ARDELYX, INC.
Form 10-K
March 04, 2016
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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, 2015

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**
FOR THE TRANSITION PERIOD FROM TO

COMMISSION FILE NUMBER 001-36485

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.)

34175 ARDENWOOD BLVD., SUITE 200

FREMONT, CALIFORNIA 94555

(ADDRESS OF PRINCIPAL EXECUTIVE OFFICES, INCLUDING ZIPCODE)

(510) 745-1700

(REGISTRANT S TELEPHONE NUMBER, INCLUDING AREA CODE)

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

Title of Each Class:	Name of Each Exchange on Which Registered:
Common Stock, par value $0.0001 per share	The NASDAQ Global Market

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

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

Indicate by check mark whether the Registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit and post such files). Yes x No ¨

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

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

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

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No 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, 2015, based on the last reported sales price of the Registrant s common stock of $15.97 per share was $230,851,093.

The number of shares of Registrant s Common Stock outstanding as of March 2, 2016 was 34,628,898.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the Registrant s Definitive Proxy Statement for its 2016 Annual Meeting of Stockholders, which will be filed with the Commission within 120 days of December 31, 2015, the close of the Registrant s 2015 fiscal year, are incorporated by reference into Part III of this Report.

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ARDELYX, INC.

FORM 10-K FOR THE FISCAL YEAR ENDED DECEMBER 31, 2015

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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, positioned, seek, should, target, will, would, and other similar expressions that are predictions of or indicate f 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:

- the timing of receipt of results for the Phase 3 clinical trials evaluating tenapanor in patients with IBS-C;
- the timing of the receipt of results for a Phase 2b clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in ESRD patients;
- the possibility that we may seek approval from the FDA to consider the tenapanor Phase 2b hyperphosphatemia clinical study as the first of two well-controlled studies;
- the timing of the initiation of a Phase 3 clinical program for RDX022;
- our expectation regarding the availability of the 505(b)(2) regulatory pathway for RDX022;
- the timing of the filing of an IND for RDX009;
- our expectations regarding our plans for and our participation in the commercialization of our products candidates;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use;
- our plans with respect to our pre-clinical programs;
- our ability to identify and validate targets and novel drug candidates using our proprietary drug discovery and design platform including APECCS;

our ability to develop, acquire and advance product candidates into, and successfully complete, clinical trials;

the timing or likelihood of regulatory filings, approvals and commercialization for our product candidates, including tenapanor and RDX022;

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 expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act of 2012, JOBS Act;

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.

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ITEM 1. BUSINESS

COMPANY OVERVIEW

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of innovative, minimally-systemic therapeutic drugs that work exclusively in the gastrointestinal, or GI, tract to treat GI and cardio-renal diseases. We have developed a proprietary drug discovery and design platform enabling us, in a rapid and cost-efficient manner, to discover and design novel drug candidates. Utilizing our platform, we discovered and designed our lead product candidate, tenapanor, which is currently being evaluated in two pivotal Phase 3 clinical studies in patients with constipation-predominant irritable bowel syndrome, or IBS-C. In a Phase 2b clinical study, tenapanor demonstrated the ability to improve the symptoms of IBS-C. In a separate Phase 2b clinical trial, tenapanor demonstrated the ability to lower elevated serum phosphorus levels in patients with end-stage renal disease, or ESRD. We have initiated an additional Phase 2b clinical trial to evaluate dosing regimens of tenapanor for the treatment of hyperphosphatemia, or elevated serum phosphorus, in ESRD patients, and we expect to receive results from this trial in the second half of 2016. We are developing another drug candidate, RDX022, for the treatment of hyperkalemia, or elevated serum potassium. In January 2016, we announced the results of an open label clinical study evaluating the pharmacodynamic activity of RDX022 in healthy adult volunteers. The study demonstrated that RDX022 was generally well-tolerated at all doses evaluated and effectively binds to potassium in the GI tract, supporting our plans to proceed with a Phase 3 clinical program, which we currently expect to initiate in the second half of 2016. We are pursuing a 505(b)(2) regulatory pathway for RDX022. We have additional drug candidates in earlier stages of research and development focused in GI and cardio-renal diseases including RDX009, a secretagogue of glucagon-like peptide-1, or GLP-1, and glucagon-like peptide-2, or GLP-2, and RDX013, a potassium secretagogue. We currently expect to file an investigational new drug application, or IND, for RDX009 in the second half of 2016.

Tenapanor is a minimally-systemic small molecule that acts locally in the GI tract to inhibit the sodium transporter NHE3 and reduce sodium and phosphorus uptake from the gut. In human studies of orally- administered tenapanor, the drug was detected in the blood in only 0.7% of more than 3,000 collected serum samples, and even in those, at very low levels (< 1.5 ng/mL). We have evaluated tenapanor in fourteen human clinical studies in over 1,000 individuals to date. We are currently evaluating tenapanor in two different programs:

IBS-C: In the fourth quarter 2015, we initiated two pivotal Phase 3 clinical trials evaluating tenapanor in patients with IBS-C, and we currently expect results from those trials in 2017. In a Phase 2b clinical study, tenapanor demonstrated the ability to improve symptoms of IBS-C. In that study, the twice daily 50 mg dose of tenapanor met the primary efficacy endpoint of an increase in the complete spontaneous bowel movement (CSBM) responder rate. Most secondary endpoints, including abdominal pain, the overall responder rate and other abdominal and IBS-C symptoms, demonstrated statistically significant and clinically meaningful improvements.

Hyperphosphatemia in ESRD patients: In the fourth quarter 2015, we initiated a second Phase 2b clinical study to evaluate the optimal dosing regimen for tenapanor for the treatment of hyperphosphatemia in ESRD patients, and we expect results from this trial in the second half of 2016. We have designed the clinical trial and the statistical analysis plan so that, assuming positive results, there is the potential that the FDA may agree that this trial could be considered the first of two well-controlled studies to support an NDA for our hyperphosphatemia indication. Results from the first Phase 2b clinical study in this indication were announced in 2015. In that study, there was a statistically significant dose-related decrease in serum

phosphate levels for tenapanor-treated patients compared to patients receiving placebo (p=0.012). It was noted, however, that the rate of diarrhea and the rate of discontinuations due to diarrhea were higher than expected based on previous clinical trials. Higher discontinuations rates due to diarrhea were observed primarily in the 30 mg once daily and 30 mg twice daily dose groups. The overall safety profile remained consistent with that observed in previous tenapanor trials.

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We believe the market opportunity for tenapanor for these two potential patient populations may be significant. Based on reports in the literature regarding the prevalence of IBS in the U.S. population and the percentage of individuals who have IBS-C as compared to other forms of IBS, we believe that 1.4% of the U.S. population, or approximately 4.4 million individuals in the United States have IBS-C, and that approximately 1.0 million of those patients have been diagnosed with IBS-C. Additionally, we estimate that there are about 6.6 million IBS-C patients in Europe and about 3.4 million in Japan.

We are developing RDX022 for the treatment of hyperkalemia. RDX022 is our proprietary oral, non-absorbed potassium-binder. It is based on polystyrene sulfonate, a well-known and well-characterized polymer, used to treat hyperkalemia. We have made numerous improvements to the polymer by engineering into RDX022 several key physical and chemical modifications in an effort to improve various properties. We also changed the counter-ion from sodium to calcium to be more consistent with standard of care in these patients. We have filed a patent application covering the composition of matter for these modifications. Data from the literature as well as independent market research suggests that hyperkalemia affects about 900,000 individuals with CKD Stage 3b or Stage 4, about 900,000 patients with HF and about 200,000 patients with ESRD. In January 2016, we announced results from an open-label pharmacodynamic study of RDX022 in healthy adult volunteers. In this study, RDX022 was administered at 4.6 g BID (9.2 g/day), 6.9 g BID (13.8 g/day), 4.6 g TID (13.8 g/day) and 9.2 g TID (27.5 g/day), and resulted in a mean increase of fecal potassium from baseline of 888 mg/day, 1,791 mg/day, 1,408 mg/day, and 1,670 mg/day, respectively. RDX022 was generally well-tolerated at all doses and demonstrated comparable results to those observed with sodium polystyrene sulfonate. Other fecal electrolytes were monitored during the study and no unexpected changes were observed; in particular, fecal magnesium remained unchanged from baseline. We currently expect to begin a Phase 3 clinical study with RDX022 in the second half of 2016.

Utilizing our proprietary drug discovery and design platform, we are pursuing other internal discovery and lead-development programs that are currently in the research phase.

RDX009 Program: Our focus is the discovery and development of minimally-systemic TGR5 agonists that stimulate GLP-1 and GLP-2 secretion. We are evaluating RDX009 in animal models for its effect in multiple indications. In December 2015, we declared a development candidate for RDX009 and currently expect to file an IND for RDX009 in the second half of 2016.

RDX013 Program: We are continuing to research RDX013, a small molecule drug candidate for hyperkalemia. This agent, a potential potassium secretagogue, is intended to enhance potassium secretion or prevent potassium absorption with a much lower pill burden than potassium binders and may provide significant advantages as a stand-alone agent or used in combination with potassium binders, including RDX022.

RDX011 Program: We intend to leverage our knowledge of NHE3 inhibitors and their effect on phosphate management as we seek to further understand tenapanor s phosphate lowering mechanism of action. We also intend to evaluate new indications for tenapanor and other NHE3 inhibitors in order to exploit the unique capabilities and tools we have developed to modulate ion transport channels located on mucosal surfaces.

OUR PROPRIETARY DRUG DISCOVERY AND DESIGN PLATFORM

Our platform, comprised of proprietary know-how and drug discovery and design tools, provides us with a competitive advantage in drug development. This platform enables us, in a rapid and cost-efficient manner, to discover and design novel drug candidates that work exclusively in the GI tract to treat GI and cardio-renal diseases. By targeting receptors and transporters localized in the GI tract, we can modulate certain important functions of the gut, such as absorption of specific nutrients and minerals, or the gut s various hormonal functions, to treat and prevent diseases while avoiding systemic toxicities.

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The pillars of our drug discovery and design platform include the following:

Medicinal Chemistry to develop minimally-systemic products: our medicinal chemistry team has developed the tools, expertise and approach to ensure that our small molecule drug candidates are potent, have appropriate drug properties, are able to be readily manufactured, and are minimally- systemic, a property that we believe is not generally targeted for most other drug programs;

In vivo **pharmacology**: Our *in vivo* pharmacology group has developed animal models and expertise in-house that allow it to rapidly assess the minimally-systemic nature of our drug candidates as well as test the hypotheses that our drug candidates can treat and prevent diseases and conditions in our targeted therapeutic fields;

GI Informatics: With genetic and proteomic informatics tools, we have identified over 3,800 human GI tract-specific RNA transcripts and proteins on the inner surface of the gut, many of which we believe may be drug targets. We intend to become leading experts in human and rodent gut physiology and the molecular pathways that lead to disease in our targeted therapeutic areas;

In vitro **expertise**: We have developed a cell-culture system that simulates gut tissue. We call this component of our discovery platform Ardelyx Primary Enterocyte and Colonocyte Culture System, or APECCS. APECCS involves the biopsy of various segments of the gut and the growth of those cells under proprietary conditions to maintain, to the extent possible, the integrity and functionality of the various cell types and substructures. We have developed this into a miniaturized format that allows us to utilize it for cell based drug screening. In addition to using APECCS in the design of our small molecule drug candidates, we use the APECCS technology to measure epithelial transport of ions and nutrients and to screen compounds to identify potential disease modulators such as inhibitors or activators using phenotypic screening. APECCS has the potential to allow us to identify novel targets, mechanisms of action and physiology as well as provide us an early understanding of how identified compounds may interact with specific gut tissues. In addition, we believe that APECCS may also provide us with a clear path to translate cell-based observations into in vivo rodent models and ultimately into human clinical studies.

OUR STRATEGY

We are a biotechnology company with a clinical pipeline of drug candidates in the fields of GI and cardio-renal diseases. We are currently advancing the clinical development of our two product candidates, tenapanor and RDX022, and we currently expect to file an IND for RDX009 in the second half of 2016.

Our goal is to use our proprietary drug discovery and design platform to discover new minimally-systemic drug candidates that prevent and treat important diseases in these same therapeutic areas of GI and cardio-renal diseases. To date, all of our drug candidates have resulted from our internal research.

If our drug candidates are approved for marketing by the U.S. Food and Drug Administration, or FDA, we expect to participate in the commercialization of our products with our own specialty-based sales force, initially targeting gastroenterologists and nephrologists.

Our executive management team, and in particular our President and Chief Executive Officer, Michael Raab, has extensive experience in developing and commercializing therapeutic drugs for the CKD and ESRD markets, and we expect to leverage this expertise in a manner that will allow us to create and retain significant value from our marketed products.

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OUR PRODUCT PIPELINE

The following table summarizes key information about our product candidates as of December 31, 2015:

Tenapanor

Tenapanor is a minimally-systemic small molecule that acts locally in the GI tract to inhibit the sodium transporter NHE3 and reduce sodium and phosphorus uptake from the gut. In human studies of orally- administered tenapanor, the drug was detected in the blood in only 0.7% of more than 3,000 collected serum samples, and even in those, at very low levels (< 1.5 ng/mL) confirming that tenapanor is minimally-systemic. We have evaluated tenapanor in fourteen human clinical studies in over 1,000 individuals to date. We are currently evaluating tenapanor for the treatment of constipation and pain in IBS-C patients and for the treatment of hyperphosphatemia in ESRD patients.

Tenapanor for treating IBS-C

IBS-C is a GI disorder in which abdominal pain or discomfort is associated with constipation, which significantly affects the health and quality of life of affected patients. In a recent study led by Dr. Joel J. Heidelbaugh (published in 2015), over 50% of IBS-C patients rated their pain, constipation and straining as being extremely bothersome. In the same study, GI symptoms led to an average 4.9 days of disrupted productivity and 0.8 days of missed work per month. Additionally, IBS-C led to over 50% of patients seeking physician care in the past 12 months and over a third were a little or not at all satisfied with their physician care. It is currently unknown what causes IBS-C. There is no specific test or biomarker for IBS-C and therefore, its presence is diagnosed by symptoms and by eliminating other disorders. IBS-C is very similar to chronic constipation and it is clinically distinguished by a significant pain component.

Clinical data supporting tenapanor in IBS-C

We conducted a Phase 2b clinical trial in IBS-C patients and announced results from that study in October 2014. The clinical trial was a randomized, double blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of three dose levels of tenapanor in 371 subjects with IBS-C as defined by the Rome III criteria and who had active disease as determined during a two-week screening period. Subjects who qualified

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and who were randomized into the study received 5, 20, or 50 mg of tenapanor or placebo twice daily for 12 consecutive weeks. At the end of this treatment period, subjects were followed for an additional 4 weeks. The results were reported on an intent-to-treat basis.

The primary endpoint, CSBM responder rate, was achieved in 60.7% of patients receiving tenapanor 50 mg twice daily versus 33.7% receiving placebo ($p<0.001$). A CSBM responder was defined as a patient who had an increase of greater than or equal to one CSBM from baseline during 6 out of 12 weeks. We also measured a more stringent CSBM response where a responder was defined as a patient who an increase of greater than or equal to one CSBM from baseline and had three or more CSBMs per week during 9 out of 12 weeks. The CSBM 9 of 12 week responder rate was achieved in 23.8% of patients receiving tenapanor 50 mg twice daily versus 7.9% receiving placebo ($p<0.004$).

An abdominal pain responder was achieved in 65.5% of patients receiving tenapanor 50 mg twice daily versus 48.3% receiving placebo ($p<0.026$). An abdominal pain responder was defined as a patient who experienced at least a 30% decrease in abdominal pain from baseline for 6 of 12 weeks. We also measured a more stringent abdominal pain responder rate where a responder was defined as a patient who experienced at least a 30% decrease in abdominal pain from baseline for 9 of 12 weeks. For this more stringent abdominal pain measurement, the abdominal pain 9 of 12 responder rate was achieved in 48.8% of patients receiving tenapanor 50 mg twice daily versus 31.5% receiving placebo ($p<0.022$).

The overall responder rate, or dual composite endpoint percent, was achieved in 50% of patients receiving tenapanor 50 mg twice daily versus 23.6% receiving placebo ($p<0.001$). An overall responder was defined as a patient who was a CSBM responder and an abdominal pain responder during the same week for 6 of 12 weeks. We also measured a more stringent overall responder rate where a responder was defined as a patient who was both a CSBM responder and an abdominal pain responder during the same week for 9 of 12 weeks. The overall 9 of 12 week responder rate was achieved in 20.2% of patients receiving tenapanor 50 mg twice daily versus 6.7% receiving placebo ($p<0.01$).

Most other secondary endpoints measured also demonstrated significant improvements for patients receiving 50 mg tenapanor twice daily compared to placebo-treated patients.

A dose response relationship among all doses was observed in the primary endpoint, as well as in most secondary endpoints, although statistical significance was not achieved at the 5 mg or 20 mg doses. Additionally, the activity of tenapanor was maintained throughout the entire 12-week treatment period.

Tenapanor was well-tolerated in these patients, and the safety results were consistent with those observed in previous tenapanor trials. The most common adverse events at 50 mg twice daily (greater than or equal to 5%) that occurred more frequently in tenapanor-treated patients compared to placebo-treated patients were diarrhea at 11.2% vs. 0%, and urinary tract infections at 5.6% vs. 4.4%. Overall rates of discontinuation due to adverse events were 4.5% for the tenapanor-treated patients (50 mg twice daily) and 3.3% for the placebo-treated patients. Based on the analysis of plasma samples tested as part of the study, the minimally-systemic nature of tenapanor was confirmed.

In the fourth quarter of 2015, we initiated two pivotal Phase 3, randomized, placebo-controlled clinical trials evaluating tenapanor in IBS-C patients. We expect to enroll approximately 600 patients in each trial, and we currently expect results from these two Phase 3 clinical trials in 2017. The primary endpoint in each of the trials is the 6 of 12 week overall responder rate. An overall responder is defined as a weekly responder for 6 of 12 weeks where both an abdominal pain response and a CSBM response criteria are met during the same week. An abdominal pain responder is defined as a patient with a 30% or greater reduction in average weekly worst abdominal pain compared to baseline during the week, and a CSBM responder is defined as a patient who has an increase of one or more in average weekly

CSBMs compared to baseline during the week. We are also evaluating other endpoints in these studies, including CSBM and abdominal pain responder rates for 6 of 12 weeks as well as for 9 of 12 weeks, abdominal symptoms and other clinically relevant endpoints.

