses for the use of our technology, the provision of services associated with the research and development of product candidates, manufacturing services, and participation in joint steering committees. The terms of these arrangements typically include payment to us of one or more of the following: non-refundable, up-front license fees; research, development, regulatory and commercial milestone payments; reimbursement of research and development services; option payments; reimbursement of certain costs; payments for manufacturing supply services; and future royalties on net sales of licensed products.

When two or more contracts are entered into with the same customer at or near the same time, we evaluate the contracts to determine whether the contracts should be accounted for as a single arrangement. Contracts are combined and accounted for as a single arrangement if one or more of the following criteria are met: (i) the contracts are negotiated as a package with a single commercial objective; (ii) the amount of consideration to be paid in one contract depends on the price or performance of the other contract; or (iii) the goods or services promised in the contracts (or some goods or services promised in each of the contracts) are a single performance obligation.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under each of our agreements, management performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including any constraints on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. As part of the accounting for contracts with customers, we develop assumptions that require judgment to determine whether promised goods and services represent distinct performance obligations and the standalone selling price for each performance obligation identified in the contract. This evaluation is subjective and requires us to make judgments about the promised goods and services and whether those goods and services are separable from other aspects of the contract. Further, determining the standalone selling price for performance obligations requires significant judgment, and when an observable price of a promised good or service is not readily available, we consider relevant assumptions to estimate the standalone selling price, including, as applicable, market conditions, development timelines, probabilities of technical and regulatory success, reimbursement rates for personnel costs, forecasted revenues, potential limitations to the selling price of the product and discount rates.

We apply judgment in determining whether a combined performance obligation is satisfied at a point in time or over time, and, if over time, concluding upon the appropriate method of measuring progress to be applied for purposes of recognizing revenue. We evaluate the measure of progress each reporting period and, as estimates related to the measure of progress change, related revenue recognition is adjusted accordingly. Changes in our estimated measure of progress are accounted for prospectively as a change in accounting estimate. We recognize collaboration revenue by measuring the progress toward complete satisfaction of the performance obligation using an input measure. In order to recognize revenue over the research and development period, we measure actual costs incurred to date compared to the overall total expected costs to satisfy the performance obligation. Revenues are recognized as the program costs are incurred. We will re-evaluate the estimate of expected costs to satisfy the performance obligation each reporting period and make adjustments for any significant changes. Amounts received prior to satisfying the revenue recognition criteria are recorded as contract liabilities in our balance sheets. If the related performance obligation is expected to be satisfied within the next twelve months, this will be classified in current liabilities. Amounts recognized as revenue prior to receipt are recorded as contract assets in our balance sheets. If we expect to have an unconditional right to receive the consideration in the next twelve months, this will be classified in current assets. A net contract asset or liability is presented for each contract with a customer.

Milestone Payments: At the inception of each arrangement that includes research and development milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Milestone payments that are not within the control of us or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraints, 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 earnings in the period of adjustment.

Manufacturing supply services: Arrangements that include a promise for the future supply of drug substance or drug product for either clinical development or commercial supply at the customer's discretion are generally considered as 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 payments are recorded in product supply revenues when the customer obtains control of the goods, which is upon delivery.

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 (i) when the related sales occur, or (ii) 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 our licensing arrangements.

Licenses of intellectual property: If a license granted to a customer to use our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue from consideration allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we apply 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, to conclude upon the appropriate method of measuring progress for purposes of recognizing revenue related to consideration allocated to the performance obligation.

Options: Customer options, such as options granted to allow a licensee to choose to research, develop and commercialize licensed compounds are evaluated at contract inception in order to determine whether those options provide a material right (i. e., an optional good or service offered for free or at a discount) to the customer. If the customer options represent a material right, the material right is treated as a separate performance obligation at the outset of the arrangement. We allocate the transaction price to material rights based on the standalone selling price, and revenue is recognized when or as the future goods or services are transferred or when the option expires. Customer options that are not material rights do not give rise to a separate performance obligation, and as such, the additional consideration that would result from a customer exercising an option in the future is not included in the transaction price for the current contract. Instead, the option is deemed a marketing offer, and additional option fee payments are recognized or being recognized as revenue when the licensee exercises the option. The exercise of an option that does not represent a material right is treated as a separate contract for accounting purposes.

Contract modifications: Contract modifications, defined as changes in the scope or price (or both) of a contract that are approved by the parties to the contract, such as a contract amendment, exist when the parties to a contract approve a modification that either creates new or changes existing enforceable rights and obligations of the parties to the contract. Depending on facts and circumstances, we account for a contract modification as one of the following: (i) a separate contract; (ii) a termination of the existing contract and a creation of a new contract; or (iii) a combination of the preceding treatments. A contract modification is accounted for as a separate contract if the scope of the contract increases because of the addition of promised goods or services that are distinct and the price of the contract increases by an amount of consideration that reflects our standalone selling prices of the additional promised goods or services. When a contract modification is not considered a separate contract and the remaining goods or services are distinct from the goods or services transferred on or before the date of the contract modification, we account for the contract modification as a termination of the existing contract and a creation of a new contract. When a contract modification is not considered a separate contract and the remaining goods or services are not distinct, we account for the contract modification as an add-on to the existing contract and as an adjustment to revenue on a cumulative catch-up basis.

We receive payments from our licensees as established in each contract. Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Where applicable, amounts are recorded as unbilled revenue when our right to consideration is unconditional. We do not assess whether a contract with a customer has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our 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 the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors related to contract manufacturing, development and distribution of clinical supplies;
- collaborator entities in connection with our collaboration agreements; and
- vendors in connection with preclinical development activities.

We record expenses related to clinical studies and manufacturing development activities based on our estimates of the services received and efforts expended pursuant to contracts with our CROs and manufacturing vendors that conduct and manage these activities on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to

contract, and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which each component of a service will be performed, and estimate, with vendor input if appropriate, the resulting level of completion of each component of the service, with such estimates often involving drivers that provide a surrogate measurement of completion such as number of enrolled subjects and/or number of sites activated in the calculation of clinical trial fee accruals. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrued or prepaid expense balance accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, we may report amounts that are too high or too low in any particular period.

Stock-Based Compensation

We estimate the fair value of stock options and Employee Stock Purchase Plan (“the ESPP”) shares using the Black-Scholes valuation model. The Black-Scholes model requires the input of highly subjective assumptions which determine the fair value of stock-based awards. These assumptions include:

Expected Term—We have limited historical information to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for our stock-option grants. As such, the expected term is estimated using the simplified method whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option. Beginning in 2021, we estimate the expected term of our options based upon historical exercises and post-vesting termination behavior, which has not resulted in a material difference as compared to using the simplified method.

Expected Volatility— We use the historic volatility of our own stock over the retrospective period corresponding to the expected remaining term of the options, or the period since our shares were first quoted on The Nasdaq Global Market, if that is shorter, to compute our expected stock price volatility.

Risk-Free Interest Rate—The risk-free interest rate assumption is based on zero-coupon U.S. Treasury instruments on the date of grant with a maturity date consistent with the expected term of our stock option grants.

Expected Dividend— To date, we have not declared or paid any cash dividends and do not have any plans to do so in the future. Therefore, we use an expected dividend yield of zero.

As required, we review our valuation assumptions at each grant date and, as a result, we are likely to change our valuation assumptions used to value employee stock-based awards granted in future periods. Employee and director stock-based compensation costs are to be recognized over the vesting period of the award, and we have elected to use the straight-line attribution method. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience.

Restricted stock units ("RSUs") are measured at the fair value of our common stock on the date of grant and expensed over the period of vesting using the straight-line attribution approach.

Performance-based RSUs ("PRSUs") are valued at grant-date fair market value. The vesting of the PRSUs is based on performance conditions. Performance conditions include: (i) a specific performance criteria and (ii) the employee’s continuous employment by the company for a stated period of time in order to earn the right to the related PRSUs to vest. The Company recognizes compensation cost with respect to the vesting of the PRSUs on a ratable basis over the requisite service period, upon the performance conditions being deemed probable of achievement.

Restructuring

We recognize restructuring charges related to reorganization plans that have been committed to by management and when liabilities have been incurred. In connection with these activities, we record restructuring charges at fair value for, (a) contractual employee termination benefits when obligations are associated to services already rendered, rights to such benefits have vested, and payment of benefits is probable and can be reasonably estimated, (b) one-time employee termination benefits when management has committed to a plan of termination, the plan identifies the employees and their expected termination dates, the details of termination benefits are complete, it is unlikely changes to the plan will be made or the plan will be withdrawn and communication to such employees has occurred, and (c) contract termination costs when a contract is terminated before the end of its term.

One-time employee termination benefits are recognized in their entirety when communication has occurred and future services are not required. If future services are required, the costs are recorded ratably over the remaining period of service. Contract termination costs to be incurred over the remaining contract term without economic benefit are recorded in their entirety when the contract is canceled.

RESULTS OF OPERATIONS

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

Revenue

Below is a summary of our total revenue (dollars in thousands):

	Year Ended December 31,			Change 2021 vs. 2020		Change 2020 vs. 2019	
	2021	2020	2019	$	%	$	%
Collaborative development revenue	$ 4,177	$ 5,364	$ 459	$ (1,187)	(22.1)%	$ 4,905	1,068.6 %
Product supply revenue	907	1,501	322	(594)	(39.6)%	1,179	366.1 %
Licensing revenue	5,013	706	4,500	4,307	610.1 %	(3,794)	(84.3)%
Total revenues	$ 10,097	$ 7,571	$ 5,281	$ 2,526	33.4 %	$ 2,290	43.4 %

Fiscal 2021 *compared to* 2020*:* The increase to total revenues is primarily attributable to a $5.0 million development milestone which we earned and recognized as licensing revenue during the current year upon the initiation by KKC of phase 3 clinical studies in Japan to evaluate tenapanor for hyperphosphatemia. The increase was partially offset by lower collaborative development revenue and product supply revenue from KKC during the current year.

Fiscal 2020 *compared to* 2019*:* The increase in our revenue was primarily attributable to $4.9 million higher collaborative development revenue recognized in connection with the KKC Agreement, which was entered into in November 2019, a $0.7 million licensing revenue recognized upon Knight's achievement of a development milestone pursuant to the Knight Agreement and a $1.4 million increase in manufacturing supply of tenapanor and other materials sold to KKC in accordance with the 2017 KKC Agreement, partially offset by $3.0 million revenue related to achievement of a milestone pursuant to the Fosun agreement during the year ended December 31, 2019.

Operating Expenses

Below is a summary of our operating expenses (dollars in thousands):

	Year Ended December 31,			Change 2021 vs. 2020		Change 2020 vs. 2019	
	2021	2020	2019	$	%	$	%
Cost of revenue	$ 1,000	$ 145	$ 600	$ 855	589.7 %	$ (455)	(75.8)%
Research and development	91,140	65,053	71,677	26,087	40.1 %	(6,624)	(9.2)%
General and administrative	72,303	33,153	24,267	39,150	118.1 %	8,886	36.6 %
Total operating expenses	$ 164,443	$ 98,351	$ 96,544	$ 66,092	67.2 %	$ 1,807	1.9 %

Cost of Revenue

Fiscal 2021 *compared to* 2020*:* The increase in cost of revenue was for payment due to AstraZeneca under the AZ Termination Agreement related to the development milestone we earned upon the initiation by KKC of phase 3 clinical studies in Japan to evaluate tenapanor for hyperphosphatemia.

Fiscal 2020 *compared to* 2019*:* Cost of revenue was $0.1 million for the year ended December 31, 2020, a decrease of $0.5 million, or 75.8%, compared to $0.6 million for the year ended December 31, 2019. Cost of revenue in both periods is the portion of tenapanor-related upfront and milestone payment from our collaboration partners that we are required to make to AstraZeneca under the AstraZeneca Termination Agreement.

Research and Development

Below is a summary of our research and development expenses (dollars in thousands):

	Year Ended December 31,			Change 2021 vs. 2020		Change 2020 vs. 2019	
	2021	2020	2019	$	%	$	%
External R&D expenses	$ 56,747	$ 37,624	$ 45,989	$ 19,123	50.8 %	$ (8,365)	(18.2)%
Employee-related expenses	27,268	20,911	19,466	6,357	30.4 %	1,445	7.4 %
Facilities, equipment and depreciation expenses	5,803	5,738	5,934	65	1.1 %	(196)	(3.3)%
Other	1,322	780	288	542	69.5 %	492	170.8 %
Total research and development expenses	$ 91,140	$ 65,053	$ 71,677	$ 26,087	40.1 %	$ (6,624)	(9.2)%

Fiscal 2021 *compared to* 2020*:* The increase in our external R&D expenses is the result of tenapanor manufacturing costs as well as clinical study costs from the advancement of our OPTIMIZE study which were partially offset by lower costs for the PHREEDOM clinical study. The increase in our employee-related expenses is related to compensation and benefits expenses for our research and development workforce. Employee-related expenses for twelve months ended December 31, 2021 include $2.7 million severance payments and other employee-related costs as discussed in *Note 11 - Restructuring* to the financial statements included elsewhere in this Annual Report.

Fiscal 2020 *compared to* 2019*:* The decrease in our external R&D expenses for the year ended December 31, 2020 primarily includes a $9.7 million decrease in our tenapanor-related expenses, partially offset by $3.0 million of higher expenses attributable to KKC Research Agreement-related research and general R&D expenses. Of the overall tenapanor-related decrease, approximately $11.0 million relates to lower clinical study costs due to the winding down of expenses associated with our Phase 3 clinical program for tenapanor for the control of hyperphosphatemia, offset by an out-of-period adjustment recorded during 2019 that reduced clinical trial expenses by $3.6 million related to our tenapanor clinical trials for the nine months ended September 30, 2019; and approximately $2.9 million related to lower manufacturing expenses due to reduced validation related expenses for tenapanor in 2020 as compared to 2019; offset by an increase of $3.1 million related to regulatory expenses that includes $2.9 million paid to the FDA for the filing of a NDA for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis in June 2020.

General and Administrative

Fiscal 2021 *compared to* 2020*:* The increase in general and administrative expenses was primarily due to increased costs associated with building and staffing our commercial infrastructure and teams as we prepared for a potential U.S. launch of tenapanor. The increase consisted of headcount and related personnel costs and an increase in external spending for disease awareness initiatives, commercial infrastructure and strategy. General and administrative expenses for the twelve months ended December 31, 2021 include $3.5 million severance payments and other employee-related costs as discussed in *Note 11 - Restructuring* to the financial statements included elsewhere in this Annual Report.

Fiscal 2020 *compared to* 2019*:* The increase in general and administrative expenses for the year ended December 31, 2020 was primarily due to an increase in costs associated with building and staffing our commercial infrastructure and teams as we prepare for the anticipated U.S. launch of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. The increase consisted of headcount and related personnel costs and an increase in external spending for disease awareness initiatives, commercial infrastructure and strategy.

Other Income, net

Below is a summary of our other income (expense), net (dollars in thousands):

	Year Ended December 31,			Change 2021 vs. 2020		Change 2020 vs. 2019	
	2021	2020	2019	$	%	$	%
Interest expense	$ (4,502)	$ (5,099)	$ (5,726)	$ 597	(11.7)%	$ 627	(11.0)%
Other income, net	687	1,568	2,352	(881)	(56.2)%	(784)	(33.3)%
Total other income, net	$ (3,815)	$ (3,531)	$ (3,374)	$ (284)	8.0 %	$ (157)	4.7 %

Fiscal 2021 *compared to* 2020*:* The decrease in interest expense was primarily due to lower interest rates on our variable-rate term loan. The changes in other income, net were primarily due to lower income earned on our investments, which was largely offset by the revaluation of our derivative liability related to our term loan agreement following receipt of the FDA CRL on July 28, 2021.

Fiscal 2020 *compared to* 2019*:* The decrease in interest expense for the year ended December 31, 2020 was primarily due to lower interest rates on our variable-rate term loan. The decrease in other income, net for the year ended December 31, 2020 was primarily due to a decrease in investment income, a lower exit fee revaluation adjustment related to our loan agreement and a decrease in currency exchange losses.

LIQUIDITY AND CAPITAL RESOURCES

Below is a summary of our cash, cash equivalents and marketable securities (in thousands):

	Year Ended December 31,		Change 2021 vs. 2020	
	2021	2020	$	%
Cash and cash equivalents	$ 72,428	$ 91,032	$ (18,604)	(20.4)%
Short-term investments	44,261	95,452	(51,191)	(53.6)%
Long-term investments	—	2,114	(2,114)	(100.0)%
Total liquid funds	$ 116,689	$ 188,598	$ (71,909)	(38.1)%

As of December 31, 2021, we had cash and investments of approximately $116.7 million. We have incurred operating losses since inception and our accumulated deficit as of December 31, 2021 is $712.9 million. Our current level of cash and investments alone is not sufficient to meet our plans for the next twelve months following the filing of these financial statements on February 28, 2022. These factors raise substantial doubt regarding our ability to continue as a going concern for a period of one year from the issuance of these financial statements. We plan to address our operating cash flow requirements with our current cash and investments, cash generated from the product launch of IBSRELA, our potential receipt of anticipated milestone payments from our collaboration partners, our ability to access the capital markets, as well as through the implementation of cash preservation activities to reduce or defer discretionary spending.

There are no assurances that our efforts to meet our operating cash flow requirements will be successful. If our current cash and investments as well as our plans to meet our operating cash flow requirements are not sufficient to fund necessary expenditures and meet our obligations for at least the next twelve months following the issuance of these financial statements, our liquidity, financial condition and business prospects will be materially affected. These financial statements have been prepared on a going concern basis and do not include any adjustments to the amounts and classification of assets and liabilities that may be necessary in the event that we can no longer continue as a going concern.

In July 2020, we filed a Form S-3 registration statement, which became effective in August 2020, containing (i) a base prospectus for the offering, issuance and sale by us of up to a maximum aggregate offering price of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units, from time to time in one or more offerings; and (ii) a prospectus supplement for the offering, issuance and sale by us of up to a maximum aggregate offering price of $100.0 million of its common stock that may be issued and sold, from time to time, under an Open Market Sales Agreement with Jefferies LLC, as sales agent, deemed to be “at the market offerings” (the "2020 Open Market Sales Agreement"). Pursuant to the 2020 Open Market Sales Agreement, Jefferies, as sales agent, received a commission of up to 3.0% of the gross sales price for shares

of common stock sold under the 2020 Open Market Sales Agreement. We sold a cumulative total of 23.3 million shares and received gross proceeds of $100.0 million at a weighted average sales price of approximately $4.30 per share under the 2020 Open Market Sales Agreement.

In August 2021, we filed an additional prospectus supplement under the Registration Statement for the offering, issuance and sale by us of up to a maximum aggregate offering price of $150.0 million of our common stock that may be issued and sold, from time to time, under an additional sales agreement we entered into with Jefferies (the "2021 Open Market Sales Agreement"), pursuant to which we may, from time to time, sell up to $150.0 million in shares of our common stock through Jefferies. We are not required to sell shares under the 2021 Open Market Sales Agreement. Pursuant to the 2021 Open Market Sales Agreement, Jefferies, as our sales agent, receives a commission of up to 3.0% of the gross sales price for shares of common stock sold under the 2021 Open Market Sales Agreement. As of December 31, 2021 we have sold 15.7 million shares and received gross proceeds of $25.0 million at a weighted average sales price of approximately $1.60 per share under the 2021 Open Market Sales Agreement.

On May 16, 2018, we entered into a loan and security agreement (the "2018 Loan Agreement") with Solar Capital Ltd. and Western Alliance Bank (“the Lenders”). The 2018 Loan Agreement provides for a $50.0 million term loan facility with a maturity date of November 1, 2022 (”the 2018 Term Loan”). The full amount of the 2018 Term Loan was funded on May 16, 2018. We received net proceeds from the loan of approximately $49.3 million, after deducting the closing fee, legal expenses and issuance costs. On October 9, 2020, we and the Lenders entered into an amendment to the 2018 Loan Agreement (“the 2020 Amendment”), as defined and discussed in *Note 6, Borrowing*, to extend the date through which we were permitted to make interest-only payments on the 2018 Term Loan by twelve months to December 1, 2021. In May and July 2021, we and the Lenders entered into additional amendments to the 2018 Loan Agreement (“the 2021 Amendments”) which together extended the period of time that we were permitted to make interest-only payments on the loan to December 1, 2021; provided that if we had not received FDA approval for our NDA for tenapanor for the control of serum phosphorus in adult patients with CDK on dialysis on or before October 25, 2021, the interest-only period would expire and principal repayments would be required to begin on November 1, 2021. If principal repayments were required to begin prior to December 1, 2021 under the 2021 Amendments, then the first such repayment was required to include all payments that would have been due if monthly principal repayment had begun on June 1, 2021. During November 2021, in compliance with the terms of our 2018 Loan Agreement, we paid the first principal repayment on the loan in the amount of $16.7 million. See *Note 6, Borrowings*, in the notes to our financial statements, included in Part II, Item 8, for details on our 2018 Loan Agreement.