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The IBS-C market opportunity

Numerous treatments exist for the constipation component of IBS-C, many of which are over-the-counter. We are aware of two prescription products marketed for IBS-C, Linzess (linaclotide) marketed by Ironwood Pharmaceuticals and Allergan and Amitiza (lubiprostone) marketed by Sucampo and Takeda. In Phase 3 clinical trials of Linzess in IBS-C patients, up to 20% more patients receiving Linzess than placebo reached the primary endpoint, overall responder rate, indicating a significant response during 6 out of 12 weeks of treatment. In these studies, Linzess caused diarrhea in up to 17% more patients than placebo.

We believe that tenapanor may offer a significant benefit over currently marketed drugs like Amitiza and Linzess, due in part to the potential to adjust the dose and/or dose frequency of tenapanor in order to optimize its efficacy and minimize diarrhea. The data we have generated in both animal and human studies have suggested that the effect of tenapanor for the treatment of IBS-C can be modulated by adjusting its dose and dose frequency.

Based on reports in the literature regarding the prevalence of IBS in the U.S. population and the percentage of individuals who have IBS-C as opposed to other forms of IBS, we estimate that approximately 1.4% of the U.S. population has IBS-C, or about 4.4 million individuals, and that approximately 1.0 million of those patients have been diagnosed with IBS-C. Additionally, we estimate there are about 6.6 million IBS-C patients in Europe and about 3.4 million in Japan.

Tenapanor for treating hyperphosphatemia in ESRD patients

CKD is the progressive deterioration of renal function that can occur over several months or years. The symptoms of worsening kidney function are nonspecific, and can include having less energy, reduced appetite, dry itchy skin, swollen feet and ankles, or generally just not feeling well. If the deterioration continues and is not halted by either changes in lifestyle or with the assistance of pharmacological intervention, the disease will likely cause significant cardiovascular morbidity, and can progress to ESRD, the final stage of CKD, where kidney function will be lost entirely.

Current management of ESRD includes hemodialysis, and peritoneal dialysis as a means to filter toxins from the blood once kidneys have failed. Unless this intervention occurs, kidney failure results in the accumulation of waste products that may ultimately cause death. Hemodialysis, the most common form of dialysis, generally requires a patient to visit a dialysis center at least three times per week for a three- to five-hour session, significantly reducing quality of life.

Phosphorus, a vital element required for most cellular processes, is present in almost every food in the Western diet, and, in individuals with normal kidney function, any excess dietary phosphorus is efficiently removed by the kidney and excreted in urine. In adults with functioning kidneys, normal serum phosphorus levels are 2.6 to 3.8 mg/dL. With kidney failure, elevated phosphorus becomes harmful and is diagnosed as hyperphosphatemia when serum phosphorus levels are greater than 5.0 mg/dL. Although patients with ESRD rely on dialysis to eliminate harmful agents, phosphorus is not readily removed by the procedure and other means of managing phosphorus levels must be employed.

In ESRD, excess levels of phosphorus have been shown to lead to an increase in cardiovascular disease risk, as well as increases in serum FGF-23, an important serum endocrine hormone that regulates phosphorus metabolism, and elevated parathyroid hormone, also known as secondary hyperparathyroidism. These endocrine changes in ESRD patients are a concern as elevated parathyroid hormone leads to the development of renal osteodystrophy, a condition of abnormal bone growth characterized by brittle bones.

Since dialysis is unable to efficiently eliminate excess phosphorus, ESRD patients are put on restrictive low phosphorus diets and are prescribed medications called phosphate binders, the only pharmacologic interventions currently marketed for the treatment of hyperphosphatemia. Binders are a collection of drugs whose function is

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to bind, or absorb, dietary phosphorus and are taken in conjunction with meals and snacks. They include calcium, iron or lanthanum, a rare-earth metal, which bind to and precipitate with dietary phosphate in the GI tract. The goal of these elemental phosphorus binders is for patients to eliminate the precipitated phosphorus in their stool. A limitation of this approach is the systemic excess absorption of calcium, iron or lanthanum, resulting in side effects and other unintended consequences for ESRD patients.

Safety and tolerability have been significant concerns with many approved phosphate binders. The more common side effects of approved phosphate binders include long-term vascular calcification, nausea and vomiting, diarrhea or constipation and ileus or disruption of the normal propulsive ability of the GI tract.

ESRD patients take on average 10-14 oral medications each day, and they are severely restricted in their fluid intake. In addition, to control their serum phosphorus, their phosphate binder-related pill burden is significant, typically consisting of nine or more pills a day. The amount of phosphate a binder can remove is limited by its binding capacity, and therefore, increasing the dose, and therefore the pill burden, of the binder is the only way to increase the amount of phosphate being bound and excreted. As a result, prescribed binder doses are intolerable for many patients.

Clinical data supporting tenapanor in hyperphosphatemia

In February 2015, we announced results from a Phase 2b clinical trial evaluating tenapanor for the control of hyperphosphatemia in ESRD patients. This Phase 2b trial was a randomized, double blind, placebo-controlled, multi-center, international study evaluating the safety and efficacy of six dose levels of tenapanor (3 and 30 mg once daily, and 1, 3, 10, and 30 mg twice daily) in 161 ESRD patients with hyperphosphatemia. The primary efficacy endpoint was the change from baseline of serum phosphate levels to the end of treatment and the endpoint was analyzed using an analysis of covariance model (ANCOVA). The study met its primary endpoint by demonstrating a statistically significant dose-related decrease in serum phosphate levels for tenapanor-treated patients compared to patients receiving placebo (p=0.012).

The Effect of Tenapanor on Serum Phosphate in ESRD Patients with Hyperphosphatemia

Group	n	LSMean* (mg/dL)	95% CI
1 mg BID	23	-0.47	(-1.18, 0.24)
3 mg BID	21	-1.18	(-1.93, -0.44)
10 mg BID	23	-1.70	(-2.41, -0.99)
30 mg BID	24	-1.98	(-2.67, -1.28)
3 mg QD	22	-0.56	(-1.28, 0.17)
30 mg QD	21	-1.11	(-1.85, -0.37)
Placebo	26	-0.54	(-1.21, 0.13)

* LSMean = least square mean

As shown in the table, a dose-response relationship was observed in the primary endpoint and twice daily dosing had better pharmacodynamic activity than once daily dosing.

As expected, due to its pharmacological actions, the most frequent adverse event was diarrhea. The rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses were higher than expected based on previous clinical trials. Higher discontinuations rates due to diarrhea were observed primarily in the 30 mg once daily and 30 mg twice

daily dose groups. There were no other notable gastrointestinal adverse events that appeared to be tenapanor related. The overall safety profile remains consistent with that observed in previous tenapanor trials in this patient population.

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Phase 2b ESRD Hyperphosphatemia: Discontinuations Due to Adverse Events

Adverse Event Term	1 mg BID	3 mg BID	10 mg BID	30 mg BID	3 mg QD	30 mg QD	Placebo
n/group	23	21	23	25	22	21	26
Discontinuations due to AE/group*	3	3	3	9	1	7	2
Abdominal Pain				1			
Diarrhea**	2	3	3	8		6	
Nausea						1	
Vomiting						1	
Serum Calcium Decrease					1		
Hyperphosphatemia	1				1		2
Dizziness						1	
Atherosclerosis		1					

* There may be multiple reasons for a single discontinuation
** Personal assessment reported by the patient

In December 2015, we initiated a Phase 2b clinical trial to evaluate the optimal dosing regimen for tenapanor for the treatment of hyperphosphatemia in ESRD patients, and we expect to receive results from this trial in the second half of 2016.

We have designed this Phase 2b clinical trial and the statistical analysis plan so that, assuming positive results, there is potential that the FDA may agree that this trial could be considered the first of two well-controlled studies to support an NDA for tenapanor for the treatment of hyperphosphatemia in ESRD patients.

Size of the hyperphosphatemia market

Phosphate binders are the only pharmacologic interventions currently marketed for the treatment of hyperphosphatemia. Calcium-based binders are the least expensive option to treat hyperphosphatemia. In hemodialysis patients, sevelamer has a 35% patient share versus 45% for calcium-based binders, 15% for lanthanum and 12% for iron-based binders. 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 marketed by Shire)

Sevelamer hydrochloride (Renagel, marketed by Sanofi)

Sevelamer carbonate (Renvela, marketed by Sanofi)

Sucroferric oxyhydroxide (Velphoro, marketed by Vifor Fresenius)

Ferric citrate (Auryxia, marketed by Keryx)

Generic sevelamer was expected to enter the U.S. market in early 2014 after expiration of Sanofi s patent, but as of early 2016, no generic sevelamer has yet been approved. Generic sevelamer was approved, however, in certain jurisdictions in Europe in 2015.

Each of these agents has certain limitations. Calcium carbonate and calcium acetate can cause long term vascular calcification.

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Lanthanum carbonate (Fosrenol) entered the market in 2004 as an alternative to calcium and aluminum based agents, but nephrologists concerns about the long term toxicity from the absorption of metals such as lanthanum and its GI side effect profile have limited its market penetration. Sevelamer hydrochloride (Renagel) is an acidic formulation of sevelamer that has been linked with worsening of metabolic acidosis in patients. Sevelamer carbonate (Renvela) was developed as an improved formulation of sevelamer to reduce incidence of acidosis. The active ingredient of both products, sevelamer, is associated long-term with vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), and flatulence (8%).

Ferric citrate (Auryxia), an iron-based phosphate binder, was approved by FDA in September 2014. While iron is often deficient in ESRD patients because of CKD-associated anemia and lack of sufficient dietary iron, the FDA has required Auryxia to add a warning of iron-overload in the label.

The hydrochloride form of sevelamer, Renagel, was launched in the United States by Genzyme Corporation in 1998 prior to its acquisition by Sanofi, and the carbonate form, Renvela, was launched in 2008. Renvela is currently priced in the United States at a cost of more than $7,000 per patient per year, Fosrenol (lanthanum carbonate) is priced at about $7,500 and calcium-based binders are approximately $900. Sevelamer is the leading phosphate binder product in the hemodialysis market with 35% patient share (versus 45% split among several calcium-based binders). Sanofi booked 935 million ($1.04 billion) in worldwide sales of sevelamer during 2015. The U.S. patents for sevelamer expired in February 2014 and generic launch was allowed in March 2014.

In addition to the currently marketed phosphate binders, we are aware of at least two other binders in development, including fermagate (Alpharen), an iron-based binder in Phase 2 being developed by Opko Health, Inc., and PT20, an iron-based binder in Phase 2 being developed by Phosphate Therapeutics.

According to the most recent data available from the U.S. Renal Data System, in 2013 there were 421,349 patients on hemodialysis in the United States. Additionally, according to the European ERA-EDTA Registry 2012 Annual Report and a study in 2010 by the Japanese Society for Dialysis Therapy, there were approximately 280,000 patients on hemodialysis in Europe and about 250,000 in Japan. We estimate, based on phosphate binder utilization, the only approved therapies for hyperphosphatemia, that there are approximately 290,000, 225,000 and 220,000 ESRD patients with hyperphosphatemia in the United States, Europe and Japan, respectively.

Because many ESRD patients with hyperphosphatemia are unable to lower serum phosphorus levels to below 5.5 mg/dL with currently marketed phosphate binders, we believe there is a significant opportunity for new agents with new mechanisms, demonstrated efficacy, a strong safety profile, and significantly lower pill burden.

We believe that tenapanor, if approved, has the potential to have the lowest pill burden among any currently marketed hyperphosphatemia drugs, with milligram rather than gram quantities dosed once or twice daily. In addition, we may evaluate whether tenapanor has the potential to be used in combination with phosphate binders for those patients who cannot achieve adequate phosphate control with a single agent.

RDX022 for treating hyperkalemia

We are developing RDX022 for the treatment of hyperkalemia. RDX022 is our proprietary oral, non-absorbed potassium-binder. It based on polystyrene sulfonate, a well-known and well-characterized polymer. We have made numerous improvements to the polymer by engineering into RDX022 several key physical and chemical modifications in an effort to improve various properties. We have filed a patent application covering the composition of matter for these modifications.

Clinical data supporting RDX022 in hyperkalemia

In January 2016, we announced results from an open-label pharmacodynamic study of RDX022 in healthy adult volunteers. The study consisted of a two-day treatment-free baseline period and a four-day treatment

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period. The study included four cohorts, and in each cohort 12 subjects received RDX022 and three subjects received a similar dose of sodium polystyrene sulfonate, or SPS for a total of 60 subjects. RDX022 was administered at 4.6 g BID (9.2 g/day), 6.9 g BID (13.8 g/day), 4.6 g TID (13.8 g/day) and 9.2 g TID (27.5 g/day), and resulted in a mean increase of fecal potassium from baseline of 888 mg/day, 1,791 mg/day, 1,408 mg/day, and 1,670 mg/day, respectively. RDX022 was generally well-tolerated at all doses and demonstrated comparable results to those observed with SPS. Other fecal electrolytes were monitored during the study and no unexpected changes were observed; in particular, fecal magnesium remained unchanged from baseline.

Sodium is currently used as a counter-ion in SPS products marketed in the United States and certain other products under development. We formulated RDX022 with a calcium counter-ion, rather than a sodium counter- ion, as adding sodium to the daily intake of the target patient population runs counter to best clinical practice. In patients with CKD and/or HF, the standard of care is a low-sodium diet as sodium can contribute to fluid overload and edema, a common experience for these patients. In addition, excess sodium diminishes the beneficial effects of blood pressure drugs that inhibit the renin-angiotensin-aldosterone system, or RAAS. We have also improved both the physical properties of polystyrene sulfonate and the formulation in a manner that we expect may lead to improved patient adherence and compliance. Notably, in a single center, randomized, crossover study to evaluate various oral formulations of RDX022 in healthy subjects, RDX022 consistently outperformed SPS in all aspects of the taste assessments, including mouth feel, texture and flavor.

We currently expect to initiate a Phase 3 clinical trial for RDX022 in the second half of 2016. The Phase 3 clinical trial will enroll patients with CKD, with or without HF, who are taking RAAS inhibitors and are diagnosed with hyperkalemia, a common side effect that occurs in patients taking RAAS inhibitors. Based on discussions with the FDA, we believe we will be able to submit an application for RDX022 under the 505(b)(2) regulatory pathway.

Size of the hyperkalemia market

Hyperkalemia is defined as the presence of blood potassium levels greater than 5.0mEq/L. Normal levels are 3.5 to 5.0 mEq/L. When hyperkalemia is severe, or above 7.0mEq/L, there is a significantly increased risk of death because of the potential for heart conductance problems.

Hyperkalemia can be caused by a variety of sources. Kidney disease can result in the build-up of potassium in the blood. Also, certain drugs such as the common blood pressure medications known as RAAS inhibitors, or inhibitors of the renin-angiotensin-aldosterone system, can cause hyperkalemia. RAAS inhibitors, though quite effective for controlling blood pressure, are often significantly reduced in patients, such as in those with CKD and HF whose potassium levels are elevated because of the fear that elevated potassium can cause significantly worse problems than hypertension including sudden cardiac arrest in severe cases.

According to a retrospective observational study of a national cohort of 246,000 veterans cared for in the Veterans Health Administration, about 21% and 42% of patients with CKD Stage 3b and Stage 4, respectively, had a hyperkalemic event during a 12-month period, suggesting that hyperkalemia affects about 900,000 individuals with CKD Stage 3b or Stage 4 in the United States. According to the United States Renal Data System 2014 Atlas of CKD & ESRD, over 50% of CKD Stage 3b and Stage 4 patients are prescribed RAAS inhibitors because of their efficacy in controlling hypertension and success in slowing the clinical course of CKD. Additionally, according to the American Heart Association, 5.7 million Americans are living today with heart failure. Our proprietary research suggests that up to 16%, or approximately 900,000, of these patients had hyperkalemia during a 12-month period. Over half of heart failure patients are prescribed RAAS inhibitors.

Despite the success of RAAS inhibitors in both of these populations, several published guidelines have suggested that physicians should reduce and possibly discontinue RAAS inhibitors in order to manage the risk of hyperkalemia in CKD and heart failure patients. The alternative medications used to control hypertension, including diuretics and calcium channel blockers, are significantly less effective than RAAS inhibitors, particularly in patients with failing kidneys and severe hypertension. According to the publication Market

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Dynamix: Hyperkalemia recently released by Spherix Global Insights, U.S. cardiologists reported that of the patients who would benefit from RAAS inhibition, up to 38% of patients with heart failure and up to 55% of patients with both heart failure and CKD are being administered a sub-optimal dose or none at all, and nephrologists reported that at least one-third of patients who would benefit from RAAS inhibition receive a sub- optimal dose or none at all. We believe there is a strong medical need for new medications that control hyperkalemia in order to allow for continued use of RAAS inhibitors to control hypertension in these patient populations.

An additional market not currently addressed by any product on the market is hyperkalemia in ESRD patients. Our proprietary research suggests that up to 48% of patients on dialysis have at least one intervention for hyperkalemia during a 12-month period despite being dialyzed, resulting in a 7% mortality rate. This suggests up to 200,000 patients with ESRD that could benefit from an agent that treats hyperkalemia.

We are aware of at least two drugs approaching or on the market for the treatment of hyperkalemia. Veltassa (patiromer FOS), an oral, polymer-based potassium binder, was approved for marketing by the FDA in October 2015 and was just recently commercially launched by Relypsa. Additionally, a new drug application, or NDA, was submitted in June 2015 for a sodium zirconium cyclosilicate-based oral potassium binder being developed for treatment of hyperkalemia by AstraZeneca after its acquisition of ZS Pharma in December 2015.

OTHER DEVELOPMENT PROGRAMS

Other product candidates in our pipeline include the following:

RDX009 Program

Our focus is the discovery and development of minimally-systemic TGR5 agonists that stimulate GLP-1 and GLP-2 secretion for various indications. In December 2015, we declared a development candidate for RDX009, and we currently expect to file an IND for RDX009 in the second half of 2016. We are evaluating RDX009 in animal models for its effect in multiple indications.

TGR5 is a receptor present on the membrane of certain cells within the GI tract that responds to bile acids secreted in response to food. In the normal physiological response, binding of bile acids to TGR5 stimulates the production of hormones such as glucagon- like peptides 1 and 2 (GLP-1 and GLP-2). GLP-1 is involved in maintaining insulin sensitivity and in aiding glucose and lipid metabolism. GLP-2 is involved in maintenance of the structural integrity of the gut as well as its growth.

We believe that endogenous and local secretion of GLP-1 and GLP-2 triggered by the stimulation of TGR5 receptors by an oral TGR5 agonist may have significant therapeutic potential for the treatment of several conditions. An injectable, stabilized form of GLP-2, called teduglutide (Gattex), is marketed for short bowel syndrome and has been studied in Crohn s disease. GLP-2 is hypothesized to work in inflammatory bowel disease, or IBD, such as Crohn s disease and ulcerative colitis, or UC, by stimulating the repair of the gut and improving the structural integrity of gut wall that is damaged in patients with IBD. Additionally, GLP-2 and its analogs have been shown to prevent chemotherapy-induced diarrhea in animal models. Injectable stabilized GLP-1 analogs that are commercially available, such as exenatide (Byetta) and liraglutide (Victoza), are commonly used to treat type 2 diabetes, among other metabolic conditions. Additionally, injectable GLP-1 analogs are being evaluated in the treatment of NASH because they are known to improve lipid metabolism in the liver. In all of these cases, GLP-1 and GLP-2 analogs are injectable thus we believe an oral agent that can emulate these effects would be welcome.

Historically one of the limitations for the development of TGR5 agonists has been the observation with systemic compounds that stimulation of TGR5 in the gallbladder results in excess gallbladder filling, potentially increasing the risk of gallstones. Utilizing our approach to design small molecules, we have created novel TGR5 agonist candidates that have extremely low systemic exposure and we have shown that these agents do not result in excess gallbladder filling in preclinical animal models.

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We have selected a development candidate for the RDX009 program. This compound, in combination with a DPP-IV inhibitor, has demonstrated proof-of-concept in an animal efficacy model of IBD, and analogs of this compound have shown activity in animal models of chemotherapy-induced diarrhea and short bowel syndrome. We continue to evaluate the development candidate in several animal models of disease as we complete our pre-clinical studies with the intent of filing an IND in the second half of 2016.

RDX013 Program

Our RDX013 program is aimed at discovering and evaluating small molecule, orally-administered drug candidates that modulate the transport of potassium in the GI tract. Our agents will be designed to enhance potassium secretion or prevent potassium absorption in the colon and correct hyperkalemia disorders in CKD patients. We believe that specific potassium transporters in the intestines may serve as useful targets for our program. We believe that such agents may be used as stand-alone agents or used in combination with potassium binders to boost efficacy or to reduce the pill burden of the potassium binders. Several agents we have developed have demonstrated significant activity in animals.

RDX011 Program

We intend to leverage our knowledge of NHE3 inhibitors and their effect on phosphate management as we seek to further understand tenapanor s phosphate lowering mechanism of action. We also intend to evaluate new indications for tenapanor and other NHE3 inhibitors in order to exploit the unique capabilities and tools we have developed to modulate ion transport channels located on mucosal surfaces.

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 proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation 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.

As a normal course of business, we pursue composition-of-matter and method-of-use patents for our product candidates in key therapeutic areas. We also seek patent protection for broader structural and functional attributes of our product candidates that enable a minimally-systemic or minimally-systemic profile.

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, or 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 United States, a patent s term

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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.

NHE3 patents

Our NHE3 patent portfolio is wholly owned by us. This portfolio includes three issued U.S. patents, two issued Japanese patents, and one issued Mexican patent. These issued patents cover the composition and methods of using tenapanor and are predicted, without extension or adjustment, to expire in 2029. We have related national patent applications pending in Europe, China, India, Israel and a number of other countries. Any patents issuing from these patent applications are also predicted without extension or adjustment to expire in 2029. Additional patent applications are pending in the United States covering the composition of or methods of using tenapanor, or its backup compounds.

NaP2b Patents

We have a portfolio of patents and patent applications claiming the compositions and methods of using our proprietary NaP2b inhibitor compounds. NaP2b is an intestinal transporter of dietary phosphorus. Our portfolio is wholly owned by us and includes four issued U.S. patents and three allowed U.S. applications covering the composition of or methods of using our NaP2b inhibitor compounds. The issued patents, and if issued, the allowed applications are predicted to expire in 2031. Numerous related patents have issued in Europe, Hong Kong and Japan Any patents resulting from these patent applications, if issued, are also predicted to expire in 2031.

RDX022

We have filed a PCT application covering the compositions and methods of using RDX022.

RDX009

We have filed a provisional application covering the compositions and methods of using our TGR5 agonists.

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MANUFACTURING

To date, we have relied upon third-party contract manufacturing organizations, or 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 our clinical trial materials for our own internal programs.

GOVERNMENT REGULATION/FDA

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, or 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 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, or GLP, regulations;

- submission to the FDA of an Investigational New Drug, or IND, application which must become effective before human clinical trials in the United States may begin;

- approval by an independent institutional review board, or 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, or 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, or 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, or 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

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trial protocol and other information, are submitted as part of an IND to the FDA. Some 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 time 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 authorized 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 the 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

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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, 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 preclinical 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 of 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, 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 will inspect the facility or the facilities at which the finished drug product, and sometimes the active pharmaceutical ingredient, or 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 cGCP 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, 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, or REMS, plan 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. For many proposed post-approval changes to an NDA, but excluding efficacy supplements to an NDA, the FDA has up to 180 days to review the application. As with new NDAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

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 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 approved by the FDA. Failure to comply with these requirements can result in, among other things, adverse publicity, warning 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

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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.

Fraud and abuse laws

In the United States, 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, or 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 Sunshine Payment 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, the Affordable Care Act, among other things, amends the intent requirement of the federal Anti-Kickback Statute and federal criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. Moreover, the Affordable Care Act provides that 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.

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. For example, pharmaceutical companies have been prosecuted under the federal False Claims Act in connection with their off-label promotion of drugs. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between $5,500 and $11,000 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, 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 and certain states have enacted laws modeled after the federal False Claims Act.

In addition to the laws described above, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively known as the Affordable Care Act, also imposed new reporting requirements on drug manufacturers for payments made to physicians 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 civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year 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. The period

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between August 1, 2013 and December 31, 2013 was the first reporting period and manufacturers were required to report aggregate payment data by March 31, 2014, and will be required to report detailed payment data and submit legal attestation to the accuracy of such data during Phase 2 of the program (which begins in May 2014 and extends for at least 30 days). Thereafter, 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 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.

Because we intend to commercialize products that could be reimbursed under a federal healthcare program and other governmental healthcare programs, we plan to develop a comprehensive compliance program that establishes internal controls to facilitate adherence to the rules and program requirements to which we will or may become subject. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Due to the breadth of these laws, the absence of guidance in the form of regulations or court decisions, and the potential for additional legal or regulatory change in this area, it is possible that our future sales and marketing practices and/or our future relationships with physicians and other healthcare providers might be challenged under such laws. 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.

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.

In addition, in July 2010, CMS released its final rule to implement a bundled prospective payment system for the treatment of ESRD patients as required by the Medicare Improvements for Patients and Providers Act, or MIPPA. The bundled payment includes all renal dialysis services furnished for outpatient maintenance dialysis, including ESRD-related drugs and biologicals. The final rule delayed the inclusion of oral medications without intravenous equivalents in the bundled payment until January 1, 2014 and in April 2014, President Obama signed the Protecting

Access to Medicare Act of 2014, which further extends this implementation date to January 1, 2024. As a result of the recent legislation, beginning in 2024, ESRD-related drugs will be included in the bundle

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and separate Medicare reimbursement will no longer be available for such drugs, as it is today under Medicare Part D. While it is too early to project the full impact bundling may have on the phosphate binder industry, the impact could potentially cause dramatic price reductions for tenapanor, if approved.

Healthcare reform

In March 2010, Congress passed and President Obama signed into law, the Patient Protection and Affordable Care Act, a healthcare reform measure, often called, the Affordable Care Act. The Affordable Care Act substantially changes the way healthcare will be financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry.

The Affordable Care Act contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement changes and fraud and abuse, which will impact existing government healthcare programs and will result 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 Affordable Care Act:

- increases the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1%;
- requires collection of rebates for drugs paid by Medicaid managed care organizations;
- expands 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;
- expands access to commercial health insurance coverage through new state-based health insurance marketplaces, or exchanges;
- requires manufacturers to participate in a coverage gap discount program, under which they must agree to offer 50 percent 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, beginning January 2011; and
- imposes a non-deductible annual fee on pharmaceutical manufacturers or importers who sell branded prescription drugs to specified federal government programs.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011 among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions to

Medicare payments to providers of 2 percent per fiscal year, which went into effect on April 1, 2013. In January 2013, the ATRA was enacted, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers. 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.

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.

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EMPLOYEES

As of December 31, 2015, we had 61 full-time employees, including a total of 20 employees with Ph.D. degrees. Within our workforce, 48 employees are engaged in research and development and the remaining 13 in general management and administration, including finance, legal, and business development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We believe that we maintain good relations with our employees.

RESEARCH AND DEVELOPMENT

The costs were $39.9 million, $25.9 million and $28.1 million in research and development in the years 2015, 2014 and 2013, respectively. See **ITEM 7. MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS** for additional detail regarding our research and development activities.

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 only one business segment, which is the research, development and commercialization of biopharmaceutical products. See Note 1 to our financial statements included in this Annual Report on Form 10-K. Our principal offices are located at 34175 Ardenwood Blvd., Suite 200, Fremont, CA 94555, and our telephone number is (510) 745-1700. Our website address is www.ardelyx.com.

We file electronically with the Securities and Exchange Commission, or 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 public may read or copy any materials we file with the SEC at the SEC s Public Reference Room at 100 F Street NE, Washington, D.C. 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. 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 related notes 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. 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 Limited Operating History, 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.

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 our clinical product candidates, tenapanor and RDX022, 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.

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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 have only a limited operating history upon which to evaluate our business and prospects. We continue to incur significant research, development and other expenses related to our ongoing operations. As of December 31, 2015, we had an accumulated deficit of $101.5 million.

We expect that our operating losses will substantially increase for the foreseeable future as we continue the development of tenapanor and RDX022. In the fourth quarter of 2015, we initiated two Phase 3 clinical trials to evaluate tenapanor for the treatment of IBS-C, and in December 2015, we initiated a Phase 2b clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in end stage renal disease patients. In addition, we expect our operating losses to substantially increase as we incur manufacturing costs for tenapanor and RDX022, advance RDX022 into a Phase 3 clinical program which we expect to initiate in the second half of 2016, and as we continue our discovery, research, development, manufacturing and commercialization activities.

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

We have no products approved for sale and 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 complete the development of and obtain the regulatory and marketing approvals necessary to commercialize one or more of our product candidates. We do not anticipate generating revenue from product sales for the foreseeable future. Our ability to generate future revenue from product sales or pursuant to milestone payments depends heavily on many factors, including but not limited to:

- the completion of nonclinical and clinical development of our product candidates;
- obtaining regulatory approvals for our product candidates, either on our own, or with one or more collaboration partners;
- our ability to successfully commercialize our product candidates, either on our own, or with one or more collaboration partners;
- developing a sustainable and scalable manufacturing process for any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can provide an adequate (in amount and quality) supply of product to support clinical development and the market demand for our product candidates, if approved;
- obtaining market acceptance of our product candidates, if approved, as viable treatment options;

addressing any competing technological and market developments;

identifying, assessing, acquiring, in-licensing and/or developing new product candidates;

negotiating favorable terms in any collaboration partnership, licensing or other arrangements into which we may enter;

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.

In cases where we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which regulatory approval is granted, the accepted price for the product, the ability to get reimbursement at any price

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and whether we are commercializing the product or the product is being commercialized by a collaboration partner, and in such case, whether we have royalty and/or co-promotion rights for that territory. If the number of patients suitable for our product candidates is not as significant as we estimate, the indication approved by regulatory authorities is narrower than 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 such products, even 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 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.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our planned clinical programs for tenapanor and RDX022, or our other product development and platform development activities.

Since our inception, most of our resources have been dedicated to our research and development activities, including developing our clinical product candidates, tenapanor and RDX022, and developing our proprietary drug discovery and design platform. We believe that we will continue to expend substantial resources for the foreseeable future, including costs associated with conducting the Phase 3 clinical programs for tenapanor and RDX022, research and development, conducting preclinical studies and clinical trials for our other programs, obtaining regulatory approvals, developing and maintaining scalable manufacturing processes for our product candidates and sales and marketing. Because the outcome of any clinical trial and/or regulatory approval process is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development, regulatory approval process and commercialization or co-promotion of any of our product candidates. Our future funding requirements will depend on many factors, including, but not limited to:

- the progress, timing, scope, results and costs of our clinical trial programs evaluating tenapanor in IBS-C and for the treatment of hyperphosphatemia in end stage renal disease patients;
- the progress, timing, scope, results and costs of our clinical program for RDX022;
- the time and cost necessary to obtain regulatory approvals for our product candidates and the costs of post-marketing studies that could be required by regulatory authorities;
- our ability to successfully commercialize our product candidates, either alone or with one or more collaboration partners;
- the manufacturing costs of our product candidates, and the availability of one or more suppliers for our product candidates at reasonable costs, both for clinical and commercial supply;

the selling and marketing costs associated with product candidates, including the cost and timing of building our sales and marketing capabilities;

our ability to establish and maintain collaboration partnerships, in-license/out-license or other similar arrangements and the financial terms of such agreements;

the timing, receipt, and amount of sales of, or royalties on, our future products, if any;

the sales price and the availability of adequate third-party reimbursement for our product candidates;

the cash requirements of any future acquisitions or discovery of product candidates;

the number and scope of preclinical and discovery programs that we decide to pursue or initiate, and any clinical trials we decide to pursue for other product candidates;

the time and cost necessary to respond to technological and market developments; and

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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 our product candidates.

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 the clinical development of tenapanor and/or RDX022, delay, limit, reduce or terminate our research activities, preclinical and clinical trials for our other product candidates and our establishment and maintenance of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates, either alone or with a collaboration partner.

Risks Related to Our Business

We are substantially dependent on the success of our lead product candidate, tenapanor, which may not be successful in nonclinical studies or clinical trials, receive regulatory approval or be successfully commercialized.

To date, we have invested a significant amount of our efforts and financial resources in the research and development of tenapanor, which is currently our lead product candidate and one of only two product candidates in clinical trials. The clinical and commercial success of tenapanor will depend on a number of factors, including the following:

our ability to, in a timely manner and under terms that are acceptable to us, to establish one or more collaborative relationships for the commercialization of tenapanor;

the ability of the third-party manufacturers we contract with, to successfully execute and scale up the manufacturing processes for tenapanor, which has not yet been demonstrated, and to manufacture supplies of tenapanor and to develop, validate and maintain a commercially viable manufacturing processes that are compliant with current good manufacturing practice, or cGMP, requirements;

whether the specifications for tenapanor drug product and drug substance will be acceptable to the FDA for use in the clinical development of tenapanor as planned, or whether we will be required to produce such material to different specifications, which if required, could delay the development of tenapanor, and result in substantial additional costs;

whether the long-term rat carcinogenicity study required for regulatory approval of tenapanor, which is currently ongoing, will provide data acceptable to the FDA, or whether we will be required to start a new long-term rat carcinogenicity study, which if required, could delay the development of tenapanor;

whether, as a result of the observation of the absorption of inactive metabolites of tenapanor seen in our radiolabeled human ADME study, the FDA or foreign regulatory authorities require additional nonclinical and/or clinical studies, which could delay the commercialization of tenapanor;

whether FDA or foreign regulatory authorities require additional clinical trials than those anticipated prior to approval to market tenapanor;

the prevalence and severity of adverse side effects of tenapanor;

whether tenapanor s safety and efficacy profile is satisfactory to the FDA and foreign regulatory authorities to gain marketing approval;

the timely receipt of necessary marketing approvals from the FDA and foreign regulatory authorities;

our ability, either alone, or with a collaboration partner, to successfully commercialize tenapanor, if approved for marketing and sale by the FDA or foreign regulatory authorities, including educating physicians and patients about the benefits, administration and use of tenapanor;

achieving and maintaining compliance with all regulatory requirements applicable to tenapanor;

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acceptance of tenapanor as safe, effective and well-tolerated by patients and the medical community;

our ability to manage the complex pricing and reimbursement negotiations associated with marketing the same product at different doses for separate indications, if tenapanor is approved for marketing and sale by the FDA or foreign regulatory authorities for both IBS-C and hyperphosphatemia in dialysis patients;

the availability, perceived advantages, relative cost, relative safety and relative efficacy of alternative and competing treatments;

obtaining and sustaining an adequate level of coverage and reimbursement for tenapanor by third-party payors;

enforcing intellectual property rights in and to tenapanor;

avoiding 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 tenapanor following approval.

As tenapanor is a first-in-class drug, there is a higher likelihood that approval may not be attained as compared to a class of drugs with approved products. We cannot be certain that tenapanor will be successful in non-clinical safety studies or clinical trials, or that it will receive regulatory approval. Further, it may not be possible or practicable to demonstrate, or if approved, to market on the basis of, certain of the benefits we believe tenapanor possesses. For example, the reduction of serum phosphorus is currently an approvable endpoint in CKD patients on dialysis, but not for the broader CKD patient population in the United States. If the number of patients in the market for tenapanor or the price that the market can bear is not as significant as we estimate, we may not generate sufficient revenue from sales of tenapanor, if approved. Accordingly, there can be no assurance that tenapanor will ever be successfully commercialized or that we will ever generate income from sales of tenapanor. If we are not successful in completing the development of, obtaining approval for, and commercializing tenapanor, or are significantly delayed in doing so, our business will be materially harmed.

Clinical drug development involves a lengthy and expensive process with an uncertain outcome, and we may encounter substantial delays in our clinical studies. Furthermore, 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 may not be predictive of the results of later-stage clinical trials. For example, the positive results generated to date in preclinical and clinical studies for tenapanor do not ensure that the ongoing Phase 3 clinical trials for tenapanor, or future clinical trials, will demonstrate similar results. 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. For example, in a Phase 2b study evaluating tenapanor for the treatment of hyperphosphatemia in end stage renal disease, or ESRD, patients, we observed that the study met its primary endpoint by demonstrating a statistically significant dose-related decrease in serum phosphate levels for tenapanor-treated patients compared to patients receiving placebo, while also observing that the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses were higher than expected based upon previous clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy despite having progressed through preclinical studies and initial clinical trials. 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

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setbacks. Even if our clinical trials are completed, the results may not be sufficient to obtain regulatory approval for our product candidates, or if such regulatory approval is obtained, the content of the label approved by regulatory authorities may materially and adversely impact our ability to commercialize the product.