As discussed in *Note 18 - Subsequent Events*, on February 23, 2022 (the “Closing Date”), we entered into a loan and security agreement (the “2022 Loan Agreement”) with SLR Investment Corp. as collateral agent (the “Agent”), and the lenders listed in the 2022 Loan Agreement (collectively the “2022 Lenders”). The 2022 Loan Agreement provides for a senior secured term loan facility, with $27.5 million (the “Term A Loan”) funded on the Closing Date and an additional $22.5 million that we may borrow on or prior to July 25, 2023; provided that (i) we have received approval by the FDA for our NDA for tenapanor for the control of serum phosphorus in chronic kidney disease patients on dialysis by December 31, 2022, and (ii) we have achieved certain product revenue milestone targets described in the 2022 Loan Agreement (the “Term B Loan”, and collectively, the Term A Loan and the Term B Loan, the “2022 Term Loan”). The Term A Loan funds are being used to repay the 2018 Term Loan with the Lenders as discussed in *Note 6 - Borrowings* and to fund our ongoing operations. We had $25.0 million principal from the 2018 Term Loan outstanding as of the Closing Date.

Our primary sources of cash have been from the sale and issuance of common stock (in both public offerings and private placements) and private placements of convertible preferred stock, funds from our collaboration partnerships and funds from our 2018 Loan Agreement. Our primary uses of cash have been to fund operating expenses, primarily research and development expenditures and pre-commercial expenses. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

Our future funding requirements are difficult to forecast and will depend on many factors, including:

- the extent to which we are able to generate product revenue from sales of IBSRELA;
- whether we are successful in our efforts under the FDR process to secure approval for our NDA for tenapanor for the Hyperphosphatemia Indication, or to reach resolution with the FDA regarding a path to address the deficiencies in the NDA noted in the CRL, and the time and cost associated with such path;
- the sales price and the availability of adequate third-party reimbursement for IBSRELA and XPHOZAH, if approved;
- the manufacturing costs of IBSRELA and XPHOZAH;

- the selling and marketing costs associated with IBSRELA and XPHOZAH, if approved;
- our ability to maintain our existing collaboration partnerships and to establish additional collaboration partnerships, in-license/out-license, joint ventures or other similar arrangements and the financial terms of such agreements;
- the timing, receipt, and amount of sales of, or royalties on, tenapanor, if any;
- the cash requirements of any future acquisitions or discovery of product candidates;
- any clinical trials we are required to or decide to pursue for tenapanor or RDX013;
- the time and cost necessary to respond to technological and market developments;
- the costs of filing, prosecuting, maintaining, defending and enforcing any patent claims and other intellectual property rights, including litigation costs and the outcome of such litigation, including costs of defending any claims of infringement brought by others in connection with the development, manufacture or commercialization of tenapanor or any of our product candidates; and
- the payment of interest and principal related to our loan and security agreement entered into with SLR Investment Corp. in February 2022.

CASH FLOW ACTIVITIES

The following table summarizes our cash flows for the periods indicated (in thousands):

	Year Ended December 31,			Change 2021 vs. 2020		Change 2020 vs. 2019	
	2021	2020	2019	$	%	$	%
Net cash used in operating activities	$ (152,551)	$ (81,435)	$ (76,484)	$ (71,116)	87.3 %	$ (4,951)	6.5 %
Net cash provided by (used in) investing activities	50,948	(31,442)	23,373	82,390	(262.0)%	(54,815)	(234.5)%
Net cash provided by financing activities	82,999	22,776	155,476	60,223	264.4 %	(132,700)	(85.4)%
Net (decrease) increase in cash and cash equivalents	$ (18,604)	$ (90,101)	$ 102,365	$ 71,497	(79.4)%	$ (192,466)	(188.0)%

Cash Flows from Operating Activities

Fiscal 2021 *compared to* 2020*:* Net cash used in operating activities during the year ended December 31, 2021 increased by $71.1 million as a result of our increased net loss for the period. The increased net loss was primarily driven by costs associated with building and staffing our commercial infrastructure and teams as we prepared for the anticipated U.S. launch of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis. In addition to the increased net loss, cash flows related to our operating assets and liabilities increased in the amount of $8.7 million.

Fiscal 2020 *compared to* 2019*:* Net cash used in operating activities during the year ended December 31, 2020 increased $5.0 million as compared to the prior year. The most significant factors that contributed to the increase was primarily a $6.2 million decrease to changes in operating assets and liabilities, primarily driven by cash received in 2019 and reported as deferred revenue for the KKC Research Agreement that was recognized as revenue in 2020, offset by a $0.6 million increase in non-cash charges and $0.6 million decrease to the net loss.

Cash Flows from Investing Activities

Fiscal 2021 *compared to* 2020*:* Net cash provided by investing activities increased by $82.4 million as our investment maturities increased to exceed the cost to purchase investments.

Fiscal 2020 *compared to* 2019*:* Net cash provided by investing activities decreased by $54.8 million during the year ended December 31, 2020, as compared to the year ended December 31, 2019. This decrease was attributable to a $48.2 million

increase in purchases of available-for-sale investments and a decrease in proceeds from maturities and redemptions of short-term investments of $6.6 million.

Cash Flows from Financing Activities

Fiscal 2021 *compared to* 2020*:* Net cash provided by financing activities increased by $60.2 million due to net proceeds from issuance of our common stock pursuant to our at-the-market offerings, which were partially offset by principal repayments for our loan payable.

Fiscal 2020 *compared to* 2019*:* Net cash provided by financing activities decreased by $132.7 million during the year ended December 31, 2020, as compared to the year ended December 31, 2019. This decrease was predominantly attributable to $134.9 million in net proceeds received in connection with underwritten public offering initiatives that was received in 2019 but did not recur in 2020. This decrease was partially offset by $2.4 million net additional proceeds received in 2020 as compared to 2019 from sales of our common stock pursuant to our at-the-market sales agreement with Jefferies LLC, employee stock plan purchases and option exercises, and the 2019 sale of common stock in the Private Placement with KKC.

SMALLER REPORTING COMPANY AND NON-ACCELERATED FILER STATUS

On June 28, 2018, the SEC adopted amendments that raise the thresholds in the smaller reporting company ("SRC") definition, whereby we were determined to qualify as an SRC. We elected to reflect that determination and avail ourselves with most of the SRC scaled disclosure accommodations in our filings subsequent to the adoption. On March 12, 2020, the SEC amended its rules to allow SRCs that have less than $100.0 million in annual revenue and a public float of less than $700.0 million to qualify as a non-accelerated filer. As a non-accelerated filer, we were not required to obtain an opinion of our independent auditors with respect to our internal controls over financial reporting for the periods through December 31, 2020.

On June 30, 2021, our public float exceeded $700.0 million and therefore, as of December 31, 2021, we no longer qualify as an SRC and are considered a large accelerated filer. The disclosures contained within this Annual Report on Form 10-K have been expanded accordingly.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Interest Rate Risk

We are subject to market risks, including interest rate fluctuation exposure through our investments, in the ordinary course of our business. However, the goals of our investment policy are the preservation of capital, fulfillment of liquidity needs and fiduciary control of cash. To achieve our goal of maximizing income without assuming significant market risk, we maintain our excess cash and cash equivalents in money market funds and short-term debt securities. Because of the short-term maturities of our cash equivalents, we do not believe that a decrease in interest rates would have any material negative impact on the fair value of our cash equivalents.

As of December 31, 2021, we had cash, cash equivalents and marketable securities of $116.7 million, which consist of bank deposits and money market funds, as well as high quality fixed income instruments including corporate bonds, commercial paper, and asset-backed securities collateralized by non-mortgage consumer receivables. The credit rating of our short-term investments must be rated A-1/P-1, or better by Standard and Poor’s and Moody’s Investors Service. Asset-backed securities must be rated AAA/Aaa. Money Market funds must be rated AAAm/Aaa. Such interest-earning instruments carry a degree of interest rate risk. However, because our investments are high quality and short-term in duration, we believe that our exposure to interest rate risk is not significant and that a 10% movement in market interest rates would not have a significant impact on the total value of our portfolio, as noted above. We do not enter into investments for trading or speculative purposes.

We are subject to interest rate fluctuation exposure through our borrowings under the 2018 Loan Agreement and our investment in money market accounts which bear a variable interest rate. Borrowings under the 2018 Loan Agreement bear interest at a rate equal to one-month London Interbank Offered Rate, or LIBOR, plus 7.45% per annum. A hypothetical increase in one-month LIBOR of 100 basis points above the current one-month LIBOR rates would have increased our interest expense by approximately $0.5 million for the year ended December 31, 2021. As of December 31, 2021 we had an aggregate principal amount of $32.3 million outstanding pursuant to our 2018 Loan Agreement.

Foreign Currency Exchange Risk

The majority of our transactions are denominated in U.S. dollars. However, we do have certain transactions that are denominated in currencies other than the U.S. dollar, primarily Swiss francs and the euro, and we therefore are subject to foreign exchange risk. The fluctuation in the value of the U.S. dollar against other currencies affects the reported amounts of expenses, assets and liabilities associated with a limited number of manufacturing activities.

We do not use derivative financial instruments for speculative trading purposes, nor do we hedge foreign currency exchange rate exposure in a manner that entirely offsets the earnings effects of changes in foreign currency exchange rates. The counterparties to our forward foreign currency exchange contracts are creditworthy commercial banks, which minimizes the risk of counterparty nonperformance.

As of December 31, 2021, we had no open forward foreign currency exchange contracts.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

ARDELYX, INC.
INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Ardelyx, Inc.

Opinion on the Financial Statements

We have audited the accompanying balance sheets of Ardelyx, Inc. (the "Company") as of December 31, 2021 and 2020, the related statements of operations and comprehensive loss, stockholders' equity, 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 "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of 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.

The Company's Ability to Continue as a Going Concern

The accompanying financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 2 to the financial statements, the Company has suffered recurring losses from operations and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 2. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

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 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 accounts or disclosures to which it relates.

Accounting for Restructuring activities

Description of the Matter

During 2021, the Company incurred $6.2 million of restructuring charges in connection with two restructuring plans that were implemented in August 2021 and October 2021, following the receipt of a Complete Response Letter from the FDA and the conclusion of an End of Review Type A meeting with the FDA, respectively. Of these charges, $2.7 million was recorded in research and development expenses, and $3.5 million was recorded in general and administrative expenses. Further, in November 2021, in connection with its announced plans to launch IBSRELA in 2022, the Company retained certain employees whose positions were originally eliminated as part of the October 2021 restructuring plan. As described in Note 11 to the financial statements, the restructuring activities consisted primarily of workforce reduction through the elimination of the Company's research organization and its commercial sales and marketing organizations. These actions resulted in restructuring charges that included one-time employee termination benefits and severance payments, as well as other employee-related costs. The Company's liability for accrued restructuring charges was $0.5 million as of December 31, 2021.

Auditing the Company's restructuring charges was especially challenging due to the multiple restructuring plans implemented during the year, various one-time termination benefit arrangements approved for different ranks and groups of the impacted employees and various retention plans approved for the remaining employees, as well as the impact of the Company's later decision to retain certain employees whose positions were originally eliminated as part of the October 2021 restructuring plan. This required the Company to maintain complete record-keeping of the multiple restructuring plans implemented, assess and evaluate the differences between the various severance agreements and retention plans executed, as well as to apply applicable technical accounting guidance in determining the timing of recognition, classification, and disclosure of restructuring charges in the financial statements. In addition, the Company needed to analyze and ensure completeness of any contract termination costs to be recorded as a result of the restructuring activities and changing needs of its business.

How We Addressed the Matter in Our Audit

To test the restructuring charges and year-end liability for accrued restructuring charges, our audit procedures included, among others, gaining an understanding of the approved restructuring plans and evaluating the accounting treatment, timing of recognition, and classification of restructuring charges incurred. In addition, we tested the accuracy and completeness of underlying data used in management's analysis and computation of restructuring charges and year-end liability for accrued restructuring charges by agreeing related details to supporting documentation. We reviewed management's analysis of contract termination costs to determine whether any amount needed to be recorded or accrued as restructuring charges during the year. We also met with internal finance and legal personnel to understand the nature and the comprehensive scope of the approved restructuring plans, as well as inspected and evaluated the accounting treatment of the terms and conditions for a sample of severance agreements and retention plans executed. Additionally, we tested subsequent cash payments made related to the restructuring activities. Further, we tested the classification and disclosure of the restructuring expenses in the financial statements.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2009.

Redwood City, California
February 28, 2022

ARDELYX, INC.
BALANCE SHEETS
(in thousands, except share and per share amounts)

	December 31,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	$ 72,428	$ 91,032
Short-term investments	44,261	95,452
Accounts receivable	502	—
Prepaid expenses and other current assets	16,458	8,202
Total current assets	133,649	194,686
Property and equipment, net	2,362	1,936
Long-term investments	—	2,114
Right-of-use assets	12,752	2,274
Other assets	1,150	552
Total assets	$ 149,913	$ 201,562
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,277	$ 5,626
Accrued compensation and benefits	5,422	5,672
Current portion of operating lease liability	3,492	2,117
Loan payable, current portion	32,264	4,167
Deferred revenue	—	4,177
Accrued expenses and other current liabilities	7,366	6,657
Total current liabilities	52,821	28,416
Operating lease liability, net of current portion	9,748	413
Loan payable, net of current portion	—	46,621
Deferred revenue, non-current	4,727	—
Total liabilities	67,296	75,450
Commitments and contingencies (Note 17)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized; no shares issued and outstanding as of December 31, 2021 and December 31, 2020, respectively.	—	—
Common stock, $0.0001 par value; 300,000,000 shares authorized; 130,182,535 and 93,599,975 shares issued and outstanding as of December 31, 2021 and December 31, 2020, respectively.	13	9
Additional paid-in capital	795,540	680,872
Accumulated deficit	(712,930)	(554,765)
Accumulated other comprehensive income (loss)	(6)	(4)
Total stockholders' equity	82,617	126,112
Total liabilities and stockholders' equity	$ 149,913	$ 201,562

The accompanying notes are an integral part of these financial statements.

ARDELYX, INC.
STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share amounts)

	Year Ended December 31,		
	2021	2020	2019
Revenues:			
Collaborative development revenue	$ 4,177	$ 5,364	$ 459
Product supply revenue	907	1,501	322
Licensing revenue	5,013	706	4,500
Total revenues	10,097	7,571	5,281
Operating expenses:			
Cost of revenue	1,000	145	600
Research and development	91,140	65,053	71,677
General and administrative	72,303	33,153	24,267
Total operating expenses	164,443	98,351	96,544
Loss from operations	(154,346)	(90,780)	(91,263)
Interest expense	(4,502)	(5,099)	(5,726)
Other income, net	687	1,568	2,352
Loss before provision for income taxes	(158,161)	(94,311)	(94,637)
Provision for income taxes	4	2	303
Net loss	$ (158,165)	$ (94,313)	$ (94,940)
Net loss per common share, basic and diluted	$ (1.52)	$ (1.05)	$ (1.47)
Shares used in computing net loss per share - basic and diluted	104,205,645	89,582,138	64,478,066
Comprehensive loss:			
Net loss	$ (158,165)	$ (94,313)	$ (94,940)
Unrealized (losses) gains on available-for-sale securities	(2)	(24)	58
Comprehensive loss	$ (158,167)	$ (94,337)	$ (94,882)

The accompanying notes are an integral part of these financial statements.

ARDELYX, INC.
STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands, except share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive (Loss) Income	Total Stockholders' Equity
	Shares	Amount				
Balance as of December 31, 2018	62,516,627	$ 6	$ 481,357	$ (365,512)	$ (38)	$ 115,813
Issuance of common stock under employee stock purchase plan	160,744	—	396	—	—	396
Issuance of common stock for services	113,136	—	312	—	—	312
Issuance of common stock upon exercise of options	68,062	—	178	—	—	178
Issuance of common stock upon vesting of restricted stock units	85,609	—	—	—	—	—
Stock-based compensation	—	—	9,936	—	—	9,936
Unrealized gains on available-for-sale securities	—	—	—	—	58	58
Issuance of common stock upon underwritten public offering, net of issuance costs	23,000,000	3	134,924	—	—	134,927
Issuance of common stock upon private placement, net of issuance costs	2,873,563	—	19,975	—	—	19,975
Net loss	—	—	—	(94,940)	—	(94,940)
Balance as of December 31, 2019	88,817,741	$ 9	$ 647,078	$ (460,452)	$ 20	$ 186,655
Issuance of common stock under employee stock purchase plan	169,931	—	834	—	—	834
Issuance of common stock for services	42,403	—	310	—	—	310
Issuance of common stock upon exercise of options	445,942	—	1,020	—	—	1,020
Issuance of common stock upon vesting of restricted stock units	866,528	—	—	—	—	—
Stock-based compensation	—	—	10,583	—	—	10,583
Unrealized gains on available-for-sale securities	—	—	—	—	(24)	(24)
Issuance of common stock in At-the-market offering	3,257,430	—	21,047	—	—	21,047
Net loss	—	—	—	(94,313)	—	(94,313)
Balance as of December 31, 2020	93,599,975	$ 9	$ 680,872	$ (554,765)	$ (4)	$ 126,112
Issuance of common stock under employee stock purchase plan	386,664	—	819	— 0	—	819
Issuance of common stock for services	25,989	—	190	—	—	190
Issuance of common stock upon exercise of options	331,310	—	584	—	—	584
Issuance of common stock upon vesting of restricted stock units	167,158	—	—	—	—	—
Taxes paid for net share settlement of equity awards	—	—	(106)	—	—	(106)
Stock-based compensation	—	—	12,039	—	—	12,039
Unrealized gains on available-for-sale securities	—	—	—	—	(2)	(2)
Issuance of common stock in At-the-market offering	35,671,439	4	101,142	—	—	101,146
Net loss	—	—	—	(158,165)	—	(158,165)
Balance as of December 31, 2021	130,182,535	$ 13	$ 795,540	$ (712,930)	$ (6)	$ 82,617

The accompanying notes are an integral part of these financial statements.

ARDELYX, INC.
STATEMENTS OF CASH FLOWS
(in thousands)

	2021	2020	2019
Operating activities			
Net loss	$ (158,165)	$ (94,313)	$ (94,940)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation expense	1,441	1,824	2,501
Amortization of deferred financing costs	638	496	670
Amortization of deferred compensation for services	240	313	309
Amortization of (discount) premium on investment securities	488	(92)	(698)
Non-cash lease expense	3,085	2,147	1,839
Stock-based compensation	12,039	10,583	9,936
Change in derivative liabilities	(678)	407	436
Non-cash interest associated with debt discount accretion	283	413	478
Changes in operating assets and liabilities:			
Unbilled revenue	—	750	4,250
Accounts receivable	(502)	—	85
Prepaid expenses and other assets	(8,904)	(4,653)	93
Accounts payable	(1,349)	3,439	39
Accrued compensation and benefits	(250)	1,219	1,730
Operating Lease liabilities	(2,853)	(2,604)	(1,892)
Accrued and other liabilities	1,386	(1,000)	(5,861)
Deferred revenue	550	(364)	4,541
Net cash used in operating activities	(152,551)	(81,435)	(76,484)
Investing activities			
Proceeds from maturities and redemptions of investments	125,550	119,734	126,369
Purchases of investments	(72,735)	(150,852)	(102,671)
Purchases of property and equipment	(1,867)	(324)	(325)
Net cash provided by (used in) investing activities	50,948	(31,442)	23,373
Financing activities			
Proceeds from underwritten public offering, net of issuance costs	—	—	134,927
Proceeds from issuance of common stock upon private placement, net of issuance costs	—	—	19,975
Proceeds from issuance of common stock in At-the-market offering, net of issuance costs	101,146	21,047	—
Proceeds from issuance of common stock under equity incentive and stock purchase plans	1,403	1,854	574
Principal repayments for loan payable	(19,444)	—	—
Payments for loan payable, net of issuance costs	—	(125)	—
Payments for taxes related to net share settlement of equity awards	(106)	—	—
Net cash provided by financing activities	82,999	22,776	155,476
Net (decrease) increase in cash and cash equivalents	(18,604)	(90,101)	102,365
Cash and cash equivalents at beginning of period	91,032	181,133	78,768
Cash and cash equivalents at end of period	$ 72,428	$ 91,032	$ 181,133
Supplementary disclosure of cash flow information:			
Cash paid for interest	$ 3,469	$ 4,200	$ 4,920
Cash paid for income taxes	$ 4	$ 1	$ 2
Supplementary disclosure of non-cash activities:			
Right-of-use assets obtained in exchange for lease obligations	$ 1,604	$ 450	$ 5,810
Issuance of common stock for services	$ 190	$ 310	$ 312

The accompanying notes are an integral part of these financial statements.

ARDELYX, INC.
NOTES TO FINANCIAL STATEMENTS

1. ORGANIZATION AND BASIS OF PRESENTATION

Ardelyx, Inc. (the "Company," "we," "us" or "our") is a biopharmaceutical company founded with a mission to discover, develop and commercialize innovative first-in-class medicines that meet significant unmet medical needs. This includes adult patients with irritable bowel syndrome with constipation ("IBS-C"), adult patients with chronic kidney disease ("CKD") on dialysis suffering from elevated serum phosphorus, or hyperphosphatemia; and adult CKD patients and/or heart failure patients with elevated serum potassium, or hyperkalemia.

We operate in one business segment, which is the development and planned commercialization of biopharmaceutical products.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP").