We do not know whether future clinical trials will begin on time, or whether our ongoing or future clinical trials will need to be redesigned, enroll an adequate number of patients on time or be completed on schedule, if at all. Clinical trials can be delayed or terminated for a variety of reasons, including delay or failure to:

- manufacture sufficient quantities of product candidate meeting specified quality standards for use in clinical trials;
- obtain regulatory approval to commence a trial, if applicable;
- reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtain institutional review board, or IRB, approval at each site;
- recruit suitable patients in a timely manner to participate in our trials;
- have patients complete a trial or return for post-treatment follow-up;
- ensure that clinical sites observe trial protocol, comply with good clinical practices, or GCPs, or continue to participate in a trial;
- address any patient safety concerns that arise during the course of a trial;
- address any conflicts with new or existing laws or regulations; or
- initiate or add a sufficient number of clinical trial sites.

Patient enrollment is a significant factor in the timing of clinical trials and is affected by many factors, including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians and patients perceptions as to the potential advantages of the drug being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by an independent data safety monitoring board for such trial 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.

Further, conducting clinical trials in foreign countries presents additional risks that may delay completion of clinical trials. These risks include the failure of physicians or enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes and political and economic risks relevant to such foreign countries. In addition, the FDA may determine that the clinical trial results obtained in foreign subjects do not represent the safety and efficacy of a product candidate when administered in U.S. patients and are thus not supportive of New Drug Application, or NDA, approval in the United States. If there are delays in the completion of, or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates may be harmed, and our ability to generate revenue from product sales from any of these product candidates will be delayed. In addition, any delays in completing the clinical trials will increase costs,

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slow down our product candidate development and approval process and jeopardize the ability to commence product sales and generate revenue from product sales. Any of these occurrences may significantly harm our business, financial condition and prospects. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

We intend to devote significant resources to the development of RDX022 which may not be successful in nonclinical studies or clinical trials, receive regulatory approval or be successfully commercialized.

With the advancement of RDX022 into human studies in June 2015, and the expected initiation of a Phase 3 clinical program for RDX022 in the second half of 2016, we expect to invest a significant amount of our efforts and financial resources in the development of RDX022. We are pursuing a 505(b)(2) regulatory path for approval of RDX022, which, among other things allows us to rely on the FDA s previous findings of safety and efficacy and may eliminate the need to conduct certain nonclinical and clinical studies of our product candidate. This regulatory pathway, which can accelerate development, may not be available to us if a pharmaceutically equivalent product to RDX022 were approved prior to the approval of our 505(b)(2) application. If we are unable to rely upon a 505(b)(2) regulatory pathway for the approval of RDX022, the development of RDX022 may be substantially delayed or we may be required to abandon such development.

The clinical and commercial success of RDX022 will depend on a number of factors, including the following:

- the ability of the third-party manufacturers we contract with, to successfully develop and scale up the manufacturing processes for RDX022, which has not yet been demonstrated, to manufacture supplies of RDX022 and to develop, validate and maintain a commercially viable manufacturing process that is compliant with current good manufacturing practice, or cGMP, requirements;

- the significant expansion of the market for the treatment of hyperkalemia beyond its currently limited size, including the success of commercial launches of new hyperkalemia products and the use of any such products by nephrologists and cardiologists in the chronic setting; our ability to successfully obtain labeling claims necessary or desirable for the commercial success of RDX022;

- our ability to successfully obtain labeling claims necessary or desirable for the commercial success of RDX022;

- the availability, perceived advantages regarding relative palatability, relative cost, relative safety, relative tolerance and relative efficacy of alternative and competing treatments;

- whether we are able to obtain intellectual property protection for RDX022, and the strength of such protection if granted

- the timely receipt of necessary marketing approvals and exclusivity periods, if any, from the FDA and foreign regulatory authorities;

our ability to successfully commercialize RDX022, if approved for marketing and sale by the FDA or foreign regulatory authorities, including educating physicians and patients about the benefits, administration and use of RDX022;

obtaining and sustaining an adequate level of coverage and reimbursement for RDX022 by third-party payors; and

the effectiveness of our marketing, sales and distribution strategy and operations.

As a result of pursuing a 505(b)(2) path for RDX022, we will not evaluate the efficacy of RDX022 in patients with hyperkalemia prior to the initiation of the Phase 3 clinical program. We cannot be certain that clinical trials evaluating RDX022 will establish a safety and efficacy profile sufficient to enable RDX022 to gain approval by the FDA, or if approved, compete effectively with alternative and competing treatments. Further, it

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may not be possible or practicable to demonstrate, or if approved, to market on the basis of, certain of the benefits we believe RDX022 may possess. Accordingly, there can be no assurance that RDX022 will ever be successfully commercialized or that we will ever generate revenue from sales of RDX022. If we are not successful in completing the development of, obtaining approval for, and commercializing RDX022, or are significantly delayed in doing so, our business will be materially harmed.

We may not be successful in our efforts to develop our product candidates that are at an early stage of development, including RDX009, or expand our pipeline of product candidates.

A key element of our strategy is to expand our pipeline of product candidates utilizing our proprietary drug discovery and design platform and to advance such product candidates through clinical development. In December 2015, we selected a development candidate for our RDX009 program. This product candidate, and those product candidates that are in the discovery and lead identification stages of preclinical development will require substantial preclinical and clinical development, testing and regulatory approval prior to commercialization. In particular, tenapanor and RDX022 are our only product candidates in clinical trials and all of our other product candidates are in the preclinical stage with significant research and development required before we could begin clinical studies. Of the large number of drugs in development, only a small percentage of such drugs successfully complete the FDA regulatory approval process and are commercialized. Accordingly, even if we are able to continue to fund our research programs, there can be no assurance that any product candidates will reach the clinic or be successfully developed or commercialized.

Research programs to identify product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Although our research and development efforts to date have resulted in several development programs, we may not be able to develop product candidates that are safe, effective and well-tolerated. Our research programs may initially show promise in identifying potential product candidates, and we may select candidates for development, yet we may fail to yield product candidates for clinical development or commercialization for many reasons, including the following:

- the research methodology used and our drug discovery and design platform may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may nevertheless be covered by third parties patents or other exclusive rights;
- the market for a product candidate may change during our program so that the continued development of that product candidate is no longer reasonable;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective, well-tolerated or otherwise does not meet applicable regulatory criteria;

- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and

- a product candidate may not be accepted as safe, effective and well-tolerated by patients, the medical community or third-party payors, if applicable.

Even if we are successful in continuing to expand our pipeline, through our own research and development efforts or by pursuing in-licensing or acquisition of product candidates, the potential product candidates for which we identify or acquire rights may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize a product pipeline, we may not be able to generate revenue from product sales in future periods or ever achieve profitability.

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Our proprietary drug discovery and design platform, and, in particular, APECCS, is a new approach to the discovery, design and development of new product candidates and may not result in any products of commercial value.

We have developed a proprietary drug discovery and design platform to enable the identification, screening, testing, design and development of new product candidates, and have developed APECCS as a component of this of this platform. We utilize APECCS in the design of our small molecules and to identify new and potentially novel targets in the GI tract. However, there can be no assurance that APECCS will be able to identify new targets in the GI tract or that any of these potential targets or other aspects of our proprietary drug discovery and design platform will yield product candidates that could enter clinical development and, ultimately, be commercially valuable.

Although we expect to continue to enhance the capabilities of our APECCS system by advancing the cell culture and screening process and/or acquiring new technologies to broaden the scope of APECCS, we may not be successful in any of our enhancement and development efforts. In addition, we may not be able to enter into agreements on suitable terms to utilize technologies required to exploit certain capabilities of APECCS, and in such case, we may be forced to limit our use or further development of APECCS, or to modify APECCS for continued use. It may not be possible to modify APECCS in manner that avoids the utilization of certain technologies, without materially and adversely affecting the performance of APECCS or without incurring substantial cost and delay in advancement of the system. In addition, we may not be successful in developing the conditions necessary to grow multiple segments of intestine or from multiple species, or otherwise develop assays or cell cultures necessary to expand these capabilities. If our enhancement or development efforts are unsuccessful, or if we are forced to limit our use or further development of APECCS due to the inability to enter into agreements on suitable terms to permit the utilization of technologies required to exploit APECCS, we may not be able to advance our drug discovery capabilities as quickly as we expect or identify as many potential drugable targets as we desire.

We rely on third parties to conduct some of our preclinical and nonclinical studies and all of our 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 or commercialize our product candidates.

We do not have the ability to independently conduct clinical trials and, in some cases, preclinical or nonclinical studies. 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 some of our preclinical and nonclinical studies and all of 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 good laboratory practices, or GLPs, for preclinical and nonclinical studies, and good clinical practices, or 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, or EEA, and comparable foreign regulatory authorities for all of our products in preclinical 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, or 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 current good manufacturing practices or cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

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Even if our product candidates obtain regulatory approval, they may never achieve market acceptance or commercial success, which will depend, in part, upon the degree of acceptance among physicians, patients, patient advocacy groups, health care payors and the medical community.

Even if our product candidates obtain FDA or other regulatory approvals, and are ultimately commercialized, our product candidates may not achieve market acceptance among physicians, patients, third-party payors, patient advocacy groups, health care payors and the medical community. Market acceptance of our product candidates for which marketing approval is obtained depends on a number of factors, including:

- the efficacy of the products as demonstrated in clinical trials;
- the prevalence and severity of any side effects and overall safety and tolerability profile of the product;
- the clinical indications for which the product is approved;
- advantages over new or traditional or existing therapies, including recently approved therapies or therapies that the physician community anticipate will be approved;
- acceptance by physicians, major operators of clinics and patients of the product as a safe, effective and well-tolerated treatment;
- relative convenience and ease of administration of our products;
- the potential and perceived advantages of our product candidates over current treatment options or alternative treatments, including future alternative treatments;
- the cost of treatment in relation to alternative treatments and willingness to pay for our products, if approved, on the part of physicians and patients;
- the availability of alternative products and their ability to meet market demand;
- the strength of our or our collaboration partners marketing and distribution organizations;
- the quality of our relationships with patient advocacy groups; and

sufficient third-party coverage or reimbursement.

Any failure by our product candidates that obtain regulatory approval to achieve market acceptance or commercial success would adversely affect our results of operations.

Our product candidates may cause undesirable side effects or have other properties that could delay our clinical trials, or delay or prevent regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following regulatory approval, if any. If any of our product candidates receives marketing approval and we or others later identify undesirable side effects caused by the product candidate, the ability to market the product candidates could be compromised.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials, result in the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authorities or limit the commercial profile of an approved label. To date, patients treated with tenapanor have experienced drug-related side effects including diarrhea, nausea, flatulence, abdominal discomfort, abdominal pain, abdominal distention and changes in electrolytes, and in the a Phase 2b clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in ESRD patients, we observed that the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses was higher than expected based upon the results of previous clinical trials. In the event that trials conducted by us with tenapanor or trials we conduct with our other product candidates, reveal an unacceptable severity and prevalence of these or other side effects, such trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of tenapanor, or any such other product candidate, for any or all targeted indications. Additionally, despite a positive efficacy profile, the prevalence and/or severity of these or other side effects could cause us to cease further development of a product candidate for a

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particular indication, or entirely. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

In addition, in the event that any of our product candidates receives regulatory approval and we or others later identify undesirable side effects caused by one of our products, a number of potentially significant negative consequences could occur, including:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we 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 Strategies, or REMS, plan that may require creation of a Medication Guide outlining the risks of such side effects for distribution to patients, as well as elements to assure safe use of the product, such as a patient registry and training and certification of prescribers;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of 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 from achieving or maintaining market acceptance of a particular product candidate, 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 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 and RDX022, as well as our other product candidates, would compete against

existing treatments. For example, tenapanor will, if approved, compete directly with phosphate binders for the treatment of hyperphosphatemia in ESRD patients, including sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela), which were launched by Genzyme. Synthon announced the successful completion of a Phase 3 multicenter, randomized, double-blind, multiple-dose, crossover trial in Europe to compare safety and demonstrate equivalence of serum phosphate control of Synthon sevelamer carbonate tablets to Renvela tablets in chronic kidney disease patients on hemodialysis in April 2014. Currently, several pharmaceutical companies are distributing Synthon manufactured sevelamer carbonate tablets in multiple European countries including, but not limited to, the United Kingdom, Spain, Sweden and Denmark. In addition to the currently marketed phosphate binders, Keryx has received FDA approval for ferric citrate (Auryxia), an iron-based binder, that is also approved in Japan and we are aware of fermagate (Alpharen), an iron-based binder in Phase 2 being developed by Opko Health. Additionally, RDX022, if approved, will compete directly with Kayexalate and its generic equivalents, known as sodium polystyrene sulfonate, on the market in the United States. In addition, Relypsa just recently commercially launched patiromer (Veltassa) for the treatment of hyperkalemia, and a new drug application, or NDA, was submitted in June 2015, for a sodium zirconium cyclosilicate-based oral potassium binder being developed for the treatment of hyperkalemia by AstraZeneca after its acquisition of ZS Pharma in December 2015.

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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 relieve temporary constipation. We are also aware of two prescription drugs currently on the U.S. market that are approved to treat IBS-C, Linzess (linaclotide), which was developed by Ironwood Pharmaceuticals and is approved for IBS-C and chronic constipation in both the United States and in Europe, and Amitiza (lubiprostone), which was first approved in the United States in 2006 and is currently marketed by Sucampo and Takeda for treatment of chronic idiopathic constipation, or CIC, IBS-C and opioid induced constipation, or OIC. Additionally, Synergy filed an NDA for Plecanatide for the treatment of CIC in January 2016, and is currently conducting two Phase 3 clinical trials of Plecanatide for the treatment of IBS-C.

It is possible that our competitors will develop and market drugs or other treatments that are 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 currently have no sales organization. If we are unable to establish sales capabilities on our own or through third parties, we may not be able to commercialize tenapanor and RDX022, or any of our other product candidates.

We currently do not have a sales organization. In order to promote tenapanor and RDX022, either alone, or with a collaboration partner, and in order to commercialize or co-promote any of our other product candidates, we must build our marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. In order to commercialize tenapanor or RDX022 outside of the United States, we expect to enter into collaborative relationships with one or more third parties. Additionally, in order to commercialize tenapanor for IBS-C, we expect to enter into a collaborative relationship with one or more third parties in the United States to address the primary care market. There can be no assurances that we will be successful in establishing such relationships in a timely manner or on terms that are acceptable to us. If one or more of our product candidates receives regulatory approval, we expect to establish a specialty sales organization with technical expertise and supporting distribution capabilities to commercialize our product candidates, which will be expensive and time consuming. As a company, we have no prior experience in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability 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. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products.

We may choose to collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. If we are unable to enter into such arrangements on acceptable terms or at all, we may not be able to successfully commercialize our product candidates.

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We rely completely on third parties to manufacture our preclinical and clinical drug supplies, and we intend to rely on third parties to produce commercial supplies of any approved product candidate. Our business would be harmed if those third parties fail to obtain approval of the FDA, Competent Authorities of the Member States of the EEA or comparable regulatory authorities, fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality levels or prices.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture our preclinical and clinical drug supplies for use in the conduct of our preclinical and clinical studies, and we lack the resources and the capability to manufacture any of our product candidates on a clinical or commercial scale. The facilities used by our contract manufacturers to manufacture any drug products must be approved by the FDA pursuant to inspections that will be conducted after an NDA is submitted to the FDA. We do not control the manufacturing process of our product candidates, and we are completely dependent on our contract manufacturing partners for compliance with the regulatory requirements, known as cGMPs, for manufacture of both active drug substances and finished drug products.

If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical studies. There are a limited number of suppliers for raw materials that we use to manufacture our drugs, and there may be a need to identify alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our product candidates for our clinical studies, and, if approved, ultimately for commercial sale. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Although we generally do not begin a clinical study unless we believe we have on hand, or will be able to manufacture, a sufficient supply of a product candidate to complete such study, any significant delay or discontinuity in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical study due to the need to replace a third-party manufacturer could considerably delay completion of our clinical studies, product testing, and potential regulatory approval of our product candidates, which could harm our business and results of operations.

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

The pricing, coverage and reimbursement of our product candidates, 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 such as ours, assuming approval. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates 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 may not be able to successfully commercialize our product candidates. 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, or CMS, an agency within the U.S.

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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.

In July 2010, CMS released its final rule to implement a bundled prospective payment system for the treatment of ESRD patients as required by the Medicare Improvements for Patients and Providers Act, or MIPPA. The bundled payment covers a bundle of 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 final rule delayed the inclusion of oral medications without intravenous equivalents in the bundled payment until January 1, 2014 and in April 2014, President Obama signed the Protecting Access to Medicare Act of 2014, which further extends this implementation date to January 1, 2024. As a result of the recent legislation, beginning in 2024, ESRD-related drugs will be included in the bundle and separate Medicare reimbursement will no longer be available for such drugs, as it is today under Medicare Part D. While it is too early to project the full impact bundling may have on the industry, the impact could potentially cause dramatic price reductions for tenapanor and RDX022, if approved. We may be unable to sell tenapanor and/or RDX022, 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 increase faster than increases in reimbursement levels.

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 our product candidates. 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 new products approved 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 any of our product candidates 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.

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

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. 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 our product candidates;

injury to our reputation;

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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 product candidates.

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. We currently carry product liability insurance covering use in our clinical trials in the amount of $10.0 million in the aggregate. Although we maintain such 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.

We are highly dependent on the services of our President and Chief Executive Officer, Michael Raab, our Executive Vice President and Chief Scientific Officer, Jeremy Caldwell, Ph.D., and our Senior Vice President of Drug Development, David Rosenbaum, Ph.D. If we are not able to retain these members of our management team, or recruit additional management, clinical and scientific personnel, our business will suffer.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified personnel. In particular, we are highly dependent upon Michael Raab, our President and Chief Executive Officer, Jeremy Caldwell, Ph.D., our Chief Scientific Officer and David Rosenbaum, Ph.D., our Senior Vice President of Drug Development. The loss of services of any of these individuals could delay or impair the successful development of our product pipeline, completion of our planned clinical trials or the commercialization of our product candidates. Although we have entered into employment agreements with our senior management team, including Mr. Raab and Drs. Caldwell and Rosenbaum, these agreements are terminable at will with or without notice and, therefore, we may not be able to retain their services as expected. Although we have not historically experienced unique difficulties attracting and retaining qualified employees, we could experience such problems in the future. For example, competition for qualified personnel in the biotechnology and pharmaceuticals field is intense due to the limited number of individuals who possess the skills and experience required by our industry. In addition to the competition for personnel, the San Francisco Bay area in particular is characterized by a high cost of living. As such, we could have difficulty attracting

experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment and retention efforts.

We will need to continue to increase the size of our organization, and we may experience difficulties in managing growth.

We will need to continue to expand our clinical, managerial, operational, finance and other resources in order to manage our operations, preclinical and clinical trials, research and development activities, regulatory filings, manufacturing and supply activities, and any marketing and commercialization activities. Our management, personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively execute our growth strategy requires that we:

expand our general and administrative functions;

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establish and build a marketing and commercial organization;

identify, recruit, retain, incentivize and integrate additional employees;

manage our internal development efforts effectively while carrying out our contractual obligations to third parties; and

continue to improve our operational, legal, financial and management controls, reporting systems and procedures.

If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Significant disruptions of information technology systems or breaches of data security could adversely affect our business.

Our business is increasingly dependent on critical, complex and interdependent information technology systems to support business processes as well as internal and external communications. The size and complexity of our computer systems make them vulnerable to breakdown, malicious intrusion and computer viruses. We have developed systems and processes that are designed to protect our information and prevent data loss and other security breaches, including systems and processes designed to reduce the impact of a security breach; however, such measures cannot provide absolute security, and we have taken, and will take, additional security measures to protect against any future intrusion. Any failure to protect against breakdowns, malicious intrusions and computer viruses may result in the impairment of production and key business processes. In addition, our systems are potentially vulnerable to data security breaches, whether by employees or others, which may expose sensitive data to unauthorized persons. Such data security breaches could lead to the loss of trade secrets or other intellectual property, or could lead to the public exposure of personal information of our employees, clinical trial patients, customers, and others. Such disruptions and breaches of security could expose us to liability and have a material adverse effect on the operating results and financial condition of our business.

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, or 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.

In addition, we are in the process of implementing an enterprise resource planning, or ERP, system for our company. An ERP system is intended to combine and streamline the management of our financial, accounting, human resources, sales and marketing and other functions, enabling us to manage operations and track

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performance more effectively. However, an ERP system will require us to complete many processes and procedures for the effective use of the system or to run our business using the system, which may result in substantial costs. Additionally, during the conversion process, we may be limited in our ability to convert any business that we acquire to the ERP. Any disruptions or difficulties in implementing or using an ERP system could adversely affect our controls and harm our business, including our ability to forecast or make sales and collect our receivables. Moreover, such disruption or difficulties could result in unanticipated costs and diversion of management attention.

We are subject to Section 404 of The Sarbanes-Oxley Act of 2002, or Section 404, and the related rules of the Securities and Exchange Commission, or SEC, which generally require our management and independent registered public accounting firm to report on the effectiveness of our internal control over financial reporting. Section 404 requires an annual management assessment of the effectiveness of our internal control over financial reporting. However, for so long as we remain an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we intend to take advantage of certain exemptions from various reporting requirements that are applicable to public companies that are emerging growth companies, including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404. Once we are no longer an emerging growth company or, if prior to such date, we opt to no longer take advantage of the applicable exemption, we will be required to include an opinion from our independent registered public accounting firm on the effectiveness of our internal controls over financial reporting. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year following the fifth anniversary of the completion of our IPO (December 31, 2019), (2) the last day of the fiscal year in which we have total annual gross revenue of at least $1.0 billion, or (3) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (4) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

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 form collaboration partnerships in the future, and we may not realize the benefits of such collaborations.

We may form collaboration partnerships, create joint ventures or enter into licensing arrangements with third parties that we believe will complement or augment our existing business. In particular, we expect to form one or more collaboration partnerships in connection with the commercialization of tenapanor outside of the United States, and in the United States for IBS-C to address the primary care market, if approved. We face significant competition in seeking appropriate collaboration partners, and the negotiation process to secure appropriate terms is time-consuming and complex. Any delays in identifying suitable 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. Moreover, we may not be successful in our efforts to establish such a collaboration partnership for any future product candidates and programs on terms that are acceptable to us, or at all. This may be because our product candidates and programs may be deemed to be at too early of a stage of development for collaborative effort, our research and development pipeline may be viewed as insufficient, and/or third parties may

not view our product candidates and programs as having sufficient potential for commercialization, including the likelihood of an adequate safety and efficacy profile. Even if we are successful in entering into a collaboration partnership or license arrangement, there is no guarantee that the collaboration

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partnership will be successful, or that any future 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 may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

We intend to consider strategic transactions, such as acquisitions of companies, asset purchases, and or in-licensing of products, product candidates or technologies. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, 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 to pay for acquisitions;
- 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, 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 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 expect that we will be subject to additional risks related to entering into 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;

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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 research and 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, research 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 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.

Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such 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 programs. For example, the loss of clinical trial data from completed or ongoing clinical trials for any of our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

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We may be adversely affected by the current 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 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 recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. We cannot anticipate all the ways in which the current global economic climate and global financial market conditions could adversely impact our business.

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, the 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, prior to the effectiveness of certain provisions of the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively known as the Affordable Care Act, 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.

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.

Our corporate headquarters and other facilities are 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 headquarters, 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

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The research, testing, manufacturing, labeling, approval, selling, import, export, marketing and distribution of drug products are subject to extensive regulation by the FDA and other regulatory authorities in the United

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States and other countries, which regulations differ from country to country. Neither we nor any of our collaboration partners is permitted to market any drug product in the United States until we receive marketing approval from the FDA. We have not submitted an application or obtained marketing approval for any of our product candidates anywhere in the world. Obtaining regulatory approval of a NDA can be a lengthy, expensive and uncertain process. In addition, failure to comply with FDA and other applicable United States and foreign regulatory requirements may subject us to administrative or judicially imposed sanctions or other actions, including:

warning letters;

civil and criminal penalties;

injunctions;

withdrawal of regulatory approval of products;

product seizure or detention;

product recalls;

total or partial suspension of production; and

refusal to approve pending NDAs or supplements to approved NDAs.

Prior to obtaining approval to commercialize a drug candidate in the United States or abroad, we or our collaboration partners must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the FDA or other foreign regulatory agencies, that such drug candidates are safe and effective for their intended uses. The number of nonclinical studies and clinical trials that will be required for FDA approval varies depending on the drug candidate, the disease or condition that the drug candidate is designed to address, and the regulations applicable to any particular drug candidate. Results from nonclinical studies and clinical trials can be interpreted in different ways. Even if we believe the nonclinical or clinical data for our drug candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities. Administering drug candidates to humans may produce undesirable side effects, which could interrupt, delay or halt clinical trials and result in the FDA or other regulatory authorities denying approval of a drug candidate for any or all targeted indications.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable, typically takes many years following the commencement of clinical studies, and depends upon numerous factors. The FDA and comparable foreign authorities have substantial discretion in the approval process and we may encounter matters with the FDA or such comparable authorities that requires us to expend additional time and resources and delay or prevent the approval of our product candidates. For example, the FDA may require us to conduct additional studies or trials for drug product either prior to or post-approval, such as additional drug-drug interaction studies or safety or efficacy

studies or trials, or it may object to elements of our clinical development program such as the number of subjects in our current clinical trials from the United States. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate s clinical development and may vary among jurisdictions, which may cause delays in the approval or result in a decision not to approve an application for regulatory approval. Despite the time and expense exerted, failure can occur at any stage. Applications for our product candidates could fail to receive regulatory approval for many reasons, including but not limited to the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our, or our collaboration partners , clinical studies;

- the population studied in the clinical program may not be sufficiently broad or representative to assure safety in the full population for which approval is sought;

- the FDA or comparable foreign regulatory authorities may disagree with the interpretation of data from preclinical studies or clinical studies;

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- the data collected from clinical studies of our product candidates may not be sufficient to support the submission of a NDA or other submission or to obtain regulatory approval in the United States or elsewhere;

- we or our collaboration partners may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate s risk-benefit ratio for its proposed indication is acceptable;

- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers responsible for clinical and commercial supplies; and

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process, as well as the unpredictability of the results of clinical studies, may result in our failure and/or that of our collaboration partners to obtain regulatory approval to market any of our product candidates, which would significantly harm our business, results of operations, and prospects. Additionally, if the FDA requires that we conduct additional clinical studies, places limitations in our label, delays approval to market our product candidates or limits the use of our products, our business and results of operations may be harmed.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Even if we receive regulatory approval for a product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, any product candidates, if approved, could be subject to labeling and 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, adverse event reporting, 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 GCPs 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.

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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 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 our product candidates. 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 that could prevent, limit or delay regulatory approval of our product candidates. 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 and our contract manufacturers are subject to significant regulation with respect to manufacturing our product candidates. 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 candidates for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates 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. 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 preparation of our product candidates or our other potential products 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.

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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. If tenapanor, RDX022 or our other product candidates receive marketing approval, we and our collaborating partners, if any, 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. We intend to implement 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 Food, Drug and Cosmetic Act, 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

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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.

If approved, tenapanor, RDX022 and our other product candidates 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, nausea, flatulence, abdominal discomfort, abdominal pain, abdominal distention and changes in electrolytes and in the Phase 2b evaluating tenapanor for the treatment of hyperphosphatemia in ESRD patients, we observed that the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses was higher than expected based upon the results of previous clinical trials. 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: (1) FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA; (2) manufacturing standards; (3) federal and state healthcare fraud and abuse laws and regulations; or (4) laws that require the reporting of true and accurate financial information and data. 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 be in compliance with such laws or regulations.

If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions

could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, 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 28 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, or MA. Before granting the MA, 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, if any, 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.

Although we do not currently have any products on the market, once we begin commercializing our products, we and our collaboration partners, if any, 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;

- 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;

federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;

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the federal physician sunshine requirements under the Affordable Care Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the CMS information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers 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 marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts; 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. Further, the Affordable Care Act, among other things, amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. In addition, the Affordable Care Act provides that 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. 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;

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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 Affordable Care Act 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 Affordable Care Act, 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 agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013. On January 2, 2013, the ATRA was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals.

It is likely that federal and state legislatures within the United States and foreign governments will continue to consider changes to existing healthcare legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect the demand for any 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.

Risks Related to Intellectual Property

We may become subject to claims alleging infringement of third parties patents or proprietary rights and/or claims seeking to invalidate our patents, which would be costly, time consuming and, if successfully asserted against us, delay or prevent the development and commercialization of tenapanor, RDX022 or our other product candidates, or prevent or delay the continued use of our drug discovery and development platform, including APECCS.

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. There can be no assurances that we will not be subject to claims alleging that the manufacture, use or sale of tenapanor, RDX022 or any other product

candidates, or that the use of our drug discovery and development platform, including APECCS 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 tenapanor, RDX022 or other product candidates or by the use of APECCS. 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 tenapanor, RDX022 or our other product candidates, or by the use of APECCS.

We may be subject to third-party patent infringement claims in the future against us or our that would cause us to incur substantial expenses and, if successful against us, 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 research, development, manufacturing or sales of the product or product candidate that is the subject of the suit. In addition, if a patent infringement suit were brought against us regarding the use of APECCS, we could be forced to stop our use of APECCS or modify our processes to avoid infringement, which may not be possible at a reasonable cost, if at all, and which could result in substantial delay in our use of APECCS for the discovery of new product candidates or potential targets. 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, 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, or to cease our use of APECCS or some other aspect of our business operations if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms. 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, 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 United States Patent and Trademark Office, or 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.

If our intellectual property related to our product candidates is not adequate or if we are not able to protect our trade secrets or our confidential information, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates, our drug discovery and development platform and our development programs. Any disclosure to or misappropriation by third parties of our confidential or proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position 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

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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 our product candidates is successfully challenged, then our ability to commercialize such product candidates 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 tenapanor or other 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 the 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 candidate, we would lose at least part, and perhaps all, of the patent protection on such 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 are actively involved in the discovery and design of our 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.

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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 our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one of the U.S. patents covering each of such approved product(s) or the use thereof may be eligible for up to five years of patent term restoration under the Hatch-Waxman Act. 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. Nevertheless, 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.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity.

Therefore, obtaining and enforcing biopharmaceutical patents is costly, time consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation, including the Leahy-Smith America Invents Act signed into law on September 16, 2011. That Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and new venues and opportunities for competitors to challenge patent portfolios. Because of that Act, the U.S. patent system is now a first to file system, which may make it more difficult to obtain patent protection for inventions and increase the uncertainties and costs surrounding the prosecution of our or our collaboration partners patent applications and the enforcement or defense of our or our collaboration partners issued patents, all of which could materially adversely affect our business, results of operations and financial condition.

The United States Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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.

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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.

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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:

- results from, or any delays in, clinical trial programs relating to our product candidates, including the ongoing and planned clinical trials for tenapanor and RDX022;
- ability to commercialize or obtain regulatory approval for our product candidates, or delays in commercializing or obtaining regulatory approval;
- announcements of regulatory approval or a complete response letter to tenapanor or RDX022, or specific label indications or patient populations for its use, or changes or delays in the regulatory review process;
- announcements relating to 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 clinical trials, manufacturing supply chain or sales and marketing activities;
- changes or developments in laws or regulations applicable to our product candidates;
- the success of our testing and clinical trials;
- 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;

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

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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.

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

As of December 31, 2015, entities affiliated with New Enterprise Associates, a venture capital fund associated with one of our directors, collectively beneficially hold approximately 39.65% of our capital stock, including warrants exercisable for shares of our common stock, and together our executive officers, directors, and affiliated stockholders beneficially owned approximately 42.39% of our capital stock, including warrants exercisable for shares of our common stock. Therefore, these stockholders may be able to determine all matters requiring stockholder approval, and the entities affiliated with New Enterprise Associates alone, will have significant ability to influence decisions through their ownership position. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that certain stockholders may feel are in their best interest as one of our stockholders.

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.

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, 2015, we had 25,964,886 shares of common stock outstanding. Of those shares, approximately 10.5 million, were held by current directors, executive officers and other affiliates, or may otherwise be subject to Rule 144 under the Securities Act of 1933, or the Securities Act.

In addition, as of December 31, 2015, approximately 1.3 million shares of common stock that are subject to outstanding options, were eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, and Rule 144 and Rule 701 under the Securities Act. In addition, approximately 2.2 million shares that are subject to outstanding warrants are eligible for sale in the public market. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

The holders of approximately 9.0 million shares of our outstanding common stock as of December 31, 2015, are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

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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 66 ⅔% 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 acquiror;
- the ability of our board of directors to alter our bylaws without obtaining stockholder approval;
- the required approval of at least 66 ⅔% 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 acquiror from conducting a solicitation of proxies to elect the acquiror 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.

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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 indemnitees, 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.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our headquarters is currently located in Fremont, California, and consists of approximately 39,781 square feet of leased office and laboratory space under a lease that currently expires in September 2019. We expect that during 2016, we will either increase the square footage available to us in our existing facility or obtain additional space in another location in order to accommodate our anticipated needs. We may also require additional space and facilities as our business expands.

ITEM 3. 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, 2015, there is no litigation pending that would reasonably be expected to have a material adverse effect on our results of operations and financial condition.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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PART II

ITEM 5. MARKET FOR REGISTRANT S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Price Range of Common Stock

Our common stock commenced trading on The NASDAQ Global Select Market under the symbol ARDX on June 19, 2014. Prior to that date, there was no public trading market for our common stock. The following table sets forth, for the periods indicated, the high and low reported sales prices of our common stock as reported on The NASDAQ Global Select Market:

	High	Low
Year ended December 31, 2015:		
First Quarter	$ 27.99	$ 13.00
Second Quarter	$ 17.66	$ 7.95
Third Quarter	$ 22.48	$ 15.00
Fourth Quarter	$ 21.27	$ 15.13

	High	Low
Year Ended December 31, 2014:		
Second Quarter (from June 19, 2014)	$ 16.00	$ 14.05
Third Quarter	$ 21.60	$ 11.37
Fourth Quarter	$ 35.48	$ 15.10

As of March 2, 2016, there were 38 holders of record of our common stock. The last reported sale price of the common stock on March 2, 2016 was $10.54 per share.

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.

Recent Sales of Unregistered Securities

On June 2, 2015, we entered into a Securities Purchase Agreement, or the Purchase Agreement, with the investors named therein, or the Investors. Pursuant to the Purchase Agreement, on June 5, 2015 we sold an aggregate of 7,242,992 shares of common stock, or the Shares, and warrants, or the Warrants, to purchase 2,172,899 shares of common stock, or Warrant Shares, for aggregate gross proceeds of approximately $77.8 million, or net proceeds, after deducting issuance costs, of approximately $74.3 million. The purchase price for each Share was $10.70, which was equal to the consolidated closing bid price on the NASDAQ Global Market on the day of pricing, June 2, 2015. The purchase price for each Warrant was equal to $0.125 for each Warrant Share, consistent with NASDAQ Global Market requirements for an at the market offering, and the Warrants are exercisable at an exercise price of $13.91 per share. Investors participating in the offering include entities associated with New Enterprise Associates, a venture capital firm that is one of our significant stockholders, and a combination of new and existing investors, including RA Capital Management, Broadfin Capital LLC, Cormorant Asset Management LLC, Foresite Capital Management, LLC, Rock Springs Capital Management LP, and a fund managed by Sabby Capital, LLC. Leerink Partners LLC

acted as the sole placement agent of the offering and Wedbush PacGrow acted as a financial advisor in connection with the offering. We expect to use the net proceeds from the offering to develop our drug candidates, tenapanor and RDX022.

In connection with the Purchase Agreement, we entered into a Registration Rights Agreement, or the Registration Rights Agreement, with the Investors. Pursuant to the Registration Rights Agreement, we agreed to prepare and file a registration statement with the Securities and Exchange Commission, or SEC, by July 20, 2015 for purposes of registering the resale of the Shares, the Warrant Shares, and any shares of common stock issued as a dividend or other distribution with respect to the Shares or Warrant Shares. We filed the registration

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statement on July 13, 2015 and it was declared effective by the SEC on July 20, 2015. We also agreed, among other things, to indemnify the selling holders under the registration statements from certain liabilities and to pay all fees and expenses (excluding underwriting discounts and selling commissions and all legal fees of any selling holder) incident to our obligations under the Registration Rights Agreement.

The financing is exempt from registration pursuant to the exemption for transactions by an issuer not involving any public offering under Section 4(2) the Securities Act of 1933, as amended, and Regulation D under the Securities Act of 1933, as amended.

Use of Proceeds

Not applicable.

Issuer Purchases of Equity Securities

Not applicable.