Prior Period Errors

In connection with our review of our financial statements as of and for the six months ended June 30, 2019, we corrected errors related to the accounting for clinical trial accruals that had resulted in an overstatement of research and development expenses during the year ended December 31, 2018. Specifically, management concluded that our research and development expenses recorded during the year ended December 31, 2018 had been overstated by $3.6 million and that our accrued expenses and other current liabilities as of December 31, 2018 had been overstated by the same amount. We analyzed the potential impact of these errors in accordance with the U.S. Securities and Exchange Commission's ("SEC") Staff Accounting Bulletin No. 108, Considering the Effects of Prior Year Misstatements when Quantifying Misstatements in Current Year Financial Statements, and concluded that while the errors were significant to our financial statements as of and for the six months ended June 30, 2019, a correction of the errors would not have been material to the full year results for 2019 and 2018 nor affect the trend of financial results. Accordingly, we reduced accrued and other liabilities by $3.6 million and recorded a cumulative adjustment of $3.6 million in the statement of operations and comprehensive loss to reduce research and development expenses in 2019.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and judgments that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, management evaluates its estimates, including those related to recognition of revenue, clinical trial accruals, contract manufacturing accruals, fair value of assets and liabilities, income taxes and stock-based compensation. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances. Actual results could materially differ from those estimates.

Liquidity

As of December 31, 2021, we had cash and investments of approximately $116.7 million. We have incurred operating losses since inception and our accumulated deficit as of December 31, 2021 is $712.9 million. Our current level of cash and investments alone is not sufficient to meet our plans for the next twelve months following the issuance of these financial statements. These factors raise substantial doubt regarding our ability to continue as a going concern for a period of one year from the issuance of these financial statements. We plan to address our operating cash flow requirements with our current cash and investments, cash generated from the product launch of IBSRELA, our potential receipt of anticipated milestones from our collaboration partners, our ability to access the capital markets, as well as through the implementation of cash preservation activities to reduce or defer discretionary spending.

There are no assurances that our efforts to meet our operating cash flow requirements will be successful. If our current cash and investments as well as our plans to meet our operating cash flow requirements are not sufficient to fund necessary expenditures and meet our obligations for at least the next twelve months following the issuance of these financial statements,

our liquidity, financial condition and business prospects will be materially affected. These financial statements have been prepared on a going concern basis and do not include any adjustments to the amounts and classification of assets and liabilities that may be necessary in the event that we can no longer continue as a going concern.

Cash and Cash Equivalents

We consider all highly liquid investments purchased with an original maturity date of 90 days or less on the date of purchase to be cash equivalents.

Short-Term Investments

Short-term investments consist of debt securities classified as available-for-sale and have maturities greater than 90 days, but less than one year, from the date of acquisition. Short-term investments are carried at fair value based upon quoted market prices. Unrealized gains and losses on available-for-sale securities are included in earnings and are reported as an allowance for credit losses on our Balance Sheets. The cost of available-for-sale securities sold is based on the specific-identification method.

Concentration of Credit Risk

Financial instruments that potentially subject us to significant concentrations of credit risk consist primarily of cash, cash equivalents, short-term investments and accounts receivable. We are exposed to credit risks in the event of default by the counterparties to the extent of the amount recorded in its balance sheet. Cash, cash equivalents and short-term investments are invested through banks and other financial institutions in the U.S.

Foreign Currency

We manage our foreign currency exposures with the use of foreign currency purchases. We primarily conduct business in U.S. dollars; however, a portion of our expense and capital activities are transacted in foreign currencies which are subject to exchange rate fluctuations that can affect cash or earnings. We have been in a loss position and therefore our primary objective is to conserve and manage cash. There are generally two methods by which we may manage the cash flow risk of foreign exchange fluctuations when a contract is signed (i) we can purchase the foreign funds, in full or in part, upon the execution of the contract, or (ii) we can obtain the right to purchase such funds, in full or in part, at the execution of the contract, i.e., obtain a forward contract from an appropriate bank, that can be exercised to obtain the currency of interest at a particular point in time. The derivative instruments that we may use to hedge the exposure shall generally not be designated as cash flow hedges, and as a result, changes in their fair value would be recorded in other income (expense), net, in our statements of operations and comprehensive loss. The fair values of forward foreign currency exchange contracts would be estimated using current exchange rates and interest rates and the current creditworthiness of the counterparties is taken into consideration.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation is computed using the straight-line method over the estimated useful lives of the respective assets, with ranges generally from three to five years. Leasehold improvements are amortized over the lesser of the estimated useful lives or the related remaining lease term.

Impairment of Long-Lived Assets

The carrying value of long-lived assets, including property and equipment, are reviewed for impairment whenever events or changes in circumstances indicate that the asset may not be recoverable. An impairment loss is recognized when the total of estimated future undiscounted cash flows, expected to result from the use of the asset and its eventual disposition, are less than the asset’s carrying amount. Impairment, if any, would be assessed using discounted cash flows or other appropriate measures of fair value. For the years ending December 31, 2021, 2020 and 2019 we have recognized no impairment losses.

Income Taxes

We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized.

Revenue Recognition

On January 1, 2018 we adopted the Financial Accounting Standards Board's ("FASB") Accounting Standards Update ("ASU") No. 2014-9, *Revenue from Contracts with Customers (Topic 606) and related amendments* ("ASC 606"), on a modified retrospective basis, which resulted in an adjustment to the opening accumulated deficit balance on the adoption date. As a result of the adoption of the new standard, on January 1, 2018, we recorded the following: (i) unbilled revenue under current assets of $5.0 million representing a future receivable related to the first milestone under our license agreement with Kyowa Kirin Co., Ltd. (formerly known as Kyowa Hakko Kirin Co., Ltd ("KHK") ("KKC"), which was subsequently achieved by KKC and collected in February 2019, thereby reducing the unbilled revenue balance to zero, (ii) uncharged license fees under current liabilities of $1.0 million representing the corresponding future payable related to AstraZeneca AB ("AstraZeneca") in accordance with our termination agreement with AstraZeneca, which, upon KKC achieving the milestone, was reclassified to accounts payable and subsequently paid to AstraZeneca during the second quarter of 2019, and (iii) a related decrease in accumulated deficit of approximately $4.0 million as the new standard permitted revenue from milestones that possess certain criteria to be recognized earlier and also contained different recognition criteria related to milestones than under the previous accounting standard.

We generate revenue primarily from research and collaboration and license agreements with customers. Goods and services in the agreements may include the grant of licenses for the use of our technology, the provision of services associated with the research and development of product candidates, manufacturing services, and participation in joint steering committees. The terms of these arrangements typically include payment to us of one or more of the following: non-refundable, up-front license fees; research, development, regulatory and commercial milestone payments; reimbursement of research and development services; option payments; reimbursement of certain costs; payments for manufacturing supply services; and future royalties on net sales of licensed products.

When two or more contracts are entered into with the same customer at or near the same time, we evaluate the contracts to determine whether the contracts should be accounted for as a single arrangement. Contracts are combined and accounted for as a single arrangement if one or more of the following criteria are met: (i) the contracts are negotiated as a package with a single commercial objective; (ii) the amount of consideration to be paid in one contract depends on the price or performance of the other contract; or (iii) the goods or services promised in the contracts (or some goods or services promised in each of the contracts) are a single performance obligation.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under each of its agreements, management performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraints on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. As part of the accounting for contracts with customers, we develop assumptions that require judgment to determine whether promised goods and services represent distinct performance obligations and the standalone selling price for each performance obligation identified in the contract. This evaluation is subjective and requires us to make judgments about the promised goods and services and whether those goods and services are separable from other aspects of the contract. Further, determining the standalone selling price for performance obligations requires significant judgment, and when an observable price of a promised good or service is not readily available, we consider relevant assumptions to estimate the standalone selling price, including, as applicable, market conditions, development timelines, probabilities of technical and regulatory success, reimbursement rates for personnel costs, forecasted revenues, potential limitations to the selling price of the product and discount rates.

We apply judgment in determining whether a combined performance obligation is satisfied at a point in time or over time, and, if over time, concluding upon the appropriate method of measuring progress to be applied for purposes of recognizing revenue. We evaluate the measure of progress each reporting period and, as estimates related to the measure of progress change, related revenue recognition is adjusted accordingly. Changes in our estimated measure of progress are accounted for prospectively as a change in accounting estimate. We recognize collaboration revenue by measuring the progress toward complete satisfaction of the performance obligation using an input measure. In order to recognize revenue over the research and development period, we measure actual costs incurred to date compared to the overall total expected costs to satisfy the performance obligation. Revenues are recognized as the program costs are incurred. We will re-evaluate the estimate of expected costs to satisfy the performance obligation each reporting period and make adjustments for any significant changes.

Amounts received prior to satisfying the revenue recognition criteria are recorded as contract liabilities in our Balance Sheets. If the related performance obligation is expected to be satisfied within the next twelve months it will be classified in current liabilities. Amounts recognized as revenue prior to receipt are recorded as contract assets in our Balance Sheets. If we

expect to have an unconditional right to receive the consideration in the next twelve months, it will be classified in current assets. A net contract asset or liability is presented for each contract with a customer.

Milestone Payments: At the inception of each arrangement that includes development milestone payments, we evaluate whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Milestone payments that are not within our control or the control of the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraints, 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 earnings in the period of adjustment.

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 as 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 payments are recorded in product supply revenue when the customer obtains control of the goods, which is upon delivery.

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 (i) when the related sales occur, or (ii) 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.

Licenses of intellectual property: If a license granted to a customer to use our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue from consideration allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we apply 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, to conclude upon the appropriate method of measuring progress for purposes of recognizing revenue related to consideration allocated to the performance obligation.

Options: Customer options, such as options granted to allow a licensee to choose to research, develop and commercialize licensed compounds are evaluated at contract inception in order to determine whether those options provide a material right (i.e., an optional good or service offered for free or at a discount) to the customer. If the customer options represent a material right, the material right is treated as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the standalone selling price, and revenue is recognized when or as the future goods or services are transferred or when the option expires. Customer options that are not material rights do not give rise to a separate performance obligation, and as such, the additional consideration that would result from a customer exercising an option in the future is not included in the transaction price for the current contract. Instead, the option is deemed a marketing offer, and additional option fee payments are recognized or being recognized as revenue when the licensee exercises the option. The exercise of an option that does not represent a material right is treated as a separate contract for accounting purposes.

Contract modifications: Contract modifications, defined as changes in the scope or price (or both) of a contract that are approved by the parties to the contract, such as a contract amendment, exist when the parties to a contract approve a modification that either creates new or changes existing enforceable rights and obligations of the parties to the contract. Depending on facts and circumstances, we account for a contract modification as one of the following: (i) a separate contract; (ii) a termination of the existing contract and a creation of a new contract; or (iii) a combination of the preceding treatments. A contract modification is accounted for as a separate contract if the scope of the contract increases because of the addition of promised goods or services that are distinct and the price of the contract increases by an amount of consideration that reflects our standalone selling prices of the additional promised goods or services. When a contract modification is not considered a separate contract and the remaining goods or services are distinct from the goods or services transferred on or before the date of the contract modification, we account for the contract modification as a termination of the existing contract and a creation of a new contract. When a contract modification is not considered a separate contract and the remaining goods or services are not distinct, we account for the contract modification as an add-on to the existing contract and as an adjustment to revenue on a cumulative catch-up basis.

We receive payments from its licensees as established in each contract. Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Where applicable, amounts are recorded as accounts receivable or unbilled revenue when our right to consideration is unconditional. We do not assess whether a contract with a customer has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

Research and Development Costs

Research and development costs are charged to expense as incurred and consisted of costs incurred to further our research and development activities and include salaries and related employee benefits, costs associated with clinical trials, costs related to pre-commercialization manufacturing activities such as manufacturing process validation activities and the manufacturing of clinical drug supply, nonclinical research and development activities, regulatory activities, research-related overhead expenses and fees paid to external service providers and contract research and manufacturing organizations that conduct certain research and development activities on our behalf.

Accrued Research and Development Expenses

We are required to estimate our accrued expenses at the end of each reporting period. This process involves reviewing open contracts and purchase orders, communicating with our 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 the actual costs. The majority of our service providers submit invoices in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in the financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with our service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- contract research organizations ("CROs") in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors related to product manufacturing, development and distribution of clinical supplies; and
- vendors in connection with preclinical development activities.

We record expenses related to clinical studies and manufacturing development activities based on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs and manufacturing vendors that conduct and manage these activities on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract, and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed, enrollment of subjects, number of sites activated and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we will adjust the accrued or prepaid expense balance accordingly.

Inventory

We consider regulatory approval of product candidates to be uncertain, and product manufactured prior to regulatory approval may not be sold unless regulatory approval is obtained. We expense manufacturing costs for product candidates incurred prior to regulatory approval as research and development expenses as manufacturing processes are performed. If and when regulatory approval of a product is obtained and we have plans to commercially launch the approved product, we begin capitalizing manufacturing costs related to the approved product into inventory. Although we received approval of IBSRELA (tenapanor) for the treatment of IBS-C in adults from the Food and Drug Administration (“FDA”) in September 2019, we did not plan to launch IBSRELA commercially at that time and, therefore, continued to expense manufacturing costs of tenapanor, which is also under development for another indication that has not received FDA approval. On November 30, 2021, we made the decision and announced our plans to commercially launch IBSRELA and as a result, in December 2021 we began to capitalize the costs of manufacturing processes associated with IBSRELA as those processes are completed. No manufacturing processes related to IBSRELA were completed in December, resulting in no inventory balance at December 31, 2021.

Stock-Based Compensation

We recognize compensation expense for all stock-based payment awards made to employees, nonemployees and directors based on estimated fair values. For employee and nonemployee stock options, we determine the grant date fair value of the awards using the Black-Scholes option-pricing model and generally recognizes the fair value as stock-based compensation expense on a straight-line basis over the vesting period of the respective awards. For restricted stock and performance-based restricted stock, to the extent they are probable, the compensation cost for these awards is based on the closing price of our common stock on the date of grant and recognized as compensation expense on a straight-line basis over the requisite service period. Stock-based compensation expense is based on the value of the portion of stock-based payment awards that is ultimately expected to vest. As such, our stock-based compensation is reduced for the estimated forfeitures at the date of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates.

Derivatives and Hedging Activities

We account for our derivative instruments as either assets or liabilities on the balance sheet and measure them at fair value. Derivatives are adjusted to fair value through other income (expense), net in the statements of operations and comprehensive loss.

Leases

We determine if an arrangement is a lease at the inception of the arrangement. Operating leases are included in right-of-use assets, current portion of operating lease liability, and operating lease liability, net of current portion in our balance sheets. Right-of-use assets represent 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. Operating lease right-of-use assets and liabilities are recognized at the lease commencement date based on the present value of lease payments over the lease term. In determining the present value of lease payments, we use our incremental borrowing rate based on the information available at the lease commencement date. The operating lease right-of-use assets also include any lease payments made and exclude lease incentives. Our lease terms may include options to extend or terminate the lease when it is reasonably certain that we will exercise any such options. Lease expense is recognized on a straight-line basis over the expected lease term. We have elected not to separate lease and non-lease components, such as common area maintenance charges, and instead it accounts for these as a single lease component.

Restructuring

We recognize restructuring charges related to reorganization plans that have been committed to by management when liabilities have been incurred. In connection with these activities, we record restructuring charges at fair value for, (a) contractual employee termination benefits when obligations are associated to services already rendered, rights to such benefits have vested, and payment of benefits is probable and can be reasonably estimated, (b) one-time employee termination benefits when management has committed to a plan of termination, the plan identifies the employees and their expected termination dates, the details of termination benefits are complete, it is unlikely changes to the plan will be made or the plan will be withdrawn and communication to such employees has occurred, and (c) contract termination costs when a contract is terminated before the end of its term.

One-time employee termination benefits are recognized in their entirety when communication has occurred and future services are not required. If future services are required, the costs are recorded ratably over the remaining period of service. Contract termination costs to be incurred over the remaining contract term without economic benefit are recorded in their entirety when the contract is canceled.

Net Loss per Share

Basic net loss per common share is calculated by dividing the net loss by the weighted-average number of common shares outstanding during the period, without consideration of potential common shares. Diluted net loss per common share in the periods presented is the same as basic net loss per common share, since the effects of potentially dilutive securities are antidilutive due to the net loss for all periods presented.

Recent Accounting Pronouncements

New Accounting Pronouncements - Recently Adopted

In December 2019, as part of its initiative to reduce complexity in the accounting standards, the Financial Accounting Standards Board (“FASB”) issued Accounting Standards Update (“ASU”) 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* (“ASU 2019-12”), which eliminates certain exceptions related to the approach for intra-period tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also clarifies and simplifies other aspects of the accounting for income taxes. The standard is effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020, with early adoption permitted. We early adopted ASU 2019-12 on April 1, 2020 and this adoption had no material impact on our financial position or results of operations.

We adopted Accounting Standards Update 2016-13, *Financial Instruments - Credit Losses: Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"), as of December 1, 2021 under the modified retrospective approach. ASU 2016-13 requires an entity to measure and recognize expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities with unrealized credit losses, the standard requires allowances to be recorded through net income instead of directly reducing the amortized cost of the investment under the previous other-than-temporary impairment model. The adoption of this standard did not have a material impact on our financial statements or a significant impact on our internal controls.

Recent Accounting Pronouncements Not Yet Adopted

There were various accounting standards and interpretations issued recently, none of which are expected to a have a material impact on our financial position, operations or cash flows.

3. CASH AND INVESTMENTS

Securities classified as cash and investments as of December 31, 2021 and 2020 are summarized below (in thousands). Estimated fair value is based on quoted market prices for these investments.

	December 31, 2021			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Fair Value
Cash and cash equivalents:				
Money market funds	$ 71,175	$ —	$ —	$ 71,175
Cash	1,253	—	—	1,253
Total cash and cash equivalents	72,428	—	—	72,428
Short-term investments:				
Commercial paper	$ 31,936	$ 1	$ (2)	$ 31,935
Corporate bonds	7,025	—	(3)	7,022
Asset-backed securities	5,306	—	(2)	5,304
U.S. treasury notes	—	—	—	—
Total short-term investments	44,267	1	(7)	44,261
Total cash equivalents and investments	$ 116,695	$ 1	$ (7)	$ 116,689

	December 31, 2020			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Fair Value
Cash and cash equivalents:				
Money market funds	$ 88,151	$ —	$ —	$ 88,151
Commercial paper	2,100	—	—	2,100
Cash	781	—	—	781
Total cash and cash equivalents	91,032	—	—	91,032
Short-term investments				
Commercial paper	$ 60,631	$ 2	$ (4)	$ 60,629
Corporate bonds	24,547	3	(6)	24,544
U.S. government-sponsored agency bonds	9,277	2	—	9,279
U.S. treasury notes	1,000	—	—	1,000
Total short-term investments	95,455	7	(10)	95,452
Long-term investments:				
Corporate bonds	$ 2,115	$ —	$ (1)	$ 2,114
Total cash equivalents and investments	$ 188,602	$ 7	$ (11)	$ 188,598

Cash equivalents consist of money market funds and other debt securities with original maturities of three months or less at the time of purchase, and the carrying amount is a reasonable approximation of fair value. We invest our cash in high quality securities of financial and commercial institutions. These securities are carried at fair value, which is based on readily available market information, with unrealized gains and losses included in accumulated other comprehensive income (loss) within stockholders' equity on ours balance sheets. We use the specific identification method to determine the amount of realized gains or losses on sales of marketable securities. Realized gains or losses have been insignificant and are included in other income (expense), net, in the statement of operations.

All short-term available-for-sale securities held as of December 31, 2021 and 2020, had contractual maturities of less than one year. The long-term securities held as of December 31, 2020 had contractual maturities greater than one year. Our available-for-sale securities are subject to a periodic impairment review. We consider a debt security to be impaired when its fair value is less than its carrying cost, in which case we would further review the investment to determine whether it is other-than-temporarily impaired. When we evaluate an investment for other-than-temporary impairment, we review factors such as the length of time and extent to which fair value has been below cost basis, the financial condition of the issuer and any changes thereto, intent to sell, and whether it is more likely than not we will be required to sell the investment before the recovery of its cost basis. If an investment is other-than-temporarily impaired, we write it down through the statement of operations to its fair value and establishes that value as a new cost basis for the investment. We did not identify any of its available-for-sale securities as other-than-temporarily impaired in any of the periods presented. As of December 31, 2021 and 2020, no investment was in a continuous unrealized loss position for more than one year and we believe that it is more likely than not that the investments will be held until maturity or a forecasted recovery of fair value.

As of December 31, 2021, the amortized cost and estimated fair value of available-for-sale debt securities by contractual maturity were as follows (in thousands):

	Amortized Cost	Fair Value
Due in one year or less	$ 44,267	$ 44,261

4. FAIR VALUE MEASUREMENTS

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs.

The three-level hierarchy for the inputs to valuation techniques is briefly summarized as follows:

Level 1 – Valuations are based on quoted prices in active markets for identical assets or liabilities and readily accessible by the Company at the reporting date. Examples of assets and liabilities utilizing Level 1 inputs are certain money market funds, U.S. treasuries and trading securities with quoted prices on active markets.

Level 2 – Valuations based on inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities. Examples of assets and liabilities utilizing Level 2 inputs are corporate bonds, commercial paper, certificates of deposit and over-the-counter derivatives.

Level 3 – Valuations based on unobservable inputs in which there is little or no market data, which require the Company to develop its own assumptions.

The following table sets forth the fair value of our financial assets and liabilities measured on a recurring basis by level within the fair value hierarchy (in thousands):

	December 31, 2021			
	Total Fair Value	Level 1	Level 2	Level 3
Assets:				
Money market funds	$ 71,175	$ 71,175	$ —	$ —
Commercial paper	31,935	—	31,935	—
Corporate bonds	7,022	—	7,022	—
Asset-backed securities	5,304	—	5,304	—
Total	$ 115,436	$ 71,175	$ 44,261	$ —
Liabilities:				
Derivative liability for exit fee	$ 698	$ —	$ —	$ 698
Total	$ 698	$ —	$ —	$ 698

	December 31, 2020			
	Total Fair Value	Level 1	Level 2	Level 3
Assets:				
Money market funds	$ 88,151	$ 88,151	$ —	$ —
Commercial paper	62,729	—	62,729	—
Corporate bonds	26,658	—	26,658	—
U.S. government-sponsored agency bonds	9,279	—	9,279	—
U.S. treasury notes	1,000	—	1,000	—
Total	$ 187,817	$ 88,151	$ 99,666	$ —
Liabilities:				
Derivative liability for exit fee	$ 1,376	$ —	$ —	$ 1,376
Total	$ 1,376	$ —	$ —	$ 1,376

Where quoted prices are available in an active market, securities are classified as Level 1. We classify money market funds, U.S. treasury securities and U.S. treasury notes as Level 1. When quoted market prices are not available for the specific security, we estimate fair value by using benchmark yields, reported trades, broker/dealer quotes and issuer spreads. We classify corporate bonds, commercial paper, asset-backed securities and foreign currency derivative contracts as Level 2. In certain cases, where there is limited activity or less transparency around inputs to valuation, securities or derivative liabilities such as the 2018 Exit Fee, as defined and discussed in *Note 7 - Derivative Liability*, are classified as Level 3.

The carrying amounts reflected in the balance sheets for cash equivalents, short-term investments, accounts receivable, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair values at both December 31, 2021 and December 31, 2020, due to their short-term nature.

Based on our procedures under the expected credit loss model, including an assessment of unrealized losses in our portfolio, we concluded that any unrealized losses on our marketable securities were not attributable to credit and, therefore, we have not recorded an allowance for credit losses for these securities as of December 31, 2021 and 2020.

Fair Value of Debt

The interest rate of our term loan facility approximates the rate at which we could obtain alternative financing. Therefore, the carrying amount of the term loan facility approximated its fair value at December 31, 2021 and 2020.

5. COLLABORATION AND LICENSING AGREEMENTS

Kyowa Kirin Co., Ltd. (2019 KKC Agreement)

In November 2019, we entered into a research collaboration and option agreement with KKC (the "2019 KKC Agreement"), to undergo research to identify two preclinical study-ready compounds for designation as development compounds, with one compound inhibiting the first undisclosed target ("Program 1") and a second inhibiting the second undisclosed target ("Program 2"). Pursuant to the 2019 KKC Agreement, upon completion of the research and designation by the research steering committee of one or more development candidates ("DCs"), KKC has the right to execute one or more separate collaborative agreements relating to the development and commercialization of one or both DCs in certain specified territories.

Under the terms of the 2019 KKC Agreement, KKC agreed to pay us a non-refundable, non-creditable upfront fee of $10.0 million, which was payable as follows: the first installment of $5.0 million within 30 days of the Effective Date, and the second installment of $5.0 million on the first anniversary of the effective date, unless the 2019 KKC Agreement was earlier terminated by KKC due to material breach by us. The term of the 2019 KKC Agreement commenced on November 11, 2019 ("the Effective Date") and ends on the earliest of: (a) two years following the Effective Date, or (b) the nomination of a program DC for both programs, (c) or the nomination of one program DC and the decision by the parties to cease research for the other program, (d) or the decision by the parties to cease research for both programs. We assessed the 2019 KKC Agreement in accordance with ASC 606 and concluded that the contract's counterparty, KKC, is a customer. Management also considered the modification guidance prescribed in ASC 606 and concluded that the 2019 KKC Agreement should be accounted for as a separate contract from the 2017 KKC Agreement, as defined and discussed below.

We identified various promises in the 2019 KKC Agreement, including the grant of an initial research license, the Program 1 research, the Program 2 research, the right to obtain certain development and commercialization rights with Program 1 in certain territories and the right to obtain development and commercialization rights with Program 2 in certain territories, and participation in a joint steering committee ("the JSC") and determined that KKC could not benefit from either of the research programs without the research license and participation in the JSC. As such, the combined license, research programs and participation in the JSC were deemed to be the highest level of goods and services that can be deemed distinct for each of the Program 1 research and Program 2 research. We concluded that the options to obtain additional development and commercialization rights that are exercisable by KKC under certain circumstances are not performance obligations of the contract at inception because the option fees reflect the standalone selling price of the options, and therefore, the options are not considered to be material rights.

At the outset of the 2019 KKC Agreement, we determined that the initial transaction price was $10.0 million and that revenue associated with the combined performance obligations should be recognized as services are provided using the input method. Since transfer of control occurs over time, in management's judgment this input method is the best measure of progress towards satisfying the performance obligations and reflects a faithful depiction of the transfer of goods and services. Revenue will be recognized over the Program 1 and Program 2 research periods. Management will re-evaluate the estimates related to the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur and adjust the timing of revenue recognition as necessary.

During the years ended December 31, 2021 and 2020, we recognized $4.2 million and $5.4 million, respectively, as revenue under the 2019 KKC Agreement in the statement of operations and comprehensive loss. The aggregate amount of the transaction price allocated to our partially unsatisfied performance obligations as of December 31, 2021 and 2020 was zero and $4.2 million, which was presented in the Balance Sheet as deferred revenue for each respective period. As of December 31,

2021, we have no material future obligations under the 2019 KKC Agreement. There were no significant changes in estimates associated with the 2019 KKC Agreement during the twelve months ended December 31, 2021.

2017 KKC Agreement

In November 2017, we entered into an exclusive license agreement with KKC (the "2017 KKC Agreement") for the development, commercialization and distribution of tenapanor in Japan for cardiorenal indications. We granted KKC an exclusive license to develop and commercialize certain sodium hydrogen exchanger 3 ("NHE3") inhibitors, including tenapanor in Japan for the treatment of cardiorenal diseases and conditions, excluding cancer. We retained the rights to tenapanor outside of Japan, and also retained the rights to tenapanor in Japan for indications other than those stated above. Pursuant to the License Agreement, KKC is responsible for all of the development and commercialization costs for tenapanor in treatment of cardiorenal diseases and conditions, excluding cancer in Japan. Under the 2017 KKC Agreement, we are responsible for supplying the tenapanor drug product for KKC's use in development and during commercialization until KKC has assumed such responsibility. Additionally, we are responsible for supplying the tenapanor drug substance for KKC's use in development and commercialization throughout the term of the 2017 KKC Agreement, provided that KKC may exercise an option to manufacture the tenapanor drug substance under certain conditions

We assessed these arrangements in accordance with ASC 606 and concluded that the contract counterparty, KKC, is a customer. Under the terms of the 2017 KKC Agreement, we received $30.0 million in up-front license fees which was recognized as revenue when the agreement was executed. Based on our assessment, we identified that the license and the manufacturing supply services were our material performance obligations at the inception of the agreement, and as such each of the performance obligations are distinct. Additionally, on January 1, 2018, we recorded unbilled revenue under current assets of $5.0 million and an increase in uncharged license fees under current liabilities of $1.0 million related to the first milestone under the 2017 KKC Agreement that KKC achieved in February 2019, reflecting revenues and cost of revenue, respectively, that would have been recognized in the fourth quarter 2017 if we had adopted ASC 606 prior to January 1, 2018. On KKC's achievement of the milestone in February 2019, the balance related to unbilled revenue was adjusted to zero. Correspondingly, the $1.0 million balance related to uncharged license fees that we owed to AstraZeneca was reclassified to accounts payable during the first quarter of 2019, and subsequently paid to AstraZeneca during the second quarter of 2019.

In addition to the up-front license fee received of $30.0 million, we may be entitled to receive up to $55.0 million in total development milestones, of which $10.0 million has been received to date, ¥8.5 billion Japanese yen for commercialization milestones, or approximately $73.9 million at the currency exchange rate on December 31, 2021, as well as reimbursement of cost, plus a reasonable overhead for the supply of product and high-teen royalties on net sales throughout the term of the agreement. The variable consideration related to the remaining development milestone payments has not been included in the transaction price as these were fully constrained at December 31, 2021.

For the years ended December 31, 2021 and 2020, $0.9 million and $1.4 million, respectively, of product supply revenue was recorded for manufacturing supply of tenapanor and other materials to KKC for product development and clinical trials in Japan, in accordance with our agreement with KKC, including $0.5 million accounts receivable as of December 31, 2021

For the years ended December 31, 2021 and 2020, $5.0 million and zero, respectively, of licensing revenue was recorded. The 2021 licensing revenue was recorded upon the initiation of phase 3 clinical studies by KKC in Japan to evaluate tenapanor for hyperphosphatemia.

During the twelve months ended December 31, 2021, we received a $3.2 million prepayment from KKC for the manufacturing of tenapanor drug substance. In addition, we have unbilled prepayments of $1.5 million from KKC for the manufacturing of tenapanor drug product reflected within prepaid and other current assets. Both amounts are reflected within our deferred revenue, non-current on our balance sheet as of December 31, 2021.

Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd. , or Fosun Pharma

In December 2017, we entered into an exclusive license agreement with Fosun Pharma (the "Fosun Agreement") for the development, commercialization and distribution of tenapanor in China for both hyperphosphatemia and IBS-C. We assessed these arrangements in accordance with ASC 606 and concluded that the contract counterparty, Fosun Pharma, is a customer. Under the terms of the Fosun Agreement, we received $12.0 million in up-front license fees which was recognized as revenue when the agreement was executed. Based on our assessment, we identified that the license and the manufacturing supply services were its material performance obligations at the inception of the agreement, and as such each of the performance obligations are distinct.

In addition, we may be entitled to additional development and commercialization milestones of up to $110.0 million, as well as reimbursement of cost plus a reasonable overhead for the supply of product and tiered royalties on net sales ranging from the mid-teens to 20%. The variable consideration related to the remaining development milestone payments has not been included in the transaction price as these were fully constrained at December 31, 2021 and 2020.

For the years ended December 31, 2021 and 2020, no revenue was recorded related to the Fosun Agreement.

Knight Therapeutics, Inc.

In March 2018, we entered into an exclusive license agreement with Knight Therapeutics, Inc., (the "Knight Agreement") for the development, commercialization and distribution of tenapanor in Canada for hyperphosphatemia and IBS-C. We assessed these arrangements in accordance with ASC 606 and concluded that the contract counterparty, Knight, is a customer. Based on our assessment, it identified that the license and the manufacturing supply services were its material performance obligations at the inception of the agreement, and as such each of the performance obligations are distinct.

Under the terms of the agreement, we received a $2.3 million nonrefundable, one-time upfront payment in March 2018 and are eligible to receive additional development and commercialization milestone payments worth up to CAD22.2 million, or $17.4 million at the currency exchange rate on December 31, 2021, reimbursement of supply costs on a schedule specifying cost per tablet, with a reasonable mark up for overhead, as well as tiered royalty rates on net sales ranging from the mid-single digits to the low twenties. The variable consideration related to the remaining development milestone payments has not been included in the transaction price as these were fully constrained at December 31, 2021 and 2020.

For the years ended December 31, 2021 and 2020, $13 thousand and $0.7 million of licensing revenue was recorded, respectively, related to the Knight Agreement. For the years ended December 31, 2021 and 2020, zero and $0.1 million product supply revenue was recorded, respectively, related to the Knight Agreement. Pursuant to the AstraZeneca Termination Agreement, $1.0 million and $0.1 million of cost of revenue was recorded during 2021 and 2020, respectively.

Xuanzhu (HK) Biopharmaceutical Limited, or XuanZhu

In November 2019, we entered into a license agreement with XuanZhu (“the XuanZhu Agreement") for a license to certain specific patent and patent applications. We assessed these arrangements in accordance with ASC 606 and concluded that the contract counterparty, XuanZhu, is a customer. Under the terms of the XuanZhu Agreement, we recognized $1.5 million in license fees when the agreement was executed, of which, $0.8 million was received upfront in November 2019 and achievement for the second $0.8 million payment was determined to be not materially at risk and probable of achievement and it was included in the transaction price as the amount was not probable of revenue reversal. Based on our assessment, we determined that we had one combined performance obligation, which is the license and the specific patent grant.

In addition to the license fee of $1.5 million, we may be entitled to receive milestone payments. The variable consideration related to the remaining milestone payments has not been included in the transaction price as these were fully constrained at December 31, 2021 and 2020.

For the years ended December 31, 2021 and 2020, no license revenue was recorded related to the XuanZhu Agreement.

AstraZeneca

In June 2015, we entered into a termination agreement with AstraZeneca (the "AstraZeneca Termination Agreement") pursuant to which we remain liable to pay AstraZeneca license fees for (i) future royalties at a royalty rate of 10% of net sales of tenapanor or other NHE3 products by us or our licensees, and (ii) 20% of non-royalty revenue received from a licensee of tenapanor or certain other NHE3 inhibitors, up to a maximum of $75.0 million in aggregate for (i) and (ii).

To date in aggregate, we have recognized $11.6 million of the $75.0 million, recorded as cost of revenue, as follows (in thousands):

	Cost of Revenue	
	Recognized	Amount Paid
Year 2017	$ 9,400 *	$ 6,000
Year 2018	466	2,864
Year 2019	600	1,002
Year 2020	145	742
Year 2021	1,000	1,003
Total	$ 11,611	$ 11,611
Maximum payment per termination agreement		75,000
Remaining potential commitment		$ 63,389

***** Includes $1.0 million adjustment recorded pursuant to the adoption of ASC 606, as discussed in Note 2.

Deferred Revenue

The following tables present changes in our current and non-current deferred revenue balances during the reporting period. The current deferred revenue balance is attributable entirely to the 2019 KKC Agreement and the non-current deferred revenue balance is attributable entirely to the 2017 KKC Agreement (in thousands):

Deferred revenue - current	**2021**	**2020**
Balance at Balance at January 1,	$ 4,177	$ 4,541
Decreases due to revenue recognized in the period for which cash has been received	(4,177)	(364)
Balance at Balance at December 31,	$ —	$ 4,177

Deferred revenue - non-current	**2021**	**2020**
Balance at Balance at January 1,	$ —	$ —
Increases due to cash received during the period	3,242	—
Increase due to unbilled prepayments recorded during the period	1,485	—
Balance at Balance at December 31,	$ 4,727	$ —

6. BORROWINGS

Solar Capital and Western Alliance Bank Loan Agreement

On May 16, 2018, we entered into a loan and security agreement (the "2018 Loan Agreement"), with Solar Capital Ltd. and Western Alliance Bank (the "Lenders"). The 2018 Loan Agreement provides for a $50.0 million term loan facility with a maturity date of November 1, 2022 (the "2018 Term Loan"). The full amount of the 2018 Term Loan was funded on May 16, 2018. We received net proceeds from the loan of approximately $49.3 million, after deducting the closing fee, legal expenses and issuance costs. On October 9, 2020, we and the Lenders entered into an amendment to the 2018 Loan Agreement ("the 2020 Amendment") to extend the date through which we were permitted to make interest-only payments on the 2018 Term Loan by twelve months to December 1, 2021 subject to the repayment terms noted below.

Borrowings under the 2018 Term Loan bear interest at a floating per annum rate equal to 7.45% plus the one-month London Inter-bank Offered Rate ("LIBOR"). We were permitted to make interest-only payments on the 2018 Term Loan through June 1, 2020, or until we achieved our primary endpoint in the Phase 3 study of tenapanor for the treatment of hyperphosphatemia in end-stage renal disease patients on dialysis prior to June 1, 2020, in which case we would have been permitted to make interest-only payments on the 2018 Term Loan through December 1, 2020. On December 3, 2019, we reported positive topline results for PHREEDOM, a long-term Phase 3 study evaluating the efficacy and safety of tenapanor as monotherapy for the treatment of hyperphosphatemia in adult patients with CKD on dialysis. The Lenders were in agreement that these positive data from the Phase 3 PHREEDOM study achieve the "Phase 3 Endpoint" required by the 2018 Term Loan to extend the interest only period by six months to December 1, 2020. Subsequent to the 2020 Amendment, the interest only period was extended an additional twelve months to December 1, 2021. Accordingly, beginning on December 1, 2021 through

the maturity date, we would have been required to make monthly payments of interest plus repayment of the 2018 Term Loan in consecutive equal monthly installments of principal. If however, either the FDA did not approve our NDA for tenapanor for control of serum phosphorus in adult patients with CKD on dialysis on or before May 31, 2021 or the FDA issued a Complete Response Letter ("CRL") for tenapanor for the control of serum phosphorus in adult CKD on dialysis, then we would begin principal payments on the earlier of June 1, 2021 or the first day of the month immediately following the date that the FDA issued a CRL to us.

In May and July 2021, we and the Lenders entered into additional amendments to the 2018 Loan Agreement (“the 2021 Amendments”) which together extended the period of time that we were permitted to make interest-only payments on the 2018 Term Loan to December 1, 2021; provided that if we had not received FDA approval for our NDA for tenapanor for the control of serum phosphorus in adult patients with CDK on dialysis on or before October 25, 2021, the interest-only period would expire and principal repayments would be required to begin on November 1, 2021. If principal repayments were required to begin prior to December 1, 2021 under the 2021 Amendments, then the first such repayment was required include all payments that would have been due if monthly principal repayment had begun on June 1, 2021. Accordingly, during November 2021, in compliance with the terms of our 2018 Loan Agreement, we paid the first principal repayment on the 2018 Term Loan in the amount of $16.7 million and have paid all other subsequently due principal payments through December 31, 2021.

We paid a closing fee of $0.5 million, upon the closing of the 2018 Term Loan and $0.1 million upon closing of the 2020 Amendment. Under the 2018 Term Loan, we were obligated to pay a final fee equal to 3.95% of the 2018 Term Loan upon the earliest to occur of the maturity date, the acceleration of the 2018 Term Loan, the prepayment or repayment of the 2018 Term Loan or the termination of the 2018 Loan Agreement. Under the 2020 Amendment, the final fee was increased to 4.95% of the 2018 Term Loan. We may voluntarily prepay the outstanding 2018 Term Loan, subject to a prepayment premium of (i) 3% of the principal amount of the 2018 Term Loan if prepaid prior to or on the first anniversary of the Closing Date, (ii) 2% of the principal amount of the 2018 Term Loan if prepaid after the first anniversary of the Closing Date through and including the second anniversary of the Closing Date, or (iii) 1% of the principal amount of the 2018 Term Loan if prepaid after the second anniversary of the Closing Date and prior to the maturity date. The 2018 Term Loan is secured by substantially all of our assets, except for our intellectual property and certain other customary exclusions. Additionally, in connection with the 2018 Term Loan, we entered into the 2018 Exit Fee Agreement, as discussed in *Note 7 - Derivative Liability*.

The 2018 Loan Agreement contains customary representations and warranties and customary affirmative and negative covenants, including restrictions on payment of dividends for our common stock. As of December 31, 2021, we were in compliance with all of the covenants set forth in the 2018 Loan Agreement.

In addition, the 2018 Loan Agreement contains customary events of default that entitle the Lender to cause our indebtedness under the 2018 Loan Agreement to become immediately due and payable, and to exercise remedies against us and the collateral securing the 2018 Term Loan, including its cash. Upon the occurrence and for the duration of an event of default, an additional default interest rate equal to 4.0% per annum will apply to all obligations owed under the 2018 Loan Agreement. As of December 31, 2021, to our knowledge, there were no facts or circumstances in existence that would give rise to an event of default.

As discussed in *Note 18 - Subsequent Events*, on February 23, 2022 (the “Closing Date”), we entered into a loan and security agreement (the “2022 Loan Agreement”) with SLR Investment Corp. as collateral agent (the “Agent”), and the lenders listed in the 2022 Loan Agreement (collectively the “2022 Lenders”). The 2022 Loan Agreement provides for a senior secured term loan facility, with $27.5 million (the “Term A Loan”) funded on the Closing Date and an additional $22.5 million that we may borrow on or prior to July 25, 2023; provided that (i) we have received approval by the FDA for our NDA for tenapanor the control of serum phosphorus in chronic kidney disease patients on dialysis by December 31, 2022, and (ii) we have achieved certain product revenue milestone targets described in the 2022 Loan Agreement (the “Term B Loan”, and collectively, the Term A Loan and the Term B Loan, the “2022 Term Loan”). The Term A Loan funds are being used to repay the Term Loan with the Lenders as discussed in *Note 6 - Borrowings* and to fund our ongoing operations. We had $25.0 million principal from the 2018 Term Loan outstanding as of the Closing Date. We have continued to classify the 2018 Term Loan balance as a current liability as of December 31, 2021 due to the determination of the existence of substantial doubt about our ability to continue operating as a going concern discussed in *Note 2 – Summary of Significant Accounting Policies* and our assessment that the material adverse change clause under the 2022 Loan Agreement is not within the Company's control. The lender has not invoked the material adverse change clause as of the date of issuance of these financial statements.