Stock Price Performance Graph

The following stock performance graph compares our total stock return with the total return for (i) the NASDAQ Composite Index (depicted in the graph as IXIC) and the (ii) the NASDAQ Biotechnology Index (depicted in the graph as NBI) for the period from June 19, 2014 (the date our common stock commenced trading on The NASDAQ Global Market) through December 31, 2015. The figures represented below assume an investment of $100 in our common stock at the closing price of $14.11 on June 19, 2014 and in the NASDAQ Composite Index and the NASDAQ Biotechnology Index on June 19, 2014 and the reinvestment of dividends into shares of common stock. The comparisons in the table are required by the Securities and Exchange Commission, or SEC, and are not intended to forecast or be indicative of possible future performance of our common stock. This graph shall not be deemed soliciting material or be deemed filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

$100 invested in stock or index	Ticker	6/19/14	6/30/14	9/30/14	12/31/14	3/31/15	6/30/15	9/30/15	12/31/15
Ardelyx, Inc	ARDX	$ 100.00	$ 113.18	$ 100.71	$ 133.88	$ 92.77	$ 113.18	$ 122.47	$ 128.42
NASDAQ Composite Index	IXIC	$ 100.00	$ 101.12	$ 103.08	$ 108.64	$ 112.42	$ 114.40	$ 105.98	$ 114.87
NASDAQ Biotechnology Index	NBI	$ 100.00	$ 102.62	$ 109.22	$ 121.38	$ 137.41	$ 147.63	$ 121.06	$ 135.24

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ITEM 6. SELECTED FINANCIAL DATA

The data set forth below is not necessarily indicative of the results of future operations and should be read in conjunction with the financial statements and the notes included elsewhere in this annual report on Form 10-K and also with **ITEM 7. MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS** and our financial statements and the related notes included in this Annual Report on Form 10-K.

	Year Ended December 31,			
	2015	2014	2013	2012
	(in thousands, except share and per share amounts)			
Statement of Operations Data:				
Revenue:				
Licensing revenue	$ 21,611	$ 18,394	$ 8,063	$ 3,182
Collaborative development revenue	2,415	13,229	20,865	2,228
Total revenue	24,026	31,623	28,928	5,410
Operating expenses:				
Research and development	39,885	25,900	28,093	10,184
General and administrative	13,530	7,287	3,700	4,031
Total operating expenses	53,415	33,187	31,793	14,215
Loss from operations	(29,389)	(1,564)	(2,865)	(8,805)
Other (expense) income, net	(261)	10	(52)	(30)
Change in fair value of preferred stock warrant liability		(1,593)	(3,506)	(950)
Loss before provision for income taxes	(29,650)	(3,147)	(6,423)	(9,785)
Benefit from (provision for) income taxes	29	(67)	(141)	
Net loss and comprehensive loss	$ (29,621)	$ (3,214)	$ (6,564)	$ (9,785)
Net loss per common share, basic and diluted	$ (1.29)	$ (0.31)	$ (5.82)	$ 11.32
Shares used to compute net loss per common share, basic and dilute	22,892,640	10,248,337	1,127,948	864,020

	As of December 31,			
	2015	2014	2013	2012
	(in thousands)			
Balance Sheet Data:				
Cash and cash equivalent	$ 107,004	$ 107,286	$ 34,435	$ 32,903
Total assets	116,946	113,414	42,904	37,884
Deferred revenue		47,053	40,298	32,662

Convertible preferred stock warrant liability			6,456	2,950
Convertible preferred stock			56,155	56,155
Accumulated deficit	(101,488)	(71,867)	(68,653)	(62,089)
Total stockholders equity (deficit)	108,901	60,682	(63,479)	(57,392)

ITEM 7. MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the section of this report entitled Selected Financial Data and 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

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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.

OVERVIEW

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of innovative, minimally-systemic therapeutic drugs that work exclusively in the gastrointestinal, or GI, tract to treat cardio-renal and GI diseases. We have developed a proprietary drug discovery and design platform enabling us, in a rapid and cost-efficient manner, to discover and design novel drug candidates. Utilizing our platform, we discovered and designed our lead product candidate, tenapanor, which is currently being evaluated in two pivotal Phase 3 clinical studies in patients with constipation-predominant irritable bowel syndrome, or IBS-C, and we currently expect to receive results from those trials in 2017. In a Phase 2b clinical study, tenapanor demonstrated the ability to improve the symptoms of IBS-C. In a separate Phase 2b clinical trial, tenapanor demonstrated the ability to lower elevated serum phosphorus levels in patients with end-stage renal disease, or ESRD. We have initiated an additional Phase 2b clinical trial to evaluate dosing regimens of tenapanor for the treatment of hyperphosphatemia, or elevated serum phosphorus, in ESRD patients, and we expect to receive results from this trial in the second half of 2016. We are developing another drug candidate, RDX022, for the treatment of hyperkalemia, or elevated serum potassium. In January 2016, we announced the results of an open label clinical study evaluating the pharmacodynamic activity of RDX022 in healthy adult volunteers. The study demonstrated that RDX022 was generally well-tolerated at all doses evaluated and effectively binds to potassium in the GI tract, supporting our plans to proceed with a Phase 3 clinical program, which we currently expect to initiate in the second half of 2016. We are pursuing a 505(b)(2) regulatory pathway for RDX022. We have additional drug candidates in earlier stages of research and development focused in GI and cardio-renal diseases including RDX009, a secretagogue of glucagon-like peptide-1, or GLP-1, and glucagon-like peptide-2, or GLP-2, and RDX013, a potassium secretagogue. We currently expect to file an investigational new drug application, or IND, for RDX009 in the second half of 2016.

Since commencing operations in October 2007, substantially all our efforts have been dedicated to our research and development activities, including developing our clinical product candidates, tenapanor and RDX022, and developing our proprietary drug discovery and design platform. We have not generated any revenues from product sales and have no products approved for commercialization. Our only revenue has been pursuant to our collaboration partnerships with AstraZenaca and Sanofi, each of which has been terminated. As of December 31, 2015, we had an accumulated deficit of $101.5 million.

We expect that our operating losses will substantially increase for the foreseeable future as we as we continue the development of tenapanor and RDX022, including costs associated with conducting the Phase 3 clinical programs for tenapanor and RDX022, research and development, conducting preclinical studies and clinical trials for our other programs, obtaining regulatory approvals, and developing and maintaining scalable manufacturing processes for our product candidates. To date, we have funded our operations from the sale and issuance of common stock, convertible preferred stock, and funds from our collaborations.

On June 24, 2014, we completed our initial public offering and sold 4,928,900 shares of our common stock, which included 642,900 shares of common stock purchased by the underwriters upon the full exercise of their option to purchase additional shares of common stock. We received cash proceeds of $61.2 million, net of underwriting discounts and commissions and expenses paid by us.

In June 2015, we closed a private placement financing in which we raised approximately $77.8 million in gross proceeds or $74.3 million in net proceeds, after deducting issuance costs.

On January 13, 2016, we completed a registered underwritten public offering and sold an aggregate of 8,625,000 shares of common stock, which included 1,125,000 shares of common stock purchased by the underwriters upon the full exercise of their option to purchase additional shares of stock. We received net proceeds of approximately $80.4 million, net of underwriting discounts and commissions and expenses paid by us.

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AstraZeneca AB (AstraZeneca)

In October 2012, we entered into a collaboration partnership with AstraZeneca for the worldwide development and commercialization of tenapanor. Under the terms of the AstraZeneca collaboration partnership agreement, or the AstraZeneca Agreement, we received an up-front license fee of $35.0 million in October 2012, a $15.0 million payment in December 2013 and a $25.0 million payment in May 2014. The amounts were recorded as deferred revenue when received and were recognized as revenue on a straight-line basis over the remaining estimated period of performance under the AstraZeneca Agreement, which during the three months ended March 31, 2015, we estimated to be December 2017.

In June 2015, we entered into a termination agreement with AstraZeneca (the Termination Agreement) pursuant to which all licenses granted to AstraZeneca to our portfolio of NHE3 inhibitors, including our lead product candidate, tenapanor, were terminated, except for the limited purpose of allowing AstraZeneca to satisfy its obligations under the Termination Agreement. Under the terms of the Termination Agreement, we agreed to pay AstraZeneca certain amounts for the return of the licenses granted to it, including (a) an upfront fee of $15.0 million, (b) future royalties at a royalty rate of 10% of net sales of tenapanor or other NHE3 products by us or our licensees, and (c) 20% of non-royalty revenue received from a new collaboration partner should we elect to license, or otherwise provide rights to develop and commercialize tenapanor or another NHE3 inhibitor. The amounts described in (a)-(c) are capped at the aggregate amount of $90.0 million. We also paid AstraZeneca $10.0 million as reimbursement for certain research and development expenses incurred by AstraZeneca under the collaboration agreement during 2015, and for the acceleration of the transfer of information and materials to us. Under the Termination Agreement, AstraZeneca was obligated to complete the manufacturing of clinical trial material necessary for the Phase 3 clinical program for tenapanor in IBS-C, and we agreed to pay AstraZeneca a maximum amount of $10 million for such clinical trial material, which maximum amount was subsequently reduced to $8.0 million pursuant to an amendment to the Termination Agreement (Amendment Number One).

As the AstraZeneca Agreement was terminated in June 2015, we recognized the remaining deferred revenue balance of $43.1 million during the three months ended June 30, 2015. In the three months ended June 30, 2015, we recorded the $15.0 million upfront payment for the return of the licenses as well as the $10.0 million payment for reimbursement of research and development expenses and the acceleration of the transfer of information and materials as a reduction in licensing revenue in the condensed statements of operations and comprehensive loss. We recorded $7.3 million in expenses incurred for the tenapanor clinical trial material from AstraZeneca during the year ended December 31, 2015.

Sanofi SA (Sanofi)

In February 2014, we entered into an option and license agreement with Sanofi, or the Sanofi Agreement, under which we granted Sanofi an exclusive worldwide license to conduct research utilizing our program evaluating small molecule NaP2b inhibitors for the treatment of hyperphosphatemia in CKD patients on dialysis. In addition, Sanofi had the option under the Sanofi Agreement to obtain an exclusive license to develop, manufacture and commercialize our NaP2b inhibitors. Under the Sanofi Agreement, we received an upfront payment of $1.25 million in March 2014, which was fully recognized as licensing revenue in May 2014 after we completed our obligation to provide Sanofi the background know-how, listed patents, and materials described in the Sanofi Agreement.

The Sanofi Agreement was terminated effective September 30, 2015 and all rights were returned to Ardelyx. There was no payment associated with termination and the return of rights to Ardelyx.

FINANCIAL OPERATIONS OVERVIEW

Revenue

We have not generated any revenue from product sales. Our revenue to date has been generated from non-refundable license payments and reimbursements for research and development expenses under our license

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agreements with AstraZeneca and Sanofi, both of which were terminated in 2015. We recognize revenue from upfront payments ratably over the term of our estimated period of performance under the agreement, which we consider to be licensing revenue. Should any of our agreements contain event based payments, such payments are recorded as revenue when we achieve the underlying milestone if it is deemed to be a substantive milestone at the date the arrangement is entered into. To the extent that non-substantive milestones are achieved and we have remaining performance obligations, milestones are deferred and recognized as revenue over the estimated remaining period of performance. Reimbursements from AstraZeneca for development costs incurred under our license and collaboration agreement with them were classified as collaborative development revenue.

Research and Development Expenses

Research and development expenses represent costs incurred to conduct research, such as the discovery and development of our unpartnered product candidates, and prior to the termination of the AstraZeneca Agreement, research and development expenses also included costs we incurred in connection with the development of tenapanor pursuant to our license agreement with AstraZeneca. We recognize all research and development expenses as they are incurred.

Research and development expenses consist of the following:

- external research and development expenses incurred under agreements with consultants, third-party contract research organizations 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;
- employee-related expenses, which include salaries, benefits 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 and other supplies.

We expect our research and development expenses will increase substantially in the future as we progress the development of tenapanor and our other our internal product candidates, advance our discovery research projects into the preclinical stage and continue our early stage research including further development of our APECCS cell-culture system. The process of conducting preclinical studies and clinical trials necessary to obtain regulatory approval is costly and time consuming. We, or our collaboration partner(s), if any, may never succeed in achieving marketing approval for any of our product candidates. The probability of success of each of the product candidates may be affected by numerous factors, including preclinical data, clinical data, competition, manufacturing capability and commercial viability.

The successful development of our product candidates is highly uncertain and may not result in approved products. Completion dates and completion costs can vary significantly for each product candidate and are difficult to predict. Given the uncertainty associated with clinical trial enrollment and the risks inherent in the development process, we are unable to determine the duration and completion costs of current or future clinical trials of our product candidates or if and to what extent we will generate revenues from the commercialization and sale of any of our product

candidates. We anticipate that we will make determinations as to which programs to pursue and how much funding to direct to each program on an ongoing basis in response to the scientific and clinical success of each product candidate, as well as an ongoing assessment as to each product candidate s commercial potential. We will need to raise additional capital and will seek additional collaboration partnerships in the future in order to complete the development and commercialization of our product candidates, including tenapanor.

General and Administrative

General and administrative expenses include personnel costs, travel expenses and other expenses for outside professional services, including legal, human resources, audit and accounting services. Personnel costs includes

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salaries, bonus, benefits and stock-based compensation. Since becoming a public company in 2014, we have incurred and expect to continue to incur expenses required of public companies, including costs to comply with the rules and regulations applicable to companies listed on a national securities exchange and costs related to compliance and reporting obligations pursuant to the rules and regulations of the SEC. Other related public company costs include increased expenses for additional insurance, investor relations and professional services.

Income Taxes

We recorded income tax benefit for the year ended December 31, 2015 primarily due to the provision to return true-up for the year ended December 31, 2014.

For each of the tax years ended December 31, 2014 and 2013, the Company recorded an income tax provision due to the minimum taxes which resulted from upfront and milestone payments received from AstraZeneca.

Due to the history of cumulative losses, the Company s deferred taxes continue to be subject to full valuation allowance for the tax years ended December 31, 2015, 2014, and 2013.

CRITICAL ACCOUNTING POLICES AND ESTIMATES

A detailed discussion of our significant accounting policies can be found in Note 1 of the Notes to Financial Statements, and the impact and risks associated with our accounting policies are discussed throughout this Annual Report on Form 10-K and in the footnotes to the financial statements. 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. We consider certain accounting policies related to revenue recognition, accrued liabilities, and use of estimates to be critical policies. 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 believe the following policies to be the most critical to an understanding of our financial condition and results of operations because they require us to make estimates, assumptions and judgments about matters that are inherently uncertain.

Revenue Recognition

Research Activities

Revenue from research activities made under collaboration partnership agreements are recognized as the services are provided and when there is persuasive evidence that an arrangement exists, delivery has occurred, the price is fixed or determinable, and collectability is reasonably assured. Revenue generated from research and license agreements typically includes up-front signing or license fees, cost reimbursements, research services, minimum sublicense fees, milestone payments, and royalties on future licensees product sales.

Multiple-Element Arrangements

For revenue agreements with multiple-element arrangements, such as license and development agreements, we allocate revenue to each non-contingent unit of accounting based on the relative selling price of each unit. When applying the relative selling price method, we determine the selling price for each deliverable using vendor-specific

objective evidence or third-party evidence. If neither exists, we use the best estimate of selling price for that deliverable. Revenue allocated is then recognized when the four basic revenue recognition criteria are met for each unit. Our obligations under the agreements may include the transfer of intellectual property rights in the form of licenses, obligations to provide research and development services and obligations to

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participate on certain development committees with the collaboration partner. We make judgments that affect the period over which we recognize revenue. On a quarterly basis, we review our estimated period of performance for our license revenue based on the progress under the arrangement and account for the impact of any changes in estimated periods of performance on a prospective basis.

Cost Reimbursement

We recognize cost reimbursement revenue under collaboration partnership agreements as the related research and development costs for services are rendered. Deferred revenue represents the portion of research or license payments received that have not been earned.

Milestone

A milestone is considered substantive when the consideration earned from the achievement of the milestone (i) is commensurate with either our performance to achieve the milestone or the enhancement of value of the item delivered as a result of a specific outcome resulting from our performance to achieve the milestone, (ii) relates solely to past performance and (iii) is reasonable relative to all deliverables and payment terms in the arrangement. Such payments that are contingent upon the achievement of a substantive milestone are recognized entirely as revenue in the period in which the milestone is achieved. To the extent that non-substantive milestones are achieved and we have remaining performance obligations, milestones are deferred and recognized as revenue over the estimated remaining period of performance. If there were no remaining performance obligations, we recognize the revenue in the period it is earned.

Research and Development Expense and Accruals

Research and development expenses include employee-related expenses, clinical trial costs, consultant fees, supplies, manufacturing costs for research and development programs and allocations of corporate costs. All such costs are charged to research and development expense as incurred. These expenses result from our independent research and development efforts as well as efforts associated with collaborations. Our expense accruals for clinical trials are based on estimates of the services received from clinical trial centers and clinical research organizations. If possible, we obtain information regarding unbilled services directly from service providers. However, we may be required to estimate these services based on information available to our product development or administrative staff. If we underestimate or overestimate the activity associated with a study or service at a given point in time, adjustments to research and development expenses may be necessary in future periods. Historically, our estimated accrued liabilities have approximated actual expense incurred.

Stock-Based Compensation

We estimate the fair value of stock options and Employee Stock Purchase Plan (ESPP) shares using the Black-Scholes valuation model. The Black-Scholes model requires the input of highly subjective assumptions. The most significant assumptions are our estimates of the expected volatility and the expected term of the award. The Black-Scholes option-pricing model requires the use of highly subjective assumptions which determine the fair value of stock-based awards. These assumptions include:

Expected Term The Company has very 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 was 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.

Expected Volatility Since the Company has limited information on the volatility of its common stock due to no significant trading history, the expected stock price volatility was calculated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle, and financial leverage of the Company.

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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 the Company s stock option grants.

Expected Dividend To date, the Company has not declared or paid any cash dividends and does not have any plans to do so in the future. Therefore, the Company used 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 to be 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.

Prior to our IPO in June 2014, our board of directors, with the assistance of management and independent consultants, performed fair value analyses for the valuation of our common stock. For grants made on dates for which there was no contemporaneous valuation to utilize in setting the exercise price of our common stock, and given the absence of an active market for our common stock prior to our IPO in June 2014, our board of directors determined the fair value of our common stock on the date of grant based on several factors, including:

- progress of our research and development efforts;
- our operating results and financial condition, including our levels of available capital resources;
- rights and preferences of our common stock compared to the rights and preferences of our other outstanding equity securities;
- material risks related to our business;
- equity market conditions affecting comparable public companies;
- the likelihood of achieving a liquidity event for the shares of common stock, such as an initial public offering given prevailing market and biotechnology sector conditions; and
- that the grants involved illiquid securities in a private company.