As of December 31, 2021, prior to restructuring our debt as discussed in *Note 18 - Subsequent Events*, our future payment obligations towards the 2018 Term Loan principal and final fee, excluding interest payments and the 2018 Exit Fee were as follows (in thousands):

2022	$ 33,031
Total repayment obligations	$ 33,031
Less: Unamortized discount and debt issuance costs	(235)
Less: Unaccreted value of final fee	(532)
Loan payable	32,264
Less: Loan payable, current portion	(32,264)
Loan payable, net of current portion	$ —

Subsequent to restructuring the 2018 Term Loan, we will have no debt repayment obligations in 2022 or 2023. We will be required to repay $6.9 million, $9.2 million, $9.2 million, and $2.3 million in Term A Loan principal repayments per year during 2024, 2025, 2026 and 2027, respectively, as well as a final fee in the amount of $1.4 million in 2027.

7. DERIVATIVE LIABILITY

Exit Fee

In May 2018, in connection with entering into the 2018 Loan Agreement, as defined and discussed in *Note 6 - Borrowing*, we entered into an agreement pursuant to which we agreed to pay $1.5 million in cash (the "2018 Exit Fee") upon any change of control transaction in respect of the Company or if we obtain both (i) FDA approval of tenapanor for the treatment of hyperphosphatemia in adult patients with CKD on dialysis and (ii) FDA approval of tenapanor for the treatment of patients with IBS-C, which was obtained on September 12, 2019 when the FDA approved IBSRELA, a 50 mg, twice daily oral pill for the treatment of IBS-C in adults (the “2018 Exit Fee Agreement”). Notwithstanding the prepayment or termination of the 2018 Term Loan, our obligation to pay the 2018 Exit Fee will expire on May 16, 2028. We concluded that the 2018 Exit Fee is a freestanding derivative which should be accounted for at fair value on a recurring basis. The estimated fair value of the 2018 Exit Fee is recorded as a derivative liability and included in accrued expense and other current liabilities on the accompanying balance sheets.

The fair value of the derivative liability was determined using a discounted cash flow analysis and is classified as a Level 3 measurement within the fair value hierarchy since our valuation utilized significant unobservable inputs. Specifically, the key assumptions included in the calculation of the estimated fair value of the derivative instrument include: i) our estimates of both the probability and timing of a potential $1.5 million payment to Solar Capital Ltd. and Western Alliance Bank as a result of the FDA approvals, and ii) a discount rate which was derived from our estimated cost of debt, adjusted with current LIBOR. Generally, increases or decreases in the probability of occurrence would result in a directionally similar impact in the fair value measurement of the derivative instrument and it is estimated that a 10% increase (decrease), not to exceed 100%, in the probability of occurrence would result in a fair value fluctuation of no more than $0.1 million.

Changes in the fair value of recurring measurements included in Level 3 of the fair value hierarchy are presented as other income (expense), net in our Statements of Operations and were as follows for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	2021	2020	2019
Fair value of exit fee derivative liability at January 1	$ 1,376	$ 969	$ 533
Change in estimated fair value of derivative liability	$ (678)	$ 407	$ 436
Fair value of exit fee derivative liability at December 31	$ 698	$ 1,376	$ 969

As discussed in *Note 18 - Subsequent Events*, on February 23, 2022, we entered into an additional exit fee agreement with Solar whereby we agreed to pay an exit fee in the amount 2% of the 2022 Term Loan funded upon the first to occur of a specified exit event or revenue achievement event.

8. LEASES

We have recorded right-of-use operating lease assets under three lease agreements. We have evaluated our facility leases and determined that, effective upon the adoption of Topic 842, the leases evaluated are all operating leases. We have performed

an evaluation of our other contracts with suppliers and collaborators in accordance with Topic 842 and have determined that, except for the facility leases described below, none of our contracts contain a lease.

We have recorded a right-of-use operating lease asset located in Fremont, California under a lease agreement entered into in September 2008 that was amended in December 2012 to extend the lease agreement to September 2016. In September 2014, we signed the second amendment to our facility lease agreement to add space and to extend the lease term through September 2019. In May 2016, we signed a third amendment to our facility lease agreement in Fremont, California to add space and to extend the lease term through September 2021 (the "Third Amendment"). During May 2021, we entered into an additional amendment to the lease for our Fremont, California facility that extended the term of the lease to March 2025. The office space consists of 72,500 square feet, which includes 10,716 square feet added in September 2019. We do not have an option to renew the lease at our current Fremont location beyond March 2025.

We have recorded a right-of-use operating lease asset located in Waltham, Massachusetts under a lease agreement entered into in October 2018. The office space consisted of 3,520 square feet with the lease terminating in September 2021. We did not renew the lease at our original Waltham, Massachusetts facility. During April 2021 and May 2021, we recorded right-of-use operating lease assets for a new facility in Waltham, Massachusetts under a lease agreement entered into during December 2020 with lease commencement dates during April and May 2021. The office space consists of 12,864 square feet with the lease terminating in June 2026. We have an option to extend the lease term for one additional five year period. This option to extend the lease term has not been included in the calculation since currently the exercise of the option is uncertain and therefore deemed not probable. We recorded a $1.6 million right-of-use asset and lease liability for the Waltham lease upon commencement of the lease.

We have recorded a right-of-use operating lease asset located in Milwaukee, Wisconsin under a lease agreement entered into in October 2020 with a lease commencement date in November 2020. The office space consists of 4,768 square feet with the lease terminating in February 2026. We have an option to extend the lease term by one additional five-year period. This option to extend the lease term has not been included in the calculation since currently the exercise of the option is uncertain and therefore deemed not probable. We recorded a $0.4 million right-of use asset and lease liability for the Milwaukee lease upon commencement of the lease.

All of our leases are operating leases and each contain customary rent escalation clauses. Certain of the leases have both lease and non-lease components. We have as elected to account for each separate lease component and the non-lease components associated with that lease component as a single lease component for all classes of underlying assets.

The following table provides additional details of the leases presented in the balance sheets (dollars in thousands):

	As of Dec 31,	
Facilities	**2021**	**2020**
Right-of-use assets	$ 12,752	$ 2,274
Current portion of lease liabilities	3,492	2,117
Operating lease liability, net of current portion	9,748	413
Total	$ 13,240	$ 2,530
Weighted-average remaining life (years)	3.40	1.50
Weighted-average discount rate	6.9 %	11.7 %

The lease costs, which are included in operating expenses in our statements of operations, were as follows (in thousands):

	Year Ended December 31,		
	2021	**2020**	**2019**
Operating lease expense	$ 3,671	$ 2,608	$ 2,592
Cash paid for operating lease	$ 3,438	$ 3,065	$ 2,645

The following table summarizes our undiscounted cash payment obligations for our operating lease liabilities as of December 31, 2021 (in thousands):

Ending December 31,	
2022	$ 4,292
2023	4,440
2024	4,589
2025	1,321
2026	252
Thereafter	—
Total undiscounted operating lease payments	14,894
Imputed interest expenses	(1,654)
Total operating lease liabilities	13,240
Less: Current portion of operating lease liability	(3,492)
Operating lease liability, net of current portion	$ 9,748

9. STOCKHOLDERS' EQUITY

In July 2020, we filed a Form S-3 registration statement, which became effective in August 2020, containing (i) a base prospectus for the offering, issuance and sale by us of up to a maximum aggregate offering price of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units, from time to time in one or more offerings; and (ii) a prospectus supplement for the offering, issuance and sale by us of up to a maximum aggregate offering price of $100.0 million of its common stock that may be issued and sold, from time to time, under an Open Market Sales Agreement with Jefferies LLC, as sales agent, deemed to be "at-the-market offerings" (the "2020 Open Market Sales Agreement"). Pursuant to the 2020 Open Market Sales Agreement, Jefferies, as sales agent, received a commission of up to 3.0% of the gross sales price for shares of common stock sold under the 2020 Open Market Sales Agreement. We sold 8.2 million shares of our common stock between the dates of November 13, 2020 through February 19, 2021, 4.0 million shares between the dates of May 11, 2021 through June 18, 2021, 3.3 million shares between the dates of August 24, 2021 through September 10, 2021 and 7.7 million between the dates of October 21, 2021 through December 31, 2021 for a cumulative total of 23.3 million shares and gross proceeds of $100.0 million at a weighted average sales price of approximately $4.30 per share which resulted in full utilization of the $100.0 million authorized amount under the 2020 Open Market Sales Agreement.

In August 2021, we filed an additional prospectus supplement under the Registration Statement for the offering, issuance and sale by us of up to a maximum aggregate offering price of $150.0 million of our common stock that may be issued and sold, from time to time, under an additional sales agreement we entered into with Jefferies (the "2021 Open Market Sales Agreement"), pursuant to which we may, from time to time, sell up to $150.0 million in shares of our common stock through Jefferies. We are not required to sell shares under the 2021 Open Market Sales Agreement. Pursuant to the 2021 Open Market Sales Agreement, Jefferies, as our sales agent, receives a commission of up to 3.0% of the gross sales price for shares of common stock sold under the 2021 Open Market Sales Agreement. As of December 31, 2021 we have sold 15.7 million shares and received gross proceeds of $25.0 million at a weighted average sales price of approximately $1.60 per share under the 2021 Open Market Sales Agreement.

On December 9, 2019, we completed an underwritten public offering of 20.0 million shares of common stock at a price of $6.25 per share before underwriting discounts and commissions (the "2019 Offering"). In connection with the 2019 Offering, we entered into an underwriting agreement, or the 2019 Underwriting Agreement, with Citigroup Global Markets Inc., Cowen and Company LLC, SVB Leerink LLC and Piper Jaffray & Co., or collectively the 2019 Underwriters, pursuant to which we granted to the 2019 Underwriters a 30-day option to purchase up to an additional 3.0 million shares of our common stock, or the 2019 Overallotment. We completed the sale of 23.0 million shares, inclusive of the 2019 Overallotment, to the 2019 Underwriters and that sale resulted in the receipt by us of aggregate gross proceeds of approximately $143.8 million, less underwriting discounts, commissions and offering expenses totaling approximately $8.9 million, which resulted in net proceeds of approximately $134.9 million.

On November 22, 2019, we and KKC entered into a stock purchase agreement, pursuant to which we sold an aggregate of approximately 2.9 million shares of its common stock at $6.96 per share for net proceeds of approximately $20.0 million, or the Private Placement. The Private Placement closed on November 25, 2019.

10. EQUITY INCENTIVE PLANS

2008 Plan

We granted options under its 2008 Stock Incentive Plan (the “2008 Plan”) until June 2014 when it was terminated as to future awards, although it continues to govern the terms of options that remain outstanding under the 2008 Plan. The 2008 Plan provided for the granting of incentive and non-qualified stock options, and stock purchase rights to employees, directors and consultants at the discretion of the Board of Directors. Stock options granted generally vest over a period of four years from the date of grant. In connection with the Board of Directors and stockholders’ approval of the 2014 Plan, all remaining shares available for future award under the 2008 Plan were transferred to 2014 Plan, and the 2008 Plan was terminated.

2014 Plan

The 2014 Equity Incentive Award Plan (the “2014 Plan”) became effective on June 18, 2014. Under the 2014 Plan, 1.4 million shares of common stock were initially reserved for issuance pursuant to a variety of stock-based compensation awards, including stock options, stock appreciation rights ("SARs"), restricted stock awards, service-based restricted stock unit (“RSU”) awards, performance-based restricted stock unit (“PRSU”) awards, deferred stock awards, deferred stock unit awards, dividend equivalent awards, stock payment awards and performance awards. In addition, 35 thousand shares that had been available for future awards under the 2008 Plan as of June 18, 2014, were added to the initial reserve available under the 2014 Plan, bringing the total reserve upon the effective date of the 2014 Plan to 1.5 million shares. The number of shares initially reserved for issuance or transfer pursuant to awards under the 2014 Plan will be increased by (i) the number of shares represented by awards outstanding under 2008 Plan on June 18, 2014, that are either forfeited or lapse unexercised or that are repurchased for the original purchase price thereof, up to a maximum of 1.2 million shares, and (ii) if approved by the Administrator of the 2014 Plan, an annual increase on the first day of each fiscal year ending in 2024 equal to the lesser of (A) four percent (4.0%) of the shares of stock outstanding (on an as converted basis) on the last day of the immediately preceding fiscal year and (B) such smaller number of shares of stock as determined by our board of directors; provided, however, that no more than 10.7 million shares of stock may be issued upon the exercise of incentive stock options.

2016 Plan

In November 2016, our board of directors approved the 2016 Employment Commencement Incentive Plan (the “Inducement Plan”) under which 1.0 million shares were reserved. In January 2021 and 2022, 0.5 million and 2.0 million shares, respectively, were added to the Inducement Plan. As of December 31, 2021, 0.4 million shares of our common stock were subject to inducement grants that were issued pursuant to the Inducement Plan.

Stock Options

The following table summarizes activity under the 2008 Plan and the 2014 Plan, including grants issued to nonemployees, in the year ended December 31, 2021:

		Options Issued and Outstanding			
	Shares Available for Grant	Number of Shares	Weighted-Average Exercise Price per Share	Weighted Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value (in thousands)
Balance at December 31, 2020	1,757,058	9,790,049	$ 6.76		
Options authorized	4,201,766	—	$ —		
Options granted	(3,409,719)	3,409,719	$ 6.60		
Options exercised	—	(331,310)	$ 1.96		
Options canceled	2,451,306	(2,451,306)	$ 6.17		
Issuance of common stock for services	(25,989)	—	—		
Balance at December 31, 2021	4,974,422	10,417,152	$ 7.00	6.57	$ —
Vested and expected to vest at December 31, 2021		10,417,152	$ 7.00	6.57	$ —
Exercisable at December 31, 2021		6,772,289	$ 7.39	5.58	$ —

The aggregate intrinsic value represents the difference between the total pre-tax value (i.e., the difference between our stock price and the exercise price) of stock options outstanding as of December 31, 2021, based on our common stock closing

price of $1.10 per share, which would have been received by the option holders had all their in-the-money options been exercised as of that date.

The intrinsic value of options exercised during the years ended December 31, 2021, 2020 and 2019, was $1.7 million, $2.7 million, and $0.4 million, respectively.

The weighted-average grant-date estimated fair value of options granted during the years ended December 31, 2021, 2020 and 2019 was $3.92, $4.82 and $1.79 per share, respectively. The estimated grant date fair value of employee stock options was calculated using the Black-Scholes option-pricing model, based on the following weighted-average assumptions:

	Year Ended December 31,		
	2021	2020	2019
Expected term (years)	4.97	6.00	6.00
Expected volatility	77 %	83 %	81 %
Risk-free interest rate	4.69 %	1.07 %	2.42 %
Dividend yield	— %	— %	— %

Expected Term—We have limited historical information to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock-option grants. As such, the expected term has been estimated using the simplified method whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option. Beginning in 2021, we estimate the expected term of our options based upon historical exercises and post-vesting termination behavior, which has not resulted in a material difference as compared to using the simplified method.

Expected Volatility—Since January 1, 2017, we use the historic volatility of our own stock over the retrospective period corresponding to the expected remaining term of the options, or the period since our shares were first quoted on The Nasdaq Global Market, if that is shorter, to compute our expected stock price volatility.

Risk-Free Interest Rate—The risk-free interest rate assumption is based on the zero-coupon U.S. treasury instruments on the date of grant with a maturity date consistent with the expected term of our stock option grants.

Dividend Yield—To date, we have not declared or paid any cash dividends and does not have any plans to do so in the future. Therefore, we use an expected dividend yield of zero.

Restricted Stock Units

The following table summarizes restricted stock unit activity under the 2014 Plan in the year ended December 31, 2021, and includes restricted stock units with time or service-based vesting and those restricted stock units with performance-based vesting:

	Number of RSUs		Weighted-Average Grant Date Fair Value Per Share
Non-vested restricted stock units at December 31, 2020	158,626	$	5.64
Granted	4,144,051	$	2.71
Vested	(193,147)	$	6.39
Forfeited	(580,848)	$	6.38
Non-vested restricted stock units at December 31, 2021	3,528,682	$	2.04

In July 2018, we granted 0.9 million PRSUs to our employees that vested upon the achievement of certain performance conditions, subject to the employees' continued service relationship with us through the achievement date. During 2020, we granted an additional 30 thousand PRSUs subject to the same performance conditions. All 0.9 million of these PRSUs vested in September 2020. None of these PRSUs vested during the years ended December 31, 2019 or 2018. We recognized zero and $1.2 million of related expense during the years ended December 31, 2021 and 2020, respectively.

The total estimated fair value of RSUs vested during the years ended December 31, 2021, 2020 and 2019 was $0.8 million, zero and $0.2 million, respectively.

Issuance of Common Stock for Services

During the years ended December 31, 2021, 2020 and 2019, we issued approximately 26 thousand, 42 thousand and 113 thousand shares, respectively, of common stock to members of the board of directors who elected to receive stock in lieu of their cash fees under our Non-Employee Director Compensation Program. The shares issued during the years ended December 31, 2021, 2020 and 2019 were valued at $0.2 million, $0.3 million and $0.3 million for each year, respectively, based on the fair value of the common stock on the date of grant.

Employee Stock Purchase Plan

We adopted the 2014 Employee Stock Purchase Plan ("ESPP") and initially reserved approximately 0.2 million shares of common stock as of its effective date of June 18, 2014. If approved by the Administrator of the ESPP, on the first day of each calendar year, ending in 2024, the number of shares in the reserve will increase by an amount equal to the lesser of (i) one percent (1.0%) of the shares of common stock outstanding on the last day of the immediately preceding fiscal year and (ii) such number of shares of common stock as determined by the board of directors; provided, however, no more than $2.2 million shares of our common stock may be issued under the ESPP.

The following table summarizes our ESPP activity during the year ended December 31, 2021:

	Shares Available for Grant	Number of Shares Purchased	Average Purchase Price per Share	Gross Proceeds (in thousands)
Balance at December 31, 2020	349,647	661,611		
Shares purchased	(386,664)	386,664	$ 2.12	$ 819
Balance at December 31, 2021	898,982	1,048,275		

The following table illustrates the weighted-average assumptions for the Black-Scholes option-pricing model used in determining the fair value of ESPP purchase rights granted to our employees:

	Year Ended December 31,		
	2021	2020	2019
Expected term (years)	0.50	0.50	0.50
Expected volatility	123 %	79 %	69 %
Risk-free interest rate	0.65 %	0.48 %	2.00 %
Dividend yield	— %	— %	— %

Stock-based Compensation Expense

Total stock-based compensation recognized was as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Research and development	$ 4,116	$ 4,061	$ 4,104
General and administrative	7,923	6,522	5,832
Total	$ 12,039	$ 10,583	$ 9,936

At December 31, 2021, the Company had total unrecognized stock-based compensation expense, net of estimated forfeitures, of the following (dollars in thousands):

	December 31, 2021	
	Unrecognized Compensation Expense	Average Remaining Vesting Period (Years)
Stock options grant	$ 14,506	2.4
RSU grants	$ 2,262	0.8
ESPP	$ 44	0.1

11. RESTRUCTURING

On July 29, 2021, our Board of Directors approved, and on August 2, 2021, we began implementing a restructuring plan to better align our workforce and anticipated commercial and development spend with our capital resources and the needs of our business following the receipt of the CRL. Under the restructuring plan, we reduced our workforce by 83 employees (approximately 33%). Impacted employees received cash payments equal to their base pay for a notice period of sixty (60) days and Company funded COBRA premiums through such notice period.

Following the conclusion of an End of Review Type A meeting with the FDA, on October 8, 2021, our Board of Directors approved and, on October 12, 2021, we began to implement an additional restructuring plan to further reduce operating costs and better align our workforce with the needs of our business. Under the additional restructuring plan, we planned to reduce our workforce by approximately 100 of our remaining employees (approximately 60%). The impacted employees received notice that their positions would be eliminated during December 2021.

On November 30, 2021, we announced plans to launch IBSRELA, our approved treatment for IBS-C in adults. In connection with the planned launch of IBSRELA, which we currently expect to commence in April 2022, we retained 28 of the employees whose positions were originally eliminated as part of the additional restructuring plan, thereby reducing the number of employees terminated as part of the restructuring plan to 72. The additional restructuring plan, which resulted in the elimination of our research organization and significantly altered our commercial sales and marketing organizations, was substantially completed in December 2021.

Impacted employees were eligible to receive severance benefits and additional Company funded COBRA premiums, contingent upon an impacted employee's execution (and non-revocation) of a separation agreement, which included a general release of claims against us. In connection with restructuring, we have incurred restructuring charges of $6.2 million, which were recorded during the twelve months ended December 31, 2021, related to one-time termination notice and severance payments and other employee-related costs. We did not incur any significant contract termination costs pursuant to restructuring. Of the charges, $2.7 million was recorded in research and development expenses, and $3.5 million was recorded in general and administrative expense in the accompanying statements of operations and comprehensive loss. Most of the cash payments related to the reduction in workforce were disbursed during the twelve months ended December 31, 2021. We have reported the remaining estimated restructuring liability of $0.5 million as accrued compensation and benefits in our Balance Sheet as of December 31, 2021.

In addition, on October 8, 2021, our Board approved, and management has implemented a retention program consisting of cash payments and grants of RSUs to our employees, including our executives, not impacted by the reduction in force.

12. PROPERTY AND EQUIPMENT, NET

Property and equipment consist of the following (in thousands):

	December 31,	
	2021	2020
Laboratory equipment	$ 7,474	$ 7,268
Office equipment and furniture	2,034	1,133
Leasehold improvements	8,745	7,985
Property and equipment, gross	18,253	16,386
Less: accumulated depreciation	(15,891)	(14,450)
Total property and equipment, net	$ 2,362	$ 1,936

We recognized depreciation expense in the amount of $1.4 million, $1.8 million, and $2.5 million for the years ended December 31, 2021, 2020 and 2019, respectively.

13. ACCRUED EXPENSES AND OTHER CURRENT LIABILITIES

Accrued expenses and other current liabilities consist of the following (in thousands):

	December 31,	
	2021	2020
Accrued clinical expenses	$ 2,522	$ 2,197
Accrued contract manufacturing expenses	2,485	1,840
Derivative liability for exit fee	698	1,376
Accrued professional and consulting services	597	243
Accrued sales and marketing expenses	256	593
Accrued interest expense	203	123
Other	605	285
Total accrued expenses and other current liabilities	$ 7,366	$ 6,657

14. INCOME TAXES

The components of our provision for income taxes for the year ended December 31, 2021, 2020 and 2019, are as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Current:			
State	$ 4	$ 2	$ 2
Foreign	—	—	301
Total current	4	2	303
Deferred:			
Federal	—	—	—
Total deferred	—	—	—
Provision for income taxes	$ 4	$ 2	$ 303

The following is a reconciliation of the statutory federal income tax rate to our effective tax rate:

	Year Ended December 31,		
	2021	2020	2019
Change in valuation allowance	(20.0)%	(22.3)%	(21.9)%
Income tax at the federal statutory rate	21.0	21.0	21.0
Tax credits	1.0	1.3	1.6
State taxes, net of federal benefit	0.4	0.7	0.3
Stock based compensation	(1.3)	(0.1)	(0.4)
Executive compensation disallowed under IRC Sec 162(m)	(1.1)	(0.5)	(0.5)
Other	—	(0.1)	(0.4)
Income tax provision	— %	— %	(0.3)%

Deferred income taxes reflect the tax effects of 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 our deferred tax assets are as follows as of December 31, 2021 and 2020 (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Amortization and depreciation	$ 61,098	$ 51,370
Net operating loss carryforwards	74,989	53,436
Tax credits	13,827	11,777
Stock-based compensation	4,054	5,524
Other	3,867	1,804
Gross deferred tax assets	157,835	123,911
Valuation allowance	(155,141)	(123,402)
Deferred tax assets net of valuation allowance	2,694	509
Deferred tax liabilities:		
Right-of-use asset	(2,689)	(479)
Other	(5)	(30)
Net deferred tax assets	$ —	$ —

Realization of deferred tax assets is dependent on future taxable income, if any, the timing and the amount of which are uncertain. We assess the available positive and negative evidence to estimate whether sufficient future taxable income will be generated to permit use of the existing deferred tax assets. A significant component of objective negative evidence evaluated was our cumulative loss incurred over the three-year period ended December 31, 2021. Such objective evidence limits the ability to consider other subjective evidence, such as our projections for future growth. On the basis of this evaluation, as of December 31, 2021, December 31, 2020 and December 31, 2019, a full valuation allowance has been recorded against our net deferred tax asset. The amount of the deferred tax asset considered realizable, however, could be adjusted if estimates of future taxable income during the carryforward period are reduced or increased or if objective negative evidence in the form of cumulative losses is no longer present and additional weight is given to subjective evidence such as our projections for growth.

As of December 31, 2021, we had net operating loss carryforwards for federal income tax purposes of approximately $386.3 million, of which approximately $236.1 million can be carried forward indefinitely and the remaining net operating losses expire beginning in 2030, if not utilized. Federal research and development tax credit carryforwards of approximately $16.4 million that expire beginning in 2027, if not utilized, and foreign tax credit carryforwards of approximately $1.2 million that expire in 2027, if not utilized.

In addition, we had net operating loss carryforwards for California income tax purposes of approximately $88.3 million that expire beginning of 2030, if not utilized, and state research and development tax credit carryforwards of approximately $8.4 million which can be carried forward indefinitely. We had approximately $0.1 million of minimum tax credit carryovers for California income tax purposes. The minimum tax credits have no expiration date. We had other state net operating losses of approximately $4.5 million that begin to expire in 2035.

The future utilization of net operating loss and tax credit carryforwards and credits may be subject to an annual limitation, pursuant to Internal Revenue Code Sections 382 and 383, as a result of ownership changes that may have occurred previously or that could occur in the future. Due to the existence of the valuation allowance, limitations under Section 382 and 383 will not impact our effective tax rate.

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act (“CARES Act”) was enacted and signed into law in response to coronavirus disease 2019 (“COVID-19”). The CARES Act, among other things, included several significant provisions that impacted corporate taxpayers’ accounting for income taxes. Prior to the enactment of the CARES Act, the 2017 Tax Cuts and Jobs Act generally eliminated the ability to carryback net operating losses (“NOLs”), and permitted the NOLs arising in tax years beginning after December 31, 2018 to be carried forward indefinitely, limited to 80% of the taxpayer’s income. The CARES Act amended the NOL rules, suspending the 80% limitation on the utilization of NOLs generated after December 31, 2018 and before January 1, 2021. Additionally, the CARES Act allows corporate NOLs arising in taxable years beginning after December 31, 2018 and before January 1, 2021, to be carried back to each of the five taxable years preceding

the taxable year of the loss. Also, the CARES Act allows companies to defer making certain payroll tax payments until future years. With the enactment of the CARES Act, the company does not expect a financial statement impact from income taxes.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows (in thousands):

	December 31,		
	2021	2020	2019
Balance at beginning of year	$ 23,624	$ 24,538	$ 23,052
Additions (subtractions) based on tax positions related to prior year	(811)	(1,388)	755
Additions based on tax positions related to current year	1,613	474	731
Balance at end of year	$ 24,426	$ 23,624	$ 24,538

We recognize a tax benefit from an uncertain tax position when it is more likely than not that the position will be sustained upon examination, including resolutions of any related appeals or litigation processes, based on the technical merits. Income tax positions must meet a more likely than not recognition at the effective date to be recognized. None of our unrecognized tax benefits would impact the effective tax rate if recognized, because the benefit would be offset by an increase in the valuation allowance.

We have elected to include interest and penalties as a component of tax expense. During the years ended December 31, 2021, 2020 and 2019, we did not recognize accrued interest and penalties related to unrecognized tax benefits. Although the timing and outcome of an income tax audit is highly uncertain, we do not anticipate that the amount of existing unrecognized tax benefits will significantly change during the next 12 months.

We file income tax returns in the U.S. federal, Alabama, Arizona, California, Colorado, Connecticut, DC, Florida, Georgia, Idaho, Illinois, Indiana, Kansas, Kentucky, Massachusetts, Maryland, Michigan, Missouri, Kansas City (MO), Mississippi, New York & New York MTA, New York City, Nebraska, New Jersey, New Mexico, North Carolina, Cincinnati (OH), Maineville (OH), Oklahoma, Pennsylvania, Tennessee, Texas, Virginia and Wisconsin tax jurisdictions. Due to our net operating loss and tax credit carryforwards, the income tax returns remain open to U.S. federal and state tax examinations. The Company is not currently under examination in any tax jurisdiction.

15. GEOGRAPHIC INFORMATION AND CONCENTRATIONS

Revenues are attributed to geographical areas based on the domicile of our collaboration partners. Our revenue by geographic areas for the years ended December 31, 2021, 2020 and 2019, are as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
United States	$ —	$ —	$ —
International:			
North America (1)	13	806	—
Asia Pacific (2) (3)	10,084	6,765	5,281
Total revenue	$ 10,097	$ 7,571	$ 5,281

(1) Revenues from North America are comprised of amounts earned from Canada in accordance with the Knight Agreement.
(2) Revenues from Asia Pacific in 2021 and 2020 are comprised of amounts earned from Japan in accordance with the 2017 KKC Agreement and 2019 KKC Agreement.
(3) Revenues from Asia Pacific in 2019 were comprised of $0.8 million from Japan in accordance with the 2017 KKC Agreement and 2019 KKC Agreement, $1.5 million from Hong Kong in accordance with the XuanZhu Agreement and $3.0 million from China in accordance with the Fosun Agreement.

Revenues recorded in the years ended December 31, 2021, 2020 and 2019, were wholly from collaboration partnerships. Collaboration partnerships accounting for more than 10% of total revenues during the years ended December 31, 2021, 2020 and 2019 are as follows:

	Year Ended December 31,		
	2021	2020	2019
KKC	100 %	89 %	15 %
Knight	— %	11 %	— %
Fosun Pharma	— %	— %	57 %
XuanZhu	— %	— %	28 %

Historically, we have not experienced credit losses from our accounts receivable. We have not recorded a reserve for credit losses as of December 31, 2021 and 2020.

16. NET LOSS PER SHARE

Basic net loss per share is calculated by dividing net loss by the weighted-average number of common shares outstanding during the period, less shares subject to repurchase, and excludes any dilutive effects of stock-based awards and warrants. Diluted net loss per common share is computed giving effect to all potential dilutive common shares, including common stock issuable upon exercise of stock options, and unvested restricted common stock and stock units. As we had net losses for the years ended December 31, 2021, 2020 and 2019, all potential common shares were determined to be anti-dilutive.

The following table sets forth the computation of net loss per common share (in thousands, except per share amounts):

	Year Ended December 31,		
	2021	2020	2019
Numerator:			
Net loss	$ (158,165)	$ (94,313)	$ (94,940)
Denominator:			
Weighted average common shares outstanding - basic and diluted	104,205,645	89,582,138	64,478,066
Net loss per share - basic and diluted	$ (1.52)	$ (1.05)	$ (1.47)

For the years ended December 31, 2021, 2020 and 2019, the total numbers of securities that could potentially dilute net income per share in the future that were not considered in the diluted net loss per share calculations because the effect would have been anti-dilutive were as follows:

	Year Ended December 31,		
	2021	2020	2019
Options to purchase common stock	11,870,778	9,246,047	7,128,247
Restricted stock units	1,602,384	26,121	—
ESPP shares issuable	206,522	94,466	78,761
Warrants to purchase common stock	—	932,091	2,172,899
Performance-based restricted stock units	—	—	867,506
Total	13,679,684	10,298,725	10,247,413

The number of potential common shares that would have been included in diluted income per share had it not been for the anti-dilutive effect caused by the net loss, computed by converting these securities using the treasury stock method during the years ended December 31, 2021, 2020 and 2019, was approximately 1.1 million, 2.1 million and 1.1 million, respectively.

17. COMMITMENTS AND CONTINGENCIES

Guarantees and Indemnifications

We indemnify each of our officers and directors for certain events or occurrences, subject to certain limits, while the officer or director is or was serving at our request in such capacity, as permitted under Delaware law and in accordance with our

certificate of incorporation and bylaws. The term of the indemnification period lasts as long as an officer or director may be subject to any proceeding arising out of acts or omissions of such officer or director in such capacity.

The maximum amount of potential future indemnification is unlimited; however, we currently hold director and officer liability insurance, which allows the transfer of risk associated with our exposure and may enable us to recover a portion of any future amounts paid. We believe that the fair value of these indemnification obligations is minimal. Accordingly, we have not recognized any liabilities relating to these obligations for any period presented.

Legal Proceedings and Claims

From time to time we may be involved in claims arising in connection with our business. Based on information currently available, management believes that the amount, or range, of reasonably possible losses in connection with any pending actions against us will not be material to our financial condition or cash flows, and no contingent liabilities were accrued as of December 31, 2021 or 2020.

18. SUBSEQUENT EVENTS

On February 23, 2022 (the "Closing Date"), we entered into a loan and security agreement (the "2022 Loan Agreement") with SLR Investment Corp. as collateral agent (the "Agent"), and the lenders listed in the 2022 Loan Agreement (collectively the "2022 Lenders"). The 2022 Loan Agreement provides for a senior secured term loan facility, with $27.5 million (the "Term A Loan") funded on the Closing Date and an additional $22.5 million that we may borrow on or prior to July 25, 2023; provided that (i) we have received approval by the FDA for our NDA for the control of serum phosphorus in chronic kidney disease patients on dialysis by December 31, 2022, and (ii) we have achieved certain product revenue milestone targets described in the 2022 Loan Agreement (the "Term B Loan", and collectively, the Term A Loan and the Term B Loan, the "2022 Term Loan"). The 2022 Term A Loan funds are being used to repay the 2018 Term Loan with the Lenders as discussed in *Note 6 - Borrowings* and to fund our ongoing operations. We owed $25.0 million in principal payments from the 2018 Term Loan as of the Closing Date. The 2022 Term Loan has a maturity date of March 1, 2027.

Borrowings under the 2022 Term Loan bear interest at a floating per annum rate equal to 7.95% plus the greater of (i) one tenth percent (0.10%) and (ii) one-month LIBOR. We are permitted to make interest-only payments on the 2022 Term Loan through March 31, 2024. Accordingly, beginning on April 1, 2024, we will be required to make monthly payments of interest plus repay the 2022 Term Loan in consecutive equal monthly installments of principal. We were obligated to pay $0.2 million, upon the closing of the Term A Loan, and we are obligated to pay $0.1 million on the earliest of (i) the funding date of the Term B Loan, (ii) July 25, 2023, and (iii) the prepayment, refinancing, substitution, or replacement of the Term A Loan on or prior to July 25, 2023. We are obligated to pay a fee equal to 4.95% of the aggregate original principal amount of the 2022 Term Loan funded upon the earliest to occur of the maturity date, the acceleration of the 2022 Term Loan, and the prepayment, refinancing, substitution, or replacement of the 2022 Term Loan. We may voluntarily prepay the outstanding 2022 Term Loan, subject to a prepayment premium of (i) 3% of the principal amount of the 2022 Term Loan if prepaid prior to or on the first anniversary of the Closing Date, (ii) 2% of the principal amount of the 2022 Term Loan if prepaid after the first anniversary of the Closing Date through and including the second anniversary of the Closing Date, or (iii) 1% of the principal amount of the 2022 Term Loan if prepaid after the second anniversary of the Closing Date and prior to the maturity date. The 2022 Term Loan is secured by substantially all of our assets, except for our intellectual property and certain other customary exclusions. Additionally, in connection with the 2022 Term Loan, we entered into an agreement, whereby we agreed to pay an exit fee in the amount 2% of the 2022 Term Loan funded (the "2022 Exit Fee") upon (i) any change of control transaction or (ii) our achievement of net revenue from the sale of any products equal to or greater than $100.0 million, measured on a six (6) months basis, tested monthly at the end of each month. Notwithstanding the prepayment or termination of the 2022 Term Loan, the 2022 Exit Fee will expire 10 years from the Closing Date.

The 2022 Loan Agreement contains customary representations and warranties and customary affirmative and negative covenants, including, among others, requirements as to financial reporting and insurance and restrictions on our ability to dispose of our business or property, to change our line of business, to liquidate or dissolve, to enter into any change in control transaction, to merge or consolidate with any other entity or to acquire all or substantially all the capital stock or property of another entity, to incur additional indebtedness, to incur liens on our property, to pay any dividends or other distributions on capital stock other than dividends payable solely in capital stock or to redeem capital stock. We have agreed to not allow our cash and cash equivalents to be less than the eighty percent (80%) of the outstanding 2022 Term Loan balance for any period in which our net revenue from the sale of any products, calculated on a trailing six (6) month basis and tested monthly, is less than sixty percent (60%) of the outstanding 2022 Term Loan balance.

In addition, the 2022 Loan Agreement contains customary events of default that entitle the Agent to cause our indebtedness under the 2022 Loan Agreement to become immediately due and payable, and to exercise remedies against us and the collateral securing the 2022 Term Loan, including our cash. Under the 2022 Loan Agreement, an event of default will occur if, among other things, we fail to make payments under the 2022 Loan Agreement, we breach any of our covenants under the 2022 Loan Agreement, subject to specified cure periods with respect to certain breaches, certain Lenders determine that a material adverse change has occurred, we or our assets become subject to certain legal proceedings, such as bankruptcy proceedings, we are unable to pay our debts as they become due or we default on contracts with third parties which would permit the holder of indebtedness to accelerate the maturity of such indebtedness or that could have a material adverse change on us. Upon the occurrence and for the duration of an event of default, an additional default interest rate equal to 4% per annum will apply to all obligations owed under the 2022 Loan Agreement.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Conclusions Regarding the Effectiveness of Disclosure Controls and Procedures

As of December 31, 2021, management, with the participation of our Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms, and that such information is accumulated and communicated to our management, including the Chief Executive Officer and the Chief Financial Officer, to allow timely decisions regarding required disclosures.

Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2021, the design and operation of our disclosure controls and procedures were effective at a 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. Internal control over financial reporting is a process designed by, or under the supervision of, our CEO and CFO, and effected by our Board of Directors, management and other personnel, 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 and includes those policies and procedures that:

- Pertain to the maintenance of records that accurately and fairly reflect in reasonable detail the transactions and dispositions of the assets of our company;

- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

- Provide reasonable assurances regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material adverse effect on our financial statements.

Our management assessed our internal control over financial reporting as of December 31, 2021, the end of the period covered by this Annual Report on Form 10-K. Management based its assessment on criteria established in "Internal Control—Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on management's assessment of our internal control over financial reporting, management concluded that, as of December 31, 2021, our internal control over financial reporting was effective.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) 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 Independent Registered Public Accounting Firm

Our independent registered public accounting firm, Ernst & Young LLP, has audited our Financial Statements included in Item 8 of this Annual Report on Form 10-K and have issued a report on our internal control over financial reporting as of December 31, 2021. Their report on the audit of internal control over financial reporting appears below.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Ardelyx, Inc.
Opinion on Internal Control over Financial Reporting

We have audited Ardelyx, 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, Ardelyx, 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 balance sheets of the Company as of December 31, 2021 and 2020, the related statements of operations and comprehensive loss, stockholders' equity, 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 that included an explanatory paragraph regarding the Company's ability to continue as a going concern.

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

Redwood City, California

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

Information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission on Schedule 14A in connection with our 2022 Annual Meeting of Stockholders (the "Proxy Statement"), which will be filed not later than 120 days after the end of our fiscal year ended December 31, 2021, under the headings "Executive Officers," "Election of Directors," "Corporate Governance," and " Section 16(a) Beneficial Ownership Reporting Compliance," and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics that applies to our officers, directors and employees which is available on our website at www.ardelyx.com. The Code of Business Conduct and Ethics is intended to qualify as a "code of ethics" within the meaning of Section 406 of the Sarbanes-Oxley Act of 2002 and Item 406 of Regulation S-K. In addition, we intend to promptly disclose (1) the nature of any amendment to our Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and (2) the nature of any waiver, including an implicit waiver, from a provision of our code of ethics that is granted to one of these specified officers, the name of such person who is granted the waiver and the date of the waiver on our website in the future.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item regarding executive compensation will be incorporated by reference to the information set forth in the sections titled "Executive Compensation" in our Proxy Statement.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this item regarding security ownership of certain beneficial owners and management will be incorporated by reference to the information set forth in the section titled "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" in our Proxy Statement.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this item regarding certain relationships and related transactions and director independence will be incorporated by reference to the information set forth in the sections titled "Certain Relationships and Related Party Transactions" and "Election of Directors", respectively, in our Proxy Statement.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by this item regarding principal accountant fees and services will be incorporated by reference to the information set forth in the section titled "Principal Accountant Fees and Services" in our Proxy Statement.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

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

1. Financial Statements

See Index to Financial Statements at Item 8 herein.

2. Financial Statement Schedules

All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

3. Exhibits

See the Exhibit Index immediately following this page.

ITEM 16. FORM 10-K SUMMARY

None.

Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
3.1	Amended and Restated Certificate of Incorporation	8-K	6/24/2014	3.1	
3.2	Amended and Restated Bylaws	8-K	6/24/2014	3.2	
4.1	Reference is made to Exhibits 3.1 and 3.2				
4.2	Form of Common Stock Certificate	S-1/A	6/18/2014	4.2	
4.4	Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934	10-K	3/8/2021	4.4	
10.1	Termination Agreement, dated June 2, 2015, by and between AstraZeneca AB and Ardelyx, Inc.	10-Q	8/12/2015	10.1	
10.2	Amendment No. 1 to Termination Agreement and to Manufacturing and Supply Agreement, dated November 2, 2015 by and between AstraZeneca AB and Ardelyx, Inc.	10-K	3/4/2016	10.1(d)	
10.3(a)	Lease, dated August 8, 2008, by and between 34175 Ardenwood Venture, LLC and Ardelyx, Inc.	S-1	5/19/2014	10.4(a)	
10.3(b)	First Amendment to Lease, dated December 20, 2012, by and between 34175 Ardenwood Venture, LLC and Ardelyx, Inc.	S-1	5/19/2014	10.4(b)	
10.3(c)	Second Amendment to Lease, dated September 5, 2014, by and between Ardelyx, Inc. and 34175 Ardenwood Venture, LLC	8-K	9/9/2014	10.1	
10.3(d)	Third Amendment to Lease, dated April 28, 2016, by and between Ardelyx, Inc. and 34175 Ardenwood Venture, LLC	10-Q	8/8/2016	10.3	
10.3(e)	Fifth Amendment to Lease, dated May 25, 2021, by and between Ardelyx, Inc. and 34175 Ardenwood Venture, LLC	8-K	6/1/2021	10.1	
10.4(a)#	Ardelyx, Inc. 2008 Stock Incentive Plan, as amended	S-1	5/19/2014	10.5(a)	
10.4(b)#	Form of Stock Option Grant Notice and Stock Option Agreement under the 2008 Stock Incentive Plan, as amended	S-1	5/19/2014	10.5(b)	
10.4(c)#	Form of Restricted Stock Purchase Grant Notice and Restricted Stock Purchase Agreement under the 2008 Stock Incentive Plan, as amended	S-1	5/19/2014	10.5(c)	
10.5(a)#	Ardelyx, Inc. 2014 Equity Incentive Award Plan	S-8	7/14/2014	99.3	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.5(b)#	Form of Stock Option Grant Notice and Stock Option Agreement under the 2014 Equity Incentive Award Plan	S-1/A	6/9/2014	10.6(b)	
10.5(c)#	Form of Restricted Stock Award Agreement and Restricted Stock Unit Award Grant Notice under the 2014 Equity Incentive Award Plan	S-1/A	6/9/2014	10.6(c)	
10.6#	Form of Indemnification Agreement for directors and officers	S-1/A	6/9/2014	10.7	
10.7#	Amended and Restated Executive Employment Agreement, dated June 6, 2014, by and between Ardelyx, Inc. and Michael Raab	S-1/A	6/9/2014	10.8	
10.8#	Retention Agreement, dated October 25, 2021, by and between Ardelyx, Inc. and Mike Raab				X
10.9#	Offer Letter, dated December 28, 2009, by and between Ardelyx, Inc. and David Rosenbaum, Ph.D.	S-1/A	6/9/2014	10.13	
10.11#	Second Amended and Restated Change in Control and Severance Agreement by and between Ardelyx, Inc. and David P. Rosenbaum, Ph.D.	10-Q	5/8/2018	10.10	
10.12#	Offer Letter, dated November 21, 2012, by and between Ardelyx, Inc. and Elizabeth Grammer, Esq.	S-1/A	6/9/2014	10.14	
10.13#	Second Amended and Restated Change in Control and Severance Agreement by and between Ardelyx, Inc. and Elizabeth Grammer.	10-Q	5/8/2018	10.00	
10.14#	Offer Letter, dated April 27, 2020, by and between Ardelyx, Inc. and Susan Rodriguez	10-Q	8/6/2020	10.10	
10.15#	Change in Control Severance Agreement dated June 2, 2020, by and between Ardelyx, Inc. and Susan Rodriguez	10-Q	8/6/2020	0.01	
10.16#	Retention Agreement, dated October 25, 2021, by and between Ardelyx, Inc. and Susan Rodriguez				X
10.17#	Offer Letter, dated June 2, 2020, by and between Ardelyx, Inc. and Justin Renz	10-Q	8/6/2020	10.30	
10.18#	Change in Control Severance Agreement, dated June 8, 2020, by and between Ardelyx, Inc. and Justin Renz	10-Q	8/6/2020	10.40	
10.19#	Retention Agreement, dated October 25, 2021, by and between Ardelyx, Inc. and Justin Renz				X
10.20#	Amendment Number One to Second Amended and Restated Change in Control Severance Agreement and Retention Agreement dated December 1, 2021 between Ardelyx, Inc. and David Rosenbaum				X
10.21#	Form of Executive Retention Agreement Version 1				X
10.22#	Form of Executive Retention Agreement Version 2				X
10.23#	Ardelyx, Inc. 2014 Employee Stock Purchase Plan	S-8	7/14/2014	99.6	
10.24(a)#	Non-Employee Director Compensation Program	S-1/A	6/9/2014	10.21	
10.24(b)#	Description of amendments to Non-Employee Director Compensation Program	8-K	3/9/2017	N/A	
10.24(c)#	Amended and Restated Non-Employee Director Compensation Program.	10-Q	5/7/2019	10.1	
10.25	Registration Rights Agreement by and among Ardelyx, Inc. and the investors signatory thereto, dated June 2, 2015	S-3	7/13/2015	99.1	
10.26	Registration Rights Agreement by and among Ardelyx, Inc. and the investors signatory thereto, dated July 14, 2016	10-Q	8/8/2016	10.2	
10.27(a)#	Ardelyx, Inc. 2016 Employment Commencement Incentive Plan	S-8	11/10/2016	99.1	
10.27(b)#	Form of Stock Option Grant Notice and Stock Option Agreement under the 2016 Employment Commencement Incentive Plan	S-8	11/10/2016	99.2	
10.27(c)#	Form of Restricted Stock Unit Award Grant Notice and Restricted Stock Unit Award Agreement under the 2016 Employment Commencement Incentive Plan	S-8	11/10/2016	99.3	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.27(d)#	Form of Restricted Stock Award Grant Notice and Restricted Stock Award Agreement under the 2016 Employment Commencement Incentive Plan	S-8	11/10/2016	99.4	
10.28††	License Agreement, dated November 27, 2017, by and between Kyowa Hakko Kirin Co. , Ltd. and Ardelyx, Inc.	10-K	3/14/2018	10.35	
10.29††	License Agreement, dated December 11, 2017, by and between Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd. and Ardelyx, Inc.	10-K	3/14/2018	10.36	
10.30	Exit Fee Agreement, dated May 16, 2018, by and between the Company and Solar Capital Ltd. and Western Alliance Bank.	10-Q	8/7/2018	10.2	
10.31††	Manufacturing Services Agreement, dated May 18, 2020, between Ardelyx, Inc. and Patheon Pharmaceuticals Inc.	10-Q	8/6/2020	10.5	
10.32	Lease Agreement, dated December 30, 2020, by and between Ardelyx, Inc. and Prospect Fifth Ave, LLC.	10-K	3/8/2021	10.31	
10.33	Open Market Sales Agreement, dated August 31, 2021 between Ardelyx, Inc. and Jefferies LLC.	8-K	8/17/2021	10.1	
23.1	Consent of Independent Registered Public Accounting Firm			—	X
31.1	Certification of Principal Executive Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended			—	X
31.2	Certification of Principal Financial Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended			—	X
32.1	Certification of Principal Executive Officer and Principal Financial Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C §1350			—	X
101.SCH	Inline XBRL Taxonomy Extension Schema Document			—	X
101.CAL	Inline XBRL Taxonomy Extension 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 XBRL Taxonomy Extension Presentation Linkbase Document			—	X

† Confidential treatment granted as to portions of this Exhibit. The confidential portions of this Exhibit have been omitted and are marked by asterisks.

†† Certain portions have been omitted pursuant to a confidential treatment request. Omitted information has been filed separately with the Securities and Exchange Commission.

# Indicates management contract or compensatory plan.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Ardelyx, Inc.

Date: February 28, 2022

By: /s/ Michael Raab

Michael Raab
President Chief Executive Officer and Director
(Principal Executive Officer)

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Michael Raab and Justin Renz, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this annual report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

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

Signature	Title	Date
/s/ Michael Raab Michael Raab	President, Chief Executive Officer and Director *(Principal Executive Officer)*	February 28, 2022
/s/ Justin Renz Justin Renz	Chief Financial Officer *(Principal Financial and Accounting Officer)*	February 28, 2022
/s/ David Mott David Mott	Chairman of the Board of Directors	February 28, 2022
/s/ Robert Bazemore Robert Bazemore	Director	February 28, 2022
/s/ William Bertrand, Jr. William Bertrand, Jr., J.D.	Director	February 28, 2022
/s/ Muna Bhanji Muna Bhanji, R.Ph	Director	February 28, 2022
/s/ Geoffrey A. Block Geoffrey A. Block, M.D.	Director	February 28, 2022
/s/ Onaiza Cadoret-Manier Onaiza Cadoret-Manier	Director	February 28, 2022
/s/ Jan M. Lundberg Jan M. Lundberg, Ph.D.	Director	February 28, 2022
/s/ Richard Rodgers Richard Rodgers	Director	February 28, 2022

RETENTION AGREEMENT

This Retention Agreement ("Agreement") is made and entered into by and between Ardelyx, Inc. ("Company") and Michael Raab ("Executive"), effective as of October 25, 2021 ("Effective Date").

Recitals

A. The Company and the Board of Directors of the Company ("Board") has determined that it is in the best interests of the Company and its stockholders to execute a second reduction in force in order to reduce operating costs and better align the Company's workforce with the needs of the business following the receipt of a complete response letter ("CRL") from the U.S. Food and Drug Administration ("FDA") on July 28, 2021.

B. The Board has determined that it is in the best interests of the Company and the stockholders to put in place arrangements designed to provide that the Company will have the continued dedication and commitment of Executive, notwithstanding the reduction in force, and to provide Executive with an incentive to continue Executive's employment and further align Executive's incentives to maximize the value of the Company for the benefit of its stockholders.

C. The Executive and the Company are parties to that certain Executive Employment Agreement dated as of February 17, 2009 ("Severance Agreement"). Capitalized terms not defined herein shall have the meaning assigned to them in the Severance Agreement.

The parties hereto agree as follows:

1 **Severance Agreement.** Except as specifically modified by the provisions of this Agreement, the Severance Agreement shall remain in full force and effect.

2 **2021 Annual Bonus.**

The Compensation Committee of the Board previously set the Executive's annual target bonus for fiscal year 2021 at an amount equal to sixty percent (60%) of the Executive's base salary ("2021 Annual Bonus"). As an incentive to continue Executive's employment with the Company, subject to the terms of this Agreement, the Executive's 2021 Annual Bonus shall be earned and paid as follows: (a) fifty percent (50%) of the 2021 Annual Bonus shall be earned on the date in January 2022 when the Company pays annual bonuses to its employees, and (b) fifty percent (50%) of the 2021 Annual Bonus shall be earned following the achievement of the 2021 Annual Bonus milestone described on **Exhibit A** hereto; *provided*, *however,* that the second fifty percent (50%) of the 2021 Annual Bonus will not be earned earlier than April 1, 2022.

The Executive shall not earn a portion of the 2021 Annual Bonus if the Executive voluntarily terminates his employment with the Company for any reason or the Company terminates his employment for Cause prior to the date that such portion of the 2021 Annual Bonus is earned.

Each portion of the 2021 Annual Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

3 **Restricted Stock Unit**

On October 8, 2021, the Company granted the Executive 300,000 restricted stock units ("RSUs"). The Executive has been or will be provided with a Restricted Stock Unit Award Grant Notice ("Notice") which sets forth the details of the RSUs and provides the terms and conditions of the grant. Subject to the provisions of this Agreement and the Notice, the RSUs will vest in full on the earliest of (a) June 1, 2022, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause , in each case, subject to the Executive remaining an employee of the Company through such applicable vesting date.

4 **Cash Bonus**

The Executive shall earn a retention bonus in the aggregate amount of $300,000, subject to applicable tax withholding ("Cash Bonus") on the earliest of (a) the date of the achievement of the Cash Bonus milestone set forth on **Exhibit A**, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause, subject to the Executive's continued employment with the Company through such earliest date.

The Executive shall not earn the Cash Bonus if the Executive voluntarily terminates his employment with the Company or the Company terminates the Executive's employment for Cause prior to the date that the Cash Bonus is earned.

The Cash Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

5 **Nature of Agreement** This Agreement is not a contract of employment for any specified term. Nothing contained in this Agreement shall confer upon Executive any right to continue in the employ of the Company or interfere in any way with the at-will nature of Executive's employment with the Company (it being understood and agreed that (so long as it is done in accordance with applicable law) the Company may terminate Executive's employment at any time for any reason or for no reason and that Executive may terminate his/her employment with the Company at any time for any reason or for no reason).

6 **Full Agreement** This Agreement, together with the Notice and the Severance Agreement referenced herein constitutes the entire agreement of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous discussions, negotiations, or understandings, written or oral, relating thereto. This Agreement may not be amended or modified except in a writing signed by both Executive and an authorized representative of the Company.

7 **Successors**

Any successor to the Company (whether direct or indirect and whether by purchase, merger, consolidation, liquidation or otherwise) to all or substantially all of the Company's business and/or assets shall assume the obligations under this Agreement and agree expressly to perform the obligations under this Agreement in the same manner and to the same extent as the Company would be required to perform such obligations in the absence of a succession. For all purposes under this Agreement, the term "Company" shall include any successor to the Company's business and/or assets which executes and delivers the assumption agreement described in the Severance Agreement or which becomes bound by the terms of this Agreement by operation of law.

The terms of this Agreement and all rights of Executive hereunder shall inure to the benefit of, and be enforceable by, Executive's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees.

8 **Choice of Law and Severability** The validity, interpretation, construction and performance of this Agreement shall be governed by the laws of the State of California. The invalidity or unenforceability of any provision or provisions of this Agreement shall not affect the validity or enforceability of any other provision hereof, which shall remain in full force and effect.

9 **Date of Signature** This Agreement shall be conveyed to Executive via DocuSign and in order to be effective, it must be signed by Executive and delivered to the Company no later than November 15, 2021. Executive may elect to electronically execute this Agreement using the DocuSign link provided, in which case this Agreement shall be automatically delivered to Kelli Shaa and Mishu Nitulescu in Human Resources upon execution. Alternatively, Executive may elect to manually sign this Agreement provided that such signature is delivered to Kelli Shaa in Human Resources no later than November 15, 2021.

Michael Raab	Ardelyx, Inc.
/s/ Michael Raab Signature	By:/s/ Elizabeth Grammer
October 23, 2021 Dated	Title: Chief Legal and Administrative Officer
	Dated:October 23, 2021

RETENTION AGREEMENT

This Retention Agreement ("Agreement") is made and entered into by and between Ardelyx, Inc. ("Company") and Susan Rodriguez ("Executive"), effective as of October 25, 2021 ("Effective Date").

Recitals

A. The Company and the Board of Directors of the Company ("Board") has determined that it is in the best interests of the Company and its stockholders to execute a second reduction in force in order to reduce operating costs and better align the Company's workforce with the needs of the business following the receipt of a complete response letter ("CRL") from the U.S. Food and Drug Administration ("FDA") on July 28, 2021.

B. The Board has determined that it is in the best interests of the Company and the stockholders to put in place arrangements designed to provide that the Company will have the continued dedication and commitment of Executive, notwithstanding the reduction in force, and to provide Executive with an incentive to continue Executive's employment and further align Executive's incentives to maximize the value of the Company for the benefit of its stockholders.

C. The Executive and the Company are parties to that certain Change in Control Severance Agreement dated as of May 18, 2020 ("Severance Agreement"). Capitalized terms not defined herein shall have the meaning assigned to them in the Severance Agreement.

The parties hereto agree as follows:

1 **Severance Agreement.** Except as specifically modified by the provisions of this Agreement, the Severance Agreement shall remain in full force and effect.

2 **2021 Annual Bonus.**

The Compensation Committee of the Board previously set the Executive's annual target bonus for fiscal year 2021 at an amount equal to forty percent (40%) of the Executive's base salary ("2021 Annual Bonus"). As an incentive to continue Executive's employment with the Company, subject to the terms of this Agreement, the Executive's 2021 Annual Bonus shall be earned and paid as follows: (a) fifty percent (50%) of the 2021 Annual Bonus shall be earned on the date in January 2022 when the Company pays annual bonuses to its employees, and (b) fifty percent (50%) of the 2021 Annual Bonus shall be earned following the achievement of the 2021 Annual Bonus milestone described on **Exhibit A** hereto; *provided*, *however,* that the second fifty percent (50%) of the 2021 Annual Bonus will not be earned earlier than April 1, 2022.

The Executive shall not earn a portion of the 2021 Annual Bonus if the Executive voluntarily terminates her employment with the Company for any reason or the Company terminates her employment for Cause prior to the date that such portion of the 2021 Annual Bonus is earned.

Each portion of the 2021 Annual Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

3 **Restricted Stock Unit**

On October 8, 2021, the Company granted the Executive 150,000 restricted stock units ("RSUs"). The Executive has been or will be provided with a Restricted Stock Unit Award Grant Notice ("Notice") which sets forth the details of the RSUs and provides the terms and conditions of the grant. Subject to the provisions of this Agreement and the Notice, the RSUs will vest in full on the earliest of (a) June 1, 2022, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause , in each case, subject to the Executive remaining an employee of the Company through such applicable vesting date.

4 **Cash Bonus**

The Executive shall earn a retention bonus in the aggregate amount of $150,000, subject to applicable tax withholding ("Cash Bonus") on the earliest of (a) the date of the achievement of the Cash Bonus milestone set forth on **Exhibit A**, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause, subject to the Executive's continued employment with the Company through such earliest date.

The Executive shall not earn the Cash Bonus if the Executive voluntarily terminates her employment with the Company or the Company terminates the Executive's employment for Cause prior to the date that the Cash Bonus is earned.

The Cash Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

5 **Nature of Agreement** This Agreement is not a contract of employment for any specified term. Nothing contained in this Agreement shall confer upon Executive any right to continue in the employ of the Company or interfere in any way with the at-will nature of Executive's employment with the Company (it being understood and agreed that (so long as it is done in accordance with applicable law) the Company may terminate Executive's employment at any time for any reason or for no reason and that Executive may terminate his/her employment with the Company at any time for any reason or for no reason).

6 **Full Agreement** This Agreement, together with the Notice and the Severance Agreement referenced herein constitutes the entire agreement of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous discussions, negotiations, or understandings, written or oral, relating thereto. This Agreement may not be amended or modified except in a writing signed by both Executive and an authorized representative of the Company.

7 **Successors**

Any successor to the Company (whether direct or indirect and whether by purchase, merger, consolidation, liquidation or otherwise) to all or substantially all of the Company's business and/or assets shall assume the obligations under this Agreement and agree expressly to perform the obligations under this Agreement in the same manner and to the same extent as the Company would be required to perform such obligations in the absence of a succession. For all purposes under this Agreement, the term "Company" shall include any successor to the Company's business and/or assets which executes and delivers the assumption agreement described in the Severance Agreement or which becomes bound by the terms of this Agreement by operation of law.

The terms of this Agreement and all rights of Executive hereunder shall inure to the benefit of, and be enforceable by, Executive's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees.

8 **Choice of Law and Severability** The validity, interpretation, construction and performance of this Agreement shall be governed by the laws of the State of California. The invalidity or unenforceability of any provision or provisions of this Agreement shall not affect the validity or enforceability of any other provision hereof, which shall remain in full force and effect.

9 **Date of Signature** This Agreement shall be conveyed to Executive via DocuSign and in order to be effective, it must be signed by Executive and delivered to the Company no later than November 15, 2021. Executive may elect to electronically execute this Agreement using the DocuSign link provided, in which case this Agreement shall be automatically delivered to Kelli Shaa and Mishu Nitulescu in Human Resources upon execution. Alternatively, Executive may elect to manually sign this Agreement provided that such signature is delivered to Kelli Shaa in Human Resources no later than November 15, 2021.

Susan Rodriguez	Ardelyx, Inc.
/s/ Susan Rodriguez Signature	By: /s/ Michael Raab
October 25, 2021 Dated	Title: Chief Executive Officer
	Dated: October 23, 2021

RETENTION AGREEMENT

This Retention Agreement ("Agreement") is made and entered into by and between Ardelyx, Inc. ("Company") and Justin Renz ("Executive"), effective as of October 25, 2021 ("Effective Date").

Recitals

A. The Company and the Board of Directors of the Company ("Board") has determined that it is in the best interests of the Company and its stockholders to execute a second reduction in force in order to reduce operating costs and better align the Company's workforce with the needs of the business following the receipt of a complete response letter ("CRL") from the U.S. Food and Drug Administration ("FDA") on July 28, 2021.

B. The Board has determined that it is in the best interests of the Company and the stockholders to put in place arrangements designed to provide that the Company will have the continued dedication and commitment of Executive, notwithstanding the reduction in force, and to provide Executive with an incentive to continue Executive's employment and further align Executive's incentives to maximize the value of the Company for the benefit of its stockholders.

C. The Executive and the Company are parties to that certain Second Amended and Restated Change in Control Severance Agreement dated as of March 9, 2021 ("Severance Agreement"). Capitalized terms not defined herein shall have the meaning assigned to them in the Severance Agreement.

The parties hereto agree as follows:

1 **Severance Agreement.** Except as specifically modified by the provisions of this Agreement, the Severance Agreement shall remain in full force and effect.

2 **2021 Annual Bonus.**

The Compensation Committee of the Board previously set the Executive's annual target bonus for fiscal year 2021 at an amount equal to forty percent (40%) of the Executive's base salary ("2021 Annual Bonus"). As an incentive to continue Executive's employment with the Company, subject to the terms of this Agreement, the Executive's 2021 Annual Bonus shall be earned and paid as follows: (a) fifty percent (50%) of the 2021 Annual Bonus shall be earned on the date in January 2022 when the Company pays annual bonuses to its employees, and (b) fifty percent (50%) of the 2021 Annual Bonus shall be earned following the achievement of the 2021 Annual Bonus milestone described on **Exhibit A** hereto; *provided*, *however,* that the second fifty percent (50%) of the 2021 Annual Bonus will not be earned earlier than April 1, 2022.

The Executive shall not earn a portion of the 2021 Annual Bonus if the Executive voluntarily terminates his employment with the Company for any reason or the Company terminates his employment for Cause prior to the date that such portion of the 2021 Annual Bonus is earned.

Each portion of the 2021 Annual Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

3 **Restricted Stock Unit**

On October 8, 2021, the Company granted the Executive 250,000 restricted stock units ("RSUs"). The Executive has been or will be provided with a Restricted Stock Unit Award Grant Notice ("Notice") which sets forth the details of the RSUs and provides the terms and conditions of the grant. Subject to the provisions of this Agreement and the Notice, the RSUs will vest in full on the earliest of (a) June 1, 2022, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause , in each case, subject to the Executive remaining an employee of the Company through such applicable vesting date.