For valuations after the completion of our initial public offering on June 18, 2014, our board of directors determined the fair value of each share of underlying common stock based on the closing price of our common stock as reported on the date of grant.

Estimated Fair Value of Convertible Preferred Stock Warrants

Freestanding warrants for shares that were contingently redeemable were classified as a liability on the balance sheet at their estimated fair value. At the end of each reporting period, the change in estimated fair value during the period was recorded in change in fair value of convertible preferred stock warrant liability in the statement of operations and comprehensive loss. Beginning in 2013, we estimated the fair value of the warrant liability using a hybrid of the options pricing method, or OPM, and the probability-weighted return method, or PWERM. The hybrid method applied the PWERM utilizing the probability of two exit scenarios, going public or being acquired, and the OPM was utilized in the remaining private scenario. The scenarios were weighted based on our estimate of the assigned probability. We continued to adjust the carrying value of the warrants until the completion of our initial public offering in June 2014, at which time the liability was reclassified to additional paid-in capital and is no longer subject to remeasurement.

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RESULTS OF OPERATIONS

Comparison of the Years Ended December 31, 2015 and 2014

Revenue

	Year Ended December 31, 2015	2014	Dollar Change
		(in thousands)	
Revenue:			
Licensing revenue	$ 21,611	$ 18,394	$ 3,217
Collaborative development revenue	2,415	13,229	(10,814)
Total revenue	$ 24,026	$ 31,623	$ (7,597)

Licensing revenue for the year ended December 31, 2015 was $21.6 million, an increase of $3.2 million, or 17%, compared to $18.4 million for the year ended December 31, 2014. The increase reflects the impact of the recognition of $3.9 million of licensing revenue for the three months ended March 31, 2015 and the recognition of the remaining deferred revenue balance of $43.1 million during the three months ended June 30, 2015 and as a result of the Termination Agreement with AstraZeneca. This recognition of deferred revenue was primarily offset by an aggregate of $25.0 million in upfront payments made to AstraZeneca in connection with the Termination Agreement.

Collaborative development revenue consists of our development expenses that were reimbursable to us by AstraZeneca as part of our license agreement. Collaborative development revenue for the year ended December 31, 2015 was $2.4 million, a decrease of $10.8 million, or 82%, compared to $13.2 million for the year ended December 31, 2014. The decrease was due to the reduction in the development activities that we performed for tenapanor in the first half of 2015, and due to the Termination Agreement with AstraZeneca.

Research and Development

	Year Ended December 31, 2015	2014	Dollar Change
		(in thousands)	
Research and development	$ 39,885	$ 25,900	$ 13,985

Research and development expenses were $39.9 million for the year ended December 31, 2015, an increase of $14.0 million, or 54%, compared to $25.9 million for the year ended December 31, 2014. The change was primarily due to the $7.3 million in expenses incurred for the tenapanor clinical trial material from AstraZeneca as well as an increase of $6.7 million in expenses incurred for clinical development activities associated with tenapanor and RDX022, and manufacturing process development for RDX022.

General and Administrative

	Year Ended December 31,

	2015	2014	Dollar Change
		(in thousands)	
General and administrative	$ 13,530	$ 7,287	$ 6,243

General and administrative expenses were $13.5 million for the year ended December 31, 2015, an increase of $6.2 million, or 86%, compared to $7.3 million for the year ended December 31, 2014. The increase was primarily due to an increase in professional services fees, personnel and public company costs.

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Change in Fair Value of Preferred Stock Warrant Liability

	Year Ended December 31, 2015	2014	Dollar Change
		(in thousands)	
Change in Fair Value of Preferred Stock Warrant Liability	$	$ (1,593)	$ 1,593

Change in fair value of preferred stock warrant liability was zero for the year ended December 31, 2015 compared to $(1.6) million for the year ended December 31, 2014. The preferred stock warrants were net exercised upon the completion of our initial public offering (IPO) in June 2014 and are no longer subject to remeasurement.

Comparison of the Years Ended December 31, 2014 and 2013

Revenue

	Year Ended December 31, 2014	2013	Dollar Change
		(in thousands)	
Revenue:			
Licensing revenue	$ 18,394	$ 8,063	$ 10,331
Collaborative development revenue	13,229	20,865	(7,636)
Total revenue	$ 31,623	$ 28,928	$ 2,695

Licensing revenue for the year ended December 31, 2014 was $18.4 million, an increase of $10.3 million, or 128%, compared to $8.1 million for the year ended December 31, 2013. The increase was primarily due to the amortization of deferred revenue from the $15.0 million development milestone payment we received in December 2013 related to the amendment to the AstraZeneca agreement and the $25.0 million development milestone payment we received in May 2014 related to the dosing of the first patient in the Phase 2b ESRD clinical trial in hyperphosphatemia in April 2014, which were both recognized ratably over the expected period of performance under the agreement. The estimated period of performance was based on the completion of all of the Phase 2 clinical trials for tenapanor, which we estimated to be December 2017. This estimated period was extended during the third quarter of 2014 from December 2016 to December 2017 due to the extension of the estimated completion date of the remaining Phase 2 clinical trials. The remaining increase was due to the $1.25 million we recognized in May 2014 pursuant to the Option and License Agreement with Sanofi upon the completion of our performance obligations.

Collaborative development revenue consists of our development expenses that are reimbursable to us by AstraZeneca as part of our license agreement. Collaborative development revenue for the year ended December 31, 2014 was $13.2 million, a decrease of $7.6 million, or 37%, compared to $20.9 million for the year ended December 31, 2013. The decrease was due to a decrease in our development activities primarily related to the clinical trials that are a part of the AstraZeneca agreement.

Research and Development

	Year Ended December 31,		
	2014	2013	Dollar Change
	(in thousands)		
Research and development	$ 25,900	$ 28,093	$ (2,193)

Research and development expenses were $25.9 million for the year ended December 31, 2014, a decrease of $2.2 million, or 8%, compared to $28.1 million for the year ended December 31, 2013. The change was due to a decrease in AstraZeneca collaboration development expense of $7.2 million which was primarily driven by the

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decrease in development activities related to tenapanor conducted by us under the license agreement with AstraZeneca. The decrease was offset by a $5.0 million increase in discovery research expenses primarily due to an increase in our personnel costs of $1.2 million, an increase in our stock-based compensation expense of $1.2 million primarily driven by the acceleration of stock option vesting related to the separation agreement with Dr. Charmot, an increase in CRO consultant service fees and other temporary consultant fees of $0.9 million, and an increase in lab supply expenses from increased research activities for unpartnered programs of $0.8 million.

General and Administrative

	Year Ended December 31,		
	2014	2013	Dollar Change
	(in thousands)		
General and administrative	$ 7,287	$ 3,700	$ 3,587

General and administrative expenses were $7.3 million for the year ended December 31, 2014, an increase of $3.6 million, or 97%, compared to $3.7 million for the year ended December 31, 2013. The increase was primarily due to an increase in professional services fees, personnel and operational costs as a result of our being a public company.

Change in Fair Value of Preferred Stock Warrant Liability

	Year Ended December 31,		
	2014	2013	Dollar Change
	(in thousands)		
Change in fair value of preferred stock warrant liability	$ (1,593)	$ (3,506)	$ 1,913

Change in fair value of preferred stock warrant liability was $1.6 million for the year ended December 31, 2014 compared to $3.5 million for the year ended December 31, 2013. The amounts recorded in each of 2014 and 2013 were due to increases in the fair value of our convertible preferred stock as compared with the prior year. The smaller amount recorded in 2014 was due to a smaller increase in the value of the underlying stock as compared with the prior year. The preferred stock warrants were net exercised upon the completion of the IPO and are no longer subject to remeasurement.

LIQUIDITY AND CAPITAL RESOURCES

	December 31, 2015	December 31, 2014
Cash and cash equivalents	$ 107,004	$ 107,286

As of December 31, 2015, we had cash and cash equivalents totaling $107.0 million, which reflects a general ledger overdraft resulting from outstanding checks in the amount of $1.5 million which is included in accounts payable in the balance sheet.

On July 13, 2015, we filed a registration statement on Form S-3 with the SEC, under which we may sell an aggregate of up to $200.0 million of common stock, preferred stock, debt securities, warrants, purchase contract and/or units.

The S-3 shelf registration statement included a prospectus covering the offering, issuance and sale of up to $50.0 million of shares of common stock from time to time in at the market offerings pursuant to an At the Market Issuance Sales Agreement entered into with Cantor Fitzgerald on July 13, 2015.

On January 13, 2016, we completed a registered underwritten public offering pursuant to our S-3 shelf registration statement and sold an aggregate of 8,625,000 shares of common stock, which included 1,125,000

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shares of common stock purchased by the underwriters upon the full exercise of their option to purchase additional shares of stock. We received net proceeds of approximately $80.4 million, net of underwriters discounts and commissions and expenses paid us.

Our primary uses of cash are to fund operating expenses, primarily research and development expenditures. We intend to use our existing cash and cash equivalents, including the net proceeds from our January equity offering to support the tenapanor and RDX022 Phase 3 clinical programs, including manufacturing of clinical trial materials, as well as to support the IND filing for RDX009 and to fund additional research and development for our earlier stage programs. 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.

We believe that our existing capital resources as of December 31, 2015, and the net proceeds from the January 2016 stock offering, will be sufficient to meet our projected operating requirements for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Further, our operating plan may change, and we may need additional funds to meet operational needs and capital requirements for clinical trials and other research and development expenditures. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, and the extent to which we may enter into additional collaboration partnerships with third parties to participate in their development and commercialization, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical studies. Our future funding requirements will depend on many factors, including the following:

- the progress, timing, scope, results and costs of our clinical trial programs evaluating tenapanor in IBS-C and for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis;
- the progress, timing, scope, results and costs of our clinical program for RDX022;
- the time and cost necessary to obtain regulatory approvals for our product candidates and the costs of post-marketing studies that could be required by regulatory authorities;
- our ability to successfully commercialize our product candidates, either alone or with one or more collaboration partners;
- the manufacturing costs of our product candidates, and the availability of one or more suppliers for our product candidates at reasonable costs, both for clinical and commercial supply;
- the selling and marketing costs associated with our product candidates, including the cost and timing of building our sales and marketing capabilities;

our ability to establish and maintain collaboration partnerships, in-license/out-license or other similar arrangements and the financial terms of such agreements;

the timing, receipt, and amount of sales of, or royalties on, our future products, if any;

the sales price and the availability of adequate third-party reimbursement for our product candidates;

the cash requirements of any future acquisitions or discovery of product candidates;

the number and scope of preclinical and discovery programs that we decide to pursue or initiate, and any clinical trials we decide to pursue for other product candidates;

the time and cost necessary to respond to technological and market developments; and

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 our product candidates.

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

	Year Ended December 31,		
	2015	2014	2013
Cash (used in) provided by operating activities	$ (71,840)	$ 13,397	$ 1,811
Cash used in investing activities	(3,454)	(1,856)	(278)
Cash provided by (used in) financing activities	75,012	61,310	(1)

Cash Flows from Operating Activities

Net cash used in operating activities during the year ended December 31, 2015 was approximately $71.8 million, compared to cash provided by operating activities of $13.4 million during 2014.The change was primarily due a decrease of $47.1 million in deferred revenue due to the Termination Agreement with AstraZeneca, net loss for each respective period adjusted for stock-based compensation, depreciation expense and other changes in working capital. Cash provided by operating activities during 2014 was approximately $13.4 million, compared to cash provided by operating activities of $1.8 million during 2013. The change was primarily due to our net loss adjusted for movements in working capital, stock-based compensation and depreciation expense.

Cash Flows from Investing Activities

Cash used in investing activities for the years ended December 31, 2015, 2014 and 2013 was related to our acquisition of property and equipment of $3.5 million, $1.9 million and $0.3 million, respectively. Purchases of property and equipment are primarily related to expansion of our laboratory and related equipment.

Cash Flows from Financing Activities

Cash provided by financing activities for the years ended December 31, 2015 and 2014 was approximately $75.0 million, and $61.3 million, respectively, and was primarily due to proceeds from issuance of common stock.

CONTRACTUAL OBLIGATIONS AND OTHER COMMITMENTS

The following table summarizes our contractual obligations as of December 31, 2015 (in thousands):

	Payments Due by Period				
Contractual Obligation:	**Less than 1 year**	**1 to 3 Years**	**4 to 5 Years**	**More Than 5 Years**	**Total**
Purchase commitments (1)	$ 2,324	$	$	$	$ 2,324
Operating leases (2)	868	1,816	653		3,337
Total contractual obligations	$ 3,192	$ 1,816	$ 653	$	$ 5,661

(1) At December 31, 2015, we had non-cancelable purchase commitments of approximately $2.3 million arising from manufacturing agreements for our clinical candidates and for tenapanor clinical trial material arising from

the Termination Agreement with AstraZeneca.

(2) Operating leases include total future minimum rent payments under non-cancelable operating lease agreements.

OFF-BALANCE SHEET ARRANGEMENTS

As of December 31, 2015, we did not have any off-balance sheet arrangements as defined in Item 303(a)(4) of Regulation S-K as promulgated by the SEC.

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RECENT ACCOUNTING PRONOUNCEMENTS

For a discussion of new accounting pronouncements refer to **NOTE 2, SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES**, to our financial statements appearing elsewhere in this Annual Report on Form 10-K.

JOBS ACT ACCOUNTING ELECTION

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards, and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. In addition, as an emerging growth company, we have reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Interest Rate Risk

We are exposed to market risks in the ordinary course of our business. These risks primarily include risk related to interest rate sensitivities. We had cash and cash equivalents of $107.0 million as of December 31, 2015, which consist of bank deposits and money market funds. Such interest-earning instruments carry a degree of interest rate risk. However, because our investments are primarily short-term in duration, we believe that our exposure to interest rate risk is not significant and a 10% movement in market interest rates would not have a significant impact on the total value of our portfolio. We do not enter into investments for trading or speculative purposes.

Foreign Currency Exchange Risk

Certain expenses related to our international activities are payable in foreign currencies. As a result, factors such as changes in foreign currency exchange rates or weak economic conditions in foreign markets will affect our financial results. We recognized net foreign exchange transaction losses of $0.1 million for the year ended December 31, 2015. We currently do not hedge foreign currency exchange rate exposure. Although the impact of currency fluctuations on our financial results has been immaterial in the past, there can be no guarantee the impact of currency fluctuations related to our international activities will not be material in the future.

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ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

ARDELYX, INC.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders

Ardelyx, Inc.

We have audited the accompanying balance sheets of Ardelyx, Inc. (the Company) as of December 31, 2015 and 2014, and the related statements of operations and comprehensive loss, convertible preferred stock and stockholders equity (deficit), and cash flows for each of the three years in the period ended December 31, 2015. These financial statements are the responsibility of the Company s management. Our responsibility is to express an opinion on these financial statements based on our audits.

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

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Ardelyx, Inc. at December 31, 2015 and 2014, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Redwood City, California

March 4, 2016

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ARDELYX, INC.

BALANCE SHEETS

(in thousands, except share and per share amounts)

	December 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$ 107,004	$ 107,286
Accounts receivable		2,584
Prepaid expenses and other current assets	5,027	1,209
Total current assets	112,031	111,079
Property and equipment, net	4,711	2,131
Other assets	104	104
Restricted cash	100	100
Total assets	$ 116,946	$ 113,414
Liabilities and stockholders equity		
Current liabilities:		
Accounts payable	$ 2,777	$ 3,129
Accrued compensation and benefits	2,366	1,648
Accrued and other liabilities	2,580	780
Deferred revenue, current portion		15,979
Total current liabilities	7,723	21,536
Other long-term liabilities	322	122
Deferred revenue, non-current		31,074
Total liabilities	8,045	52,732
Commitments and contingencies (Note 12)		
Stockholders equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized as of December 31, 2015 and December 31, 2014, respectively; no shares issued and outstanding as of December 31, 2015 and December 31, 2014, respectively.		
Common stock, $0.0001 par value; 300,000,000 shares authorized as of December 31, 2015 and December 31, 2014, respectively; 25,964,886 and 18,589,245 shares issued and outstanding as of December 31, 2015 and December 31, 2014, respectively.	3	2
Additional paid-in capital	210,386	132,547
Accumulated deficit	(101,488)	(71,867)
Total stockholders equity	108,901	60,682

Total liabilities and stockholders equity	$ 116,946	$ 113,414

See accompanying notes.

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ARDELYX INC.

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(in thousands, except share and per share amounts)

	Year Ended December 31,		
	2015	2014	2013
	(in thousands, except share and per share amounts)		
Revenue:			
Licensing revenue	$ 21,611	$ 18,394	$ 8,063
Collaborative development revenue	2,415	13,229	20,865
Total revenue	24,026	31,623	28,928
Operating expenses:			
Research and development	39,885	25,900	28,093
General and administrative	13,530	7,287	3,700
Total operating expenses	53,415	33,187	31,793
Loss from operations	(29,389)	(1,564)	(2,865)
Other income (expense), net	(261)	10	(52)
Change in fair value of preferred stock warrant liability		(1,593)	(3,506)
Loss before provision for income taxes	(29,650)	(3,147)	(6,423)
Benefit from (provision for) income taxes	29	(67)	(141)
Net loss and comprehensive loss	$ (29,621)	$ (3,214)	$ (6,564)
Net loss per common share, basic and diluted	$ (1.29)	$ (0.31)	$ (5.82)
Shares used to compute net loss per common share, basic and diluted	22,892,640	10,248,337	1,127,948

See accompanying notes.

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ARDELYX, INC.

STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS EQUITY (DEFICIT)

(in thousands, except share amounts)

	Convertible Preferred Stock		Common Stock				
	Shares	Amount	Shares	Amount	Additional Paid-In Capital	Accumulated Deficit	Total Stockholders (Deficit) Equity
Balance as of December 31, 2012	11,517,222	$ 56,155	1,001,616	$	$ 4,697	$ (62,089)	$ (57,392)
Exercise of stock options and vesting of early exercised stock options, net of repurchases			223,865		125		125
Stock-based compensation					352		352
Net loss						(6,564)	(6,564)
Balance as of December 31, 2013	11,517,222	56,155	1,225,481		5,174	$ (68,653)	$ (63,479)
Conversion of convertible preferred stock to common stock in connection with initial public offering	(11,517,222)	(56,155)	11,517,222	1	56,154		56,155
Net exercise and conversion of preferred stock warrants to common stock in connection with initial public offering			571,244		8,049		8,049
Exercise of stock options and vesting of early exercised stock options, net of repurchases			336,398		238		238
Issuance of common stock in connection with initial public offering, net of offering costs			4,928,900	1	61,240		61,241
Issuance of common stock for services			10,000		208		208
					1,484		1,484

Stock-based compensation					
Net loss				(3,214)	(3,214)
Balance as of December 31, 2014	18,589,245	2	132,547	(71,867)	60,682
Issuance of common stock upon exercise of options	77,784		111		111
Issuance of common stock under employee stock purchase plan	41,580		548		548
Issuance of common stock and warrants in connection with the private placement, net of expenses of $3,449	7,242,992	1	74,322		74,323
Stock-based compensation			2,634		2,634
Issuance of common stock for services	13,285		194		194
Other			30		30
Net loss				(29,621)	(29,621)
Balance as of December 31, 2015	$ 25,964,886	$ 3	$ 210,386	$ (101,488)	$ 108,901

See accompanying notes.