4 **Cash Bonus**

The Executive shall earn a retention bonus in the aggregate amount of $250,000, subject to applicable tax withholding ("Cash Bonus") on the earliest of (a) the date of the achievement of the Cash Bonus milestone set forth on **Exhibit A**, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause, subject to the Executive's continued employment with the Company through such earliest date.

The Executive shall not earn the Cash Bonus if the Executive voluntarily terminates his employment with the Company or the Company terminates the Executive's employment for Cause prior to the date that the Cash Bonus is earned.

The Cash Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

5 **Nature of Agreement** This Agreement is not a contract of employment for any specified term. Nothing contained in this Agreement shall confer upon Executive any right to continue in the employ of the Company or interfere in any way with the at-will nature of Executive's employment with the Company (it being understood and agreed that (so long as it is done in accordance with applicable law) the Company may terminate Executive's employment at any time for any reason or for no reason and that Executive may terminate his/her employment with the Company at any time for any reason or for no reason).

6 **Full Agreement** This Agreement, together with the Notice and the Severance Agreement referenced herein constitutes the entire agreement of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous discussions, negotiations, or understandings, written or oral, relating thereto. This Agreement may not be amended or modified except in a writing signed by both Executive and an authorized representative of the Company.

7 **Successors**

Any successor to the Company (whether direct or indirect and whether by purchase, merger, consolidation, liquidation or otherwise) to all or substantially all of the Company's business and/or assets shall assume the obligations under this Agreement and agree expressly to perform the obligations under this Agreement in the same manner and to the same extent as the Company would be required to perform such obligations in the absence of a succession. For all purposes under this Agreement, the term "Company" shall include any successor to the Company's business and/or assets which executes and delivers the assumption agreement described in the Severance Agreement or which becomes bound by

the terms of this Agreement by operation of law.

The terms of this Agreement and all rights of Executive hereunder shall inure to the benefit of, and be enforceable by, Executive's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees.

8 **Choice of Law and Severability** The validity, interpretation, construction and performance of this Agreement shall be governed by the laws of the State of California. The invalidity or unenforceability of any provision or provisions of this Agreement shall not affect the validity or enforceability of any other provision hereof, which shall remain in full force and effect.

9 **Date of Signature** This Agreement shall be conveyed to Executive via DocuSign and in order to be effective, it must be signed by Executive and delivered to the Company no later than November 15, 2021. Executive may elect to electronically execute this Agreement using the DocuSign link provided, in which case this Agreement shall be automatically delivered to Kelli Shaa and Mishu Nitulescu in Human Resources upon execution. Alternatively, Executive may elect to manually sign this Agreement provided that such signature is delivered to Kelli Shaa in Human Resources no later than November 15, 2021.

Justin Renz	Ardelyx, Inc.
/s/ Justin Renz Signature	By: /s/ Michael Raab
	Title: Chief Executive Officer
Dated: October 24, 2021	Dated: October 23, 2021

Amendment Number One
To
Second Amended and Restated Change in Control Severance Agreement and to Retention Agreement

This Amendment Number One to Second Amended and Restated Change in Control Severance Agreement and to Retention Agreement ("Amendment Number One") is made and entered into this first day of December, 2021, by and between David P. Rosenbaum (the "Executive") and Ardelyx, Inc. (the "Company").

Whereas, the Company and the Executive are parties to that certain Second Amended and Restated Change in Control Severance Agreement made and entered into the 7th day of May 2018 (the "Agreement");

Whereas, the Company and the Executive are parties to that certain Retention Agreement made and entered into the 23rd day of October 2021 (the "Retention Agreement"); and

Whereas, the Board of Directors of the Company (the "Board") has determined that it is in the best interest of the Company and the stockholders to amend the Agreement and the Retention Agreement in order to ensure that the Company will continue to have the dedication and commitment of the Executive and to provide the Executive with an incentive to continue Executive's employment and further align Executive's incentives to maximize the value of the Company for the benefit of its stockholders;

The parties hereto agree as follows:

1. **Definition of Covered Termination**. The definition of Covered Termination set forth in Section 7 (e) of the Agreement shall be revised to read in full as follows:

   (e) Covered Termination. "Covered Termination" means (a) Executive's voluntary resignation for any reason; provided that (i) written notice of such voluntary resignation is delivered in writing to the Company in the sixty (60) day period after the Cash Bonus (as defined in the Retention Agreement) is earned by the Executive and (ii) such resignation is effective no later than February 15 of the year following the year in which the Cash Bonus is earned (it being understood that the effective resignation timing requirement of subclause (ii) may require written notice to be provided earlier than would otherwise apply under subclause (i)); (b) an Involuntary Termination Without Cause; or (c) a Voluntary Resignation for Good Reason, provided that such termination or resignation constitutes a Separation from Service.
2. **Timing of Effective and Irrevocable Delivery of Release of Claims.** The initial clause of each of Section 3 and Section 4 of the Agreement shall be modified in their entirety as set forth below. The remaining provisions of each of Section 3 and Section 4 shall remain unchanged.
   a. 3. **Covered Termination Other Than During a Change in Control Period.** If Executive experiences a Covered Termination other than during a Change in Control Period, and if Executive delivers to the Company a general release of all claims against the Company and its affiliates in a form acceptable to the Company ("a **Release of Claims**") that becomes effective and irrevocable within twenty-eight (28) days, or such shorter period of time specified by the Company, following such Covered Termination, then in addition to any accrued but unpaid salary, bonus, vacation and expense reimbursement payable in accordance with applicable law, the Company shall provide Executive with the following:"
   b. 4. **Covered Termination During a Change in Control Period.** If Executive experiences a Covered Termination during a Change in Control Period, and if Executive delivers to the Company a Release of Claims that becomes effective and irrevocable within twenty-eight (28) days, or such shorter period of time specified by the Company, following such Covered Termination, then in addition to any accrued but unpaid salary,

bonus, vacation and expense reimbursement payable in accordance with applicable law, the Company shall provide Executive with the following:"

3. **Other Changes.** Except as set forth in this Amendment Number One, the Agreement remains unchanged and in full force and effect. The Retention Agreement is amended as set forth below and except for this Amendment Number One, remains unchanged and in full force and effect.

    a. Section 1, Severance Agreement, now provides: "The Severance Agreement shall remain in full force and effect, except as modified by Amendment Number One to the Severance Agreement, executed on December 1, 2021."

    b. Section 2, Annual Bonus. The second paragraph shall be modified with the addition of the following: "The Executive shall earn and receive such portion of the 2021 Annual Bonus if the Company terminates the Executive's employment without cause before such portion is otherwise earned."

    c. Section 6, Full Agreement. The initial sentence shall be modified in its entirety by replacing it with the following: "This Agreement, together with the Notice and the Severance Agreement referenced herein, as modified by Amendment Number One executed on December 1, 2021, constitutes the entire agreement of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous discussions, negotiations, or understandings, written or oral, relating thereto." The second sentence in Section 6 remains unchanged.

4. **Governing Law.** The validity, interpretation, construction and performance of this Amendment Number One shall be governed by the laws of the State of California.

5. **Miscellaneous**. This Amendment Number One may be signed by facsimile and in one or more counterparts, each of which shall be deemed an original but all of which shall be deemed to constitute a single instrument. Signatures of the parties transmitted by facsimile, PDF or other electronic file shall be deemed to be their original signatures for all purposes and the exchange of copies of this agreement and of signature pages by facsimile transmission, PDF or other electronic file shall constitute effective execution and delivery of this letter agreement as to the parties and may be used in lieu of the original agreement for all purposes.

IN WITNESS WHEREOF, each of the parties has executed this Amendment Number One, in the case of the Company, by its duly authorized officer, as of the day and year set forth above.

ARDELYX, INC.

By: /s/ Michael Raab

Title: Chief Executive Officer

Date: December 1, 2021

EXECUTIVE

/s/ David P. Rosenbaum

David P. Rosenbaum

Date: December 1, 2021

RETENTION AGREEMENT

This Retention Agreement ("Agreement") is made and entered into by and between Ardelyx, Inc. ("Company") and _____ ("Executive"), effective as of October 25, 2021 ("Effective Date").

Recitals

A. The Company and the Board of Directors of the Company ("Board") has determined that it is in the best interests of the Company and its stockholders to execute a second reduction in force in order to reduce operating costs and better align the Company's workforce with the needs of the business following the receipt of a complete response letter ("CRL") from the U.S. Food and Drug Administration ("FDA") on July 28, 2021.

B. The Board has determined that it is in the best interests of the Company and the stockholders to put in place arrangements designed to provide that the Company will have the continued dedication and commitment of Executive, notwithstanding the reduction in force, and to provide Executive with an incentive to continue Executive's employment and further align Executive's incentives to maximize the value of the Company for the benefit of its stockholders.

C. The Executive and the Company are parties to that certain _____("Severance Agreement"). Capitalized terms not defined herein shall have the meaning assigned to them in the Severance Agreement.

The parties hereto agree as follows:

1 **Severance Agreement.** Except as specifically modified by the provisions of this Agreement, the Severance Agreement shall remain in full force and effect.

2 **2021 Annual Bonus.**

The Compensation Committee of the Board previously set the Executive's annual target bonus for fiscal year 2021 at an amount equal to forty percent (40%) of the Executive's base salary ("2021 Annual Bonus"). As an incentive to continue Executive's employment with the Company, subject to the terms of this Agreement, the Executive's 2021 Annual Bonus shall be earned and paid as follows: (a) fifty percent (50%) of the 2021 Annual Bonus shall be earned on the date in January 2022 when the Company pays annual bonuses to its employees, and (b) fifty percent (50%) of the 2021 Annual Bonus shall be earned following the achievement of the 2021 Annual Bonus milestone described on **Exhibit A** hereto; *provided, however,* that the second fifty percent (50%) of the 2021 Annual Bonus will not be earned earlier than April 1, 2022.

The Executive shall not earn a portion of the 2021 Annual Bonus if the Executive voluntarily terminates his employment with the Company for any reason or the Company terminates his employment for Cause prior to the date that such portion of the 2021 Annual Bonus is earned.

Each portion of the 2021 Annual Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

3 **Restricted Stock Unit**

On October 8, 2021, the Company granted the Executive 250,000 restricted stock units ("RSUs"). The Executive has been or will be provided with a Restricted Stock Unit Award Grant Notice ("Notice") which sets forth the details of the RSUs and provides the terms and conditions of the grant. Subject to the provisions of this Agreement and the Notice, the RSUs will vest in full on the earliest of (a) June 1, 2022, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause , in each case, subject to the Executive remaining an employee of the Company through such applicable vesting date.

4 **Cash Bonus**

The Executive shall earn a retention bonus in the aggregate amount of $250,000, subject to applicable tax withholding ("Cash Bonus") on the earliest of (a) the date of the achievement of the Cash Bonus milestone set forth on **Exhibit A**, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause, subject to the Executive's continued employment with the Company through such earliest date.

The Executive shall not earn the Cash Bonus if the Executive voluntarily terminates his employment with the Company or the Company terminates the Executive's employment for Cause prior to the date that the Cash Bonus is earned.

The Cash Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

5 **Nature of Agreement** This Agreement is not a contract of employment for any specified term. Nothing contained in this Agreement shall confer upon Executive any right to continue in the employ of the Company or interfere in any way with the at-will nature of Executive's employment with the Company (it being understood and agreed that (so long as it is done in accordance with applicable law) the Company may terminate Executive's employment at any time for any reason or for no reason and that Executive may terminate his/her employment with the Company at any time for any reason or for no reason).

6 **Full Agreement** This Agreement, together with the Notice and the Severance Agreement referenced herein constitutes the entire agreement of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous discussions, negotiations, or understandings, written or oral, relating thereto. This Agreement may not be amended or modified except in a writing signed by both Executive and an authorized representative of the Company.

7 **Successors**

Any successor to the Company (whether direct or indirect and whether by purchase, merger, consolidation, liquidation or otherwise) to all or substantially all of the Company's business and/or assets shall assume the obligations under this Agreement and agree expressly to perform the obligations under this Agreement in the same manner and to the same extent as the Company would be required to perform such obligations in the absence of a succession. For all purposes under this Agreement, the term "Company" shall include any successor to the Company's business and/or assets which executes and delivers the assumption agreement described in the Severance Agreement or which becomes bound by the terms of this Agreement by operation of law.

The terms of this Agreement and all rights of Executive hereunder shall inure to the benefit of, and be enforceable by, Executive's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees.

8 **Choice of Law and Severability** The validity, interpretation, construction and performance of this Agreement shall be governed by the laws of the State of California. The invalidity or unenforceability of any provision or provisions of this Agreement shall not affect the validity or enforceability of any other provision hereof, which shall remain in full force and effect.

9 **Date of Signature** This Agreement shall be conveyed to Executive via DocuSign and in order to be effective, it must be signed by Executive and delivered to the Company no later than November 15, 2021. Executive may elect to electronically execute this Agreement using the DocuSign link provided, in which case this Agreement shall be automatically delivered to Kelli Shaa and Mishu Nitulescu in Human Resources upon execution. Alternatively, Executive may elect to manually sign this Agreement provided that such signature is delivered to Kelli Shaa in Human Resources no later than November 15, 2021.

Executive	Ardelyx, Inc.
_____ Signature	By:_____
_____ Dated	Title: Chief Executive Officer
	Dated:_____

RETENTION AGREEMENT

This Retention Agreement ("Agreement") is made and entered into by and between Ardelyx, Inc. ("Company") and _____ ("Executive"), effective as of October 25, 2021 ("Effective Date").

Recitals

A. The Company and the Board of Directors of the Company ("Board") has determined that it is in the best interests of the Company and its stockholders to execute a second reduction in force in order to reduce operating costs and better align the Company's workforce with the needs of the business following the receipt of a complete response letter ("CRL") from the U.S. Food and Drug Administration ("FDA") on July 28, 2021.

B. The Board has determined that it is in the best interests of the Company and the stockholders to put in place arrangements designed to provide that the Company will have the continued dedication and commitment of Executive, notwithstanding the reduction in force, and to provide Executive with an incentive to continue Executive's employment and further align Executive's incentives to maximize the value of the Company for the benefit of its stockholders.

C. The Executive and the Company are parties to that certain _____ ("Severance Agreement"). Capitalized terms not defined herein shall have the meaning assigned to them in the Severance Agreement.

The parties hereto agree as follows:

1 **Severance Agreement.** Except as specifically modified by the provisions of this Agreement, the Severance Agreement shall remain in full force and effect.

2 **2021 Annual Bonus.**

The Compensation Committee of the Board previously set the Executive's annual target bonus for fiscal year 2021 at an amount equal to forty percent (40%) of the Executive's base salary ("2021 Annual Bonus"). As an incentive to continue Executive's employment with the Company, subject to the terms of this Agreement, the Executive's 2021 Annual Bonus shall be earned and paid as follows: (a) fifty percent (50%) of the 2021 Annual Bonus shall be earned on the date in January 2022 when the Company pays annual bonuses to its employees, and (b) fifty percent (50%) of the 2021 Annual Bonus shall be earned following the achievement of the 2021 Annual Bonus milestone described on **Exhibit A** hereto; *provided*, *however,* that the second fifty percent (50%) of the 2021 Annual Bonus will not be earned earlier than April 1, 2022.

The Executive shall not earn a portion of the 2021 Annual Bonus if the Executive voluntarily terminates his employment with the Company for any reason or the Company terminates his employment for Cause prior to the date that such portion of the 2021 Annual Bonus is earned.

Each portion of the 2021 Annual Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

3 **Restricted Stock Unit**

On October 8, 2021, the Company granted the Executive 150,000 restricted stock units ("RSUs"). The Executive has been or will be provided with a Restricted Stock Unit Award Grant Notice ("Notice") which sets forth the details of the RSUs and provides the terms and conditions of the grant. Subject to the provisions of this Agreement and the Notice, the RSUs will vest in full on the earliest of (a) June 1, 2022, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause , in each case, subject to the Executive remaining an employee of the Company through such applicable vesting date.

4 **Cash Bonus**

The Executive shall earn a retention bonus in the aggregate amount of $150,000, subject to applicable tax withholding ("Cash Bonus") on the earliest of (a) the date of the achievement of the Cash Bonus milestone set forth on **Exhibit A**, (b) the closing of a Change in Control or (c) the date the Executive's employment with the Company is terminated by the Company without Cause, subject to the Executive's continued employment with the Company through such earliest date.

The Executive shall not earn the Cash Bonus if the Executive voluntarily terminates his employment with the Company or the Company terminates the Executive's employment for Cause prior to the date that the Cash Bonus is earned.

The Cash Bonus shall be paid in full, less applicable withholdings, as soon as practicable following the date on which it is earned.

5 **Nature of Agreement** This Agreement is not a contract of employment for any specified term. Nothing contained in this Agreement shall confer upon Executive any right to continue in the employ of the Company or interfere in any way with the at-will nature of Executive's employment with the Company (it being understood and agreed that (so long as it is done in accordance with applicable law) the Company may terminate Executive's employment at any time for any reason or for no reason and that Executive may terminate his/her employment with the Company at any time for any reason or for no reason).

6 **Full Agreement** This Agreement, together with the Notice and the Severance Agreement referenced herein constitutes the entire agreement of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous discussions, negotiations, or understandings, written or oral, relating thereto. This Agreement may not be amended or modified except in a writing signed by both Executive and an authorized representative of the Company.

7 **Successors**

Any successor to the Company (whether direct or indirect and whether by purchase, merger, consolidation, liquidation or otherwise) to all or substantially all of the Company's business and/or assets shall assume the obligations under this Agreement and agree expressly to perform the obligations under this Agreement in the same manner and to the same extent as the Company would be required to perform such obligations in the absence of a succession. For all purposes under this Agreement, the term "Company" shall include any successor to the Company's business and/or assets which executes and delivers the assumption agreement described in the Severance Agreement or which becomes bound by the terms of this Agreement by operation of law.

The terms of this Agreement and all rights of Executive hereunder shall inure to the benefit of, and be enforceable by, Executive's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees.

8 **Choice of Law and Severability** The validity, interpretation, construction and performance of this Agreement shall be governed by the laws of the State of California. The invalidity or unenforceability of any provision or provisions of this Agreement shall not affect the validity or enforceability of any other provision hereof, which shall remain in full force and effect.

9 **Date of Signature** This Agreement shall be conveyed to Executive via DocuSign and in order to be effective, it must be signed by Executive and delivered to the Company no later than November 15, 2021. Executive may elect to electronically execute this Agreement using the DocuSign link provided, in which case this Agreement shall be automatically delivered to Kelli Shaa and Mishu Nitulescu in Human Resources upon execution. Alternatively, Executive may elect to manually sign this Agreement provided that such signature is delivered to Kelli Shaa in Human Resources no later than November 15, 2021.

Executive	Ardelyx, Inc.
_____ Signature	By:_____
_____ Dated	Title: Chief Executive Officer
	Dated:_____

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

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

1. Registration Statement on Form S-8 (No. 333-197408) pertaining to the 2008 Stock Incentive Plan, as amended, the 2014 Equity Incentive Award Plan and the 2014 Employee Stock Purchase Plan of Ardelyx, Inc.

2. Registration Statements on Form S-8 (Nos. 333-202663 and 333-230156) pertaining to the 2014 Equity Incentive Award Plan and the 2014 Employee Stock Purchase Plan of Ardelyx, Inc.

3. Registration Statements on Form S-3 (Nos. 333-205630, 333-213085 and 333-239764) of Ardelyx, Inc.

4. Registration Statements on Form S-8 (Nos. 333-210079, 333-216154, 333-223694 and 333-237057) pertaining to the 2014 Equity Incentive Award Plan of Ardelyx, Inc.

5. Registration Statement on Form S-8 (No. 333-214538) pertaining to the 2016 Employment Commencement Incentive Plan of Ardelyx, Inc.

6. Registration Statement on Form S-8 (No. 333-254187) pertaining to the 2014 Equity Incentive Award Plan, the 2014 Employee Stock Purchase Plan and the 2016 Employment Commencement Incentive Plan of Ardelyx, Inc.

of our reports dated February 28, 2022, with respect to the financial statements of Ardelyx, Inc. and the effectiveness of internal control over financial reporting of Ardelyx, Inc. included in this Annual Report (Form 10-K) of Ardelyx, Inc. for the year ended December 31, 2021.

/s/ Ernst & Young LLP
Redwood City, California

February 28, 2022

Exhibit 31.1

CERTIFICATION

I, Michael Raab, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ardelyx, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

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

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 28, 2022

By: /s/ Michael Raab

Michael Raab
President, Chief Executive Officer and Director
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

I, Justin Renz, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ardelyx, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

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

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 28, 2022

By: /s/ Justin Renz

Justin Renz
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906
OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Ardelyx, Inc. (the "Company") on Form 10-K for the period ending December 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Michael Raab, President and Chief Executive Officer of the Company, and Justin Renz, Chief Financial Officer of the Company, respectively, do each hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: February 28, 2022 By: /s/ Michael Raab

Michael Raab
President, Chief Executive Officer and Director
(Principal Executive Officer)

Date: February 28, 2022 By: /s/ Justin Renz

Justin Renz
Chief Financial Officer
(Principal Financial Officer)