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ARDELYX, INC.

STATEMENTS OF CASH FLOWS

(in thousands)

	Year Ended December 31,		
	2015	**2014**	**2013**
Operating activities			
Net loss	$ (29,621)	$ (3,214)	$ (6,564)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation expense	829	302	592
Amortization of deferred financing costs	351		
Amortization of deferred compensation for services	107		
Stock-based compensation	2,634	1,692	352
Change in fair value of preferred stock warrant liability		1,593	3,506
Loss from disposal of fixed assets	65		
Changes in operating assets and liabilities:			
Accounts receivable	2,584	3,852	(3,364)
Prepaid expenses and other assets	(4,083)	96	(438)
Accounts payable	(371)	831	1,138
Accrued compensation and benefits	718	721	(38)
Accrued and other liabilities	2,000	647	(1,009)
Deferred revenue	(47,053)	6,755	7,636
Other long-term liabilities		122	
Net cash (used in) provided by operating activities	(71,840)	13,397	1,811
Investing activities			
Purchases of property and equipment	(3,454)	(1,856)	(278)
Net cash used in investing activities	(3,454)	(1,856)	(278)
Financing activities			
Proceeds from issuance of common stock, net	74,323	61,241	
Proceeds from issuance of common stock from exercise of options	659	71	1
Other	30	(2)	(2)
Net cash provided by (used in) financing activities	75,012	61,310	(1)
Net increase in cash and cash equivalents	(282)	72,851	1,532
Cash and cash equivalents at beginning of period	107,286	34,435	32,903
Cash and cash equivalents at end of period	$ 107,004	$ 107,286	$ 34,435
Supplementary disclosure of cash flow information			

Income taxes paid	$ 69	$	$ 160
Supplementary disclosure of non-cash financing information:			
Acquisition of property and equipment included in accounts payable and accrued liabilities	$	$	$
Services settled through the issuance of common stock	$	$ 208	$
Reclassification of convertible preferred warrant liability to additional paid-in capital	$	$ 8,049	$
Conversion of convertible preferred stock to common stock at closing of initial public offering	$	$ 56,155	$

See accompanying notes.

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ARDELYX, INC.

NOTES TO FINANCIAL STATEMENTS

1. ORGANIZATION AND BASIS OF PRESENTATION

Ardelyx, Inc. (the Company) is a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of innovative, minimally-systemic therapeutic drugs that work exclusively in the gastrointestinal, or GI, tract to treat GI and cardio-renal. The Company has developed a proprietary drug discovery and design platform enabling it, in a rapid and cost-efficient manner, to discover and design novel drug candidates. Utilizing its platform, the Company discovered and designed its lead product candidate, tenapanor, which is currently being evaluated in two pivotal Phase 3 clinical studies in patients with constipation-predominant irritable bowel syndrome, or IBS-C. In a Phase 2b clinical study, tenapanor demonstrated the ability to lower elevated serum phosphorus levels in patients with end-stage renal disease, or ESRD. The Company has initiated an additional Phase 2b clinical trial to evaluate dosing regimens of tenapanor for the treatment of hyperphosphatemia, or elevated serum phosphorus in ESRD patients. The Company is developing another drug candidate, RDX022, for the treatment of hyperkalemia, or elevated serum potassium. The Company is pursuing a 505(b)(2) regulatory pathway for RDX022. The Company has additional drug candidates in earlier stages of research and development focused in GI and cardio-renal diseases including RDX009, a secretagogue of glucagon-like peptide-1, or GLP-1, and glucagon-like peptide-2, or GLP-2, and RDX013, a potassium secretagogue.

The Company was incorporated in Delaware on October 17, 2007, under the name Nteryx and changed its name to Ardelyx, Inc. in June 2008. The Company operates in only one business segment, which is the development of biopharmaceutical products.

Initial Public Offering

On June 18, 2014, the Company s registration statement on Form S-1 (File No. 333-196090) relating to the initial public offering (the IPO) of its common stock was declared effective by the SEC, and the IPO closed on June 24, 2014. The Company sold 4,928,900 shares of its common stock, which included the exercise in full by the underwriters of the IPO of their option to purchase 642,900 additional shares of the Company s common stock, and the Company received cash proceeds of $61.2 million from the IPO, net of $7.8 million underwriting discounts and commissions and expenses paid by the Company.

On June 24, 2014, prior to the closing of the IPO, all outstanding shares of convertible preferred stock converted into 11,517,222 shares of common stock with the related carrying value of $56.2 million being reclassified to common stock and additional paid-in capital. In addition, all convertible preferred stock warrants were net exercised and the related convertible preferred stock warrant liability was reclassified to additional paid-in capital.

On June 24, 2014, the Company s Amended and Restated Certificate of Incorporation became effective and the number of shares of capital stock the Company is authorized to issue was increased to 305,000,000 shares, of which 300,000,000 shares may be common stock and 5,000,000 shares may be preferred stock. Both the common stock and preferred stock have a par value of $0.0001 per share. There are no shares of preferred stock outstanding at December 31, 2015 or 2014.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The Company s financial statements have been prepared in accordance with U.S. generally accepted accounting principles (U.S. GAAP).

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Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States 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 revenue recognition, clinical trial accruals, 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 may differ from those estimates.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with an original maturity date of 90 days or less on the date of purchase to be cash equivalents. The Company invests its cash in bank deposits and money market funds.

Cash overdrafts

An overdraft totaling $1.5 million was classified as accounts payable at December 31, 2015. The Company s policy is to report the change in overdrafts as an operating activity in the Statements of Cash Flows.

Restricted Cash

The Company is required to guarantee the credit limit on its corporate credit card with a certificate of deposit of $0.1 million. The collateral will be released upon the cancellation of the corporate credit card.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash and cash equivalents. Cash and cash equivalents are invested through banks and other financial institutions in the United States. Such deposits may be in excess of insured limits. The Company maintains cash and cash equivalents and investments with various high credit quality and capitalized financial institutions.

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, generally 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 its carrying amount. Impairment, if any, would be assessed using discounted cash flows or other appropriate measures of fair value. Through December 31, 2015, there have been no such impairment losses.

Income Taxes

The Company uses 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

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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

Revenue from research activities made under collaboration partnership agreements are recognized as the services are provided and when there is persuasive evidence that an arrangement exists, delivery has occurred, the price is fixed or determinable, and collectability is reasonably assured. Revenue generated from research and licensing agreements typically includes up-front signing or license fees, cost reimbursements, research services, minimum sublicense fees, milestone payments, and royalties on future licensees product sales.

For revenue agreements with multiple-element arrangements, such as license and development agreements, the Company allocates revenue to each unit of accounting based on the relative selling price of each unit. When applying the relative selling price method, the Company determines the selling price for each deliverable using vendor-specific objective evidence or third-party evidence. If neither exists, the Company uses its best estimate of selling price for that deliverable. Revenue allocated is then recognized when the four basic revenue recognition criteria are met for each deliverable.

The Company recognizes revenue from upfront payments ratably over the term of its estimated period of performance under the agreement which is recorded as licensing revenue. Reimbursements for development costs incurred under the Company s license agreement with AstraZeneca are classified as collaborative development revenue. The Company recognizes cost reimbursement revenue under collaboration partnership agreements as the related research and development costs for services are rendered. Deferred revenue represents the portion of research or license payments received which has not been earned.

Revenues from milestones, if they are nonrefundable and deemed substantive, are recognized upon successful accomplishment of the milestones. To the extent that non-substantive milestones are achieved and the Company has remaining performance obligations, milestones are deferred and recognized as revenue over the estimated remaining period of performance. The Company will recognize revenue associated with the non-substantive milestones upon achievement of the milestone if there are no undelivered units and it has no remaining performance obligations. The Company will account for sales-based milestones as royalties that will be recognized as revenue upon achievement of the milestone.

Stock-Based Compensation

The Company measures its stock-based payment awards made to employees and directors based on the estimated fair values of the awards and recognizes the compensation expense over the requisite service period. The Company has selected the Black-Scholes option-pricing model to estimate the fair value of its stock-based awards. Stock-based compensation expense is recognized using the straight-line method. 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, the Company s 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.

The Company accounts for compensation expense related to stock options granted to non-employees based on the fair values estimated using the Black-Scholes model. Stock options granted to non-employees are remeasured at each reporting date until the award is vested.

Research and Development Costs

Research and development expenditures are expensed as incurred. Major components of research and development expenses consist of personnel costs, materials and supplies, and allocations of facilities-related costs, as well as fees paid to consultants and third parties that conduct certain research and development activities

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on the Company s behalf. Payments made to other entities are under agreements that are generally cancelable by the Company. Nonrefundable advance payments for goods or services to be rendered in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Convertible Preferred Stock Warrant Liability

The Company accounted for freestanding warrants to purchase shares of convertible preferred stock that were contingently redeemable as liabilities in the balance sheets at their estimated fair value. Convertible preferred stock warrants were subject to remeasurement at each balance sheet date, and any change in fair value was recognized as a component of other expense, net in the statements of operations and comprehensive loss. The Company continued to adjust the carrying value of the warrants until the closing of the IPO, at which time the warrants were net exercised for shares of the Company s common stock and the liability was reclassified to stockholders equity (deficit).

Comprehensive Loss

Comprehensive loss is composed of two components: net loss and other comprehensive loss. Other comprehensive income (loss) refers to gains and losses that under GAAP are recorded as an element of stockholders equity (deficit), but are excluded from net loss. The Company did not record any transactions within other comprehensive income (loss) in the periods presented and, therefore, the net loss and comprehensive loss were the same for all periods presented.

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 common stock equivalents. 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.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) 2014-09, *Revenue from Contracts with Customers* (ASU 2014-09). This standard outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. The main principle of ASU 2014-09 is to recognize revenues when promised goods or services are transferred to customers in an amount that reflects the consideration that is expected to be received for those goods or services. ASU 2014-09 provides companies with two implementation methods: (i) apply the standard retrospectively to each prior reporting period presented (full retrospective application); or (ii) apply the standard retrospectively with the cumulative effect of initially applying the standard as an adjustment to the opening balance of retained earnings of the annual reporting period that includes the date of initial application (modified retrospective application). This guidance is effective for annual reporting periods beginning after December 15, 2017, including interim periods within that reporting period. The Company has not yet selected an implementation date or a transition method nor has it determined the effect of the standard on its ongoing financial reporting.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements Going Concern: Disclosure of Uncertainties about an Entity s Ability to Continue as a Going Concern (* ASU 2014-15). ASU 2014-15 is intended to define management s responsibility to evaluate whether there is substantial doubt about an organization s

ability to continue as a going concern and to provide related footnote disclosures, if required. ASU 2014-15 is effective for annual reporting periods ending after December 15, 2016, and applies to annual and interim periods thereafter. The Company is evaluating the impact that the adoption of ASU 2014-15 will have on its financial statements and related disclosures.

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In November 2015, the FASB issued ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes*, which eliminates the current requirement to present deferred tax assets and liabilities as current and noncurrent in a classified balance sheet. Instead, entities will be required to classify all deferred tax assets and liabilities as noncurrent. The Company early adopted this accounting standard update, on a prospective basis as of December 31, 2015. All deferred tax assets and liabilities, as of December 31, 2015, have been classified as noncurrent in the accompanying Balance Sheets and the notes thereto. The adoption had no material impact on the Company s balance sheet. No prior periods were retrospectively adjusted.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)*. Under the new guidance, lessees will be required to recognize a lease liability and a right-of-use asset for all leases (with the exception of short-term leases) at the commencement date. Lessor accounting under ASU 2016-02 is largely unchanged. ASU 2016-02 is effective for annual and interim periods beginning on or after December 15, 2018 and early adoption is permitted. Under ASU 2016-02, lessees (for capital and operating leases) and lessors (for sales-type, direct financing, and operating leases) must apply a modified retrospective transition approach for leases existing at, or entered into after, the beginning of the earliest comparative period presented in the financial statements. Lessees and lessors may not apply a full retrospective transition approach. The Company has not yet selected an implementation date nor has it determined the effect of the standard on its ongoing financial reporting.

The Company has reviewed all other significant newly-issued accounting pronouncements and concluded that they either are not applicable to the Company s operations or that no material effect is expected on its financial statements as a result of future adoption.

3. 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 us 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 the quoted prices in active markets that are observable either directly or indirectly in active markets. Examples of assets and liabilities utilizing Level 2 inputs are U.S. government agency bonds, 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 us to develop our own assumptions.

The following table sets forth the fair value of the Company s financial assets and liabilities measured on a recurring basis by level within the fair value hierarchy:

	December 31, 2015			
	Total	**Level 1**	**Level 2**	**Level 3**
		(in thousands)		
Assets:				
Money market funds	$ 105,819	$ 105,819	$	$
Certificates of deposit	100		100	
Total	$ 105,919	$ 105,819	$ 100	$

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	December 31, 2014			
	Total	Level 1	Level 2	Level 3
		(in thousands)		
Assets:				
Money market funds	$ 105,410	$ 105,410	$	$
Certificates of deposit	100		100	
Total	$ 105,510	$ 105,410	$ 100	$

Where quoted prices are available in an active market, securities are classified as Level 1. The Company classifies money market funds as Level 1. When quoted market prices are not available for the specific security, then the Company estimates fair value by using benchmark yields, reported trades, broker/dealer quotes, and issuer spreads. The Company classifies certificates of deposit as Level 2. In certain cases where there is limited activity or less transparency around inputs to valuation, securities are classified as Level 3. There were no transfers between Level 1 and Level 2 during the periods presented.

The carrying amounts reflected in the balance sheets for cash equivalents, accounts receivable, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair values at both December 31, 2015 and December 31, 2014, due to their short-term nature.

4. PROPERTY AND EQUIPMENT

Property and equipment consist of the following:

	December 31,	
	2015	2014
	(in thousands)	
Laboratory equipment	$ 4,471	$ 3,039
Office equipment and furniture	134	229
Construction in progress		362
Leasehold improvements	3,914	2,135
Property and equipment, gross	8,519	5,765
Less: accumulated depreciation	(3,808)	(3,634)
Total property and equipment, net	$ 4,711	$ 2,131

Depreciation and amortization expense totaled $0.8 million, $0.3 million and $0.6 million for the years ended December 31, 2015, 2014 and 2013.

5. COLLABORATION AND LICENSING AGREEMENTS

AstraZeneca AB (AstraZeneca)

In October 2012, the Company entered into a collaboration partnership with AstraZeneca for the worldwide development and commercialization of tenapanor. Under the terms of the AstraZeneca collaboration partnership

agreement, or the AstraZeneca Agreement, the Company received an up-front license fee of $35.0 million in October 2012, a $15.0 million payment in December 2013 and a $25.0 million payment in May 2014. The amounts were recorded as deferred revenue when received and were recognized as revenue on a straight-line basis over the remaining estimated period of performance under the AstraZeneca Agreement, which during the three months ended March 31, 2015, the Company estimated to extend to December 2017.

In June 2015, the Company entered into a termination agreement with AstraZeneca (the Termination Agreement) pursuant to which all licenses granted to AstraZeneca to the Company s portfolio of NHE3 inhibitors, including the Company s lead product candidate, tenapanor, were terminated, except for the limited

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purpose of allowing AstraZeneca to satisfy its obligations under the Termination Agreement. Under the terms of the Termination Agreement, the Company agreed to pay AstraZeneca certain amounts for the return of the licenses granted to it, including (a) an upfront fee of $15.0 million, (b) future royalties at a royalty rate of 10% of net sales of tenapanor or other NHE3 products by the Company or its licensees, and (c) 20% of non-royalty revenue received from a new collaboration partner should the Company elect to license, or otherwise provide rights to develop and commercialize tenapanor, or another NHE3 inhibitor. The amounts payable by the Company as described in (a)-(c) are capped at the aggregate amount of $90.0 million. The Company also paid AstraZeneca $10.0 million as reimbursement for certain research and development expenses incurred by AstraZeneca under the collaboration agreement during 2015 and in consideration of the acceleration of the transfer of information and materials to the Company. In addition, AstraZeneca was obligated to supply the Company with clinical trial materials, drug substance and drug product. The maximum amount that the Company was obligated to pay for such materials was set at $10 million in the Termination Agreement, which maximum amount was subsequently reduced to $8.0 million pursuant to an amendment to the Termination Agreement (Amendment Number One).

As the AstraZeneca Agreement was terminated in June 2015, the Company recognized the remaining deferred revenue balance of $43.1 million during the three months ended June 30, 2015. Also in the three months ended June 30, 2015, the Company recorded the $15.0 million upfront payment for the return of the licenses as well as the $10.0 million payment for reimbursement of research and development expenses and the acceleration of the transfer of information and materials as a reduction in licensing revenue. The Company recorded $7.3 million in expenses incurred for the tenapanor clinical trial material from AstraZeneca during the year ended December 31, 2015.

Sanofi SA (Sanofi)

In February 2014, the Company entered into a license option and license agreement with Sanofi (the Sanofi Agreement) for its phosphate transport NaP2b inhibitor program. Under the terms of the Sanofi Agreement, the Company granted Sanofi an exclusive worldwide license to conduct research utilizing the Company s small molecule NaP2b inhibitors. In addition, Sanofi had the option to obtain an exclusive license to develop, manufacture and commercialize potential products under the agreement. Under the Sanofi Agreement, the Company received a payment of $1.25 million in March 2014, which was fully recognized as licensing revenue in May 2014 after the Company completed its obligation to provide to Sanofi the background know-how, listed patents, and materials described in the Sanofi Agreement.

The Sanofi Agreement was terminated effective September 30, 2015 and all rights were returned to the Company. There was no payment associated with termination and the return of rights to the Company.

6. CONVERTIBLE PREFERRED STOCK

On June 24, 2014, prior to the closing of the IPO, all outstanding shares of convertible preferred stock converted into 11,517,222 shares of common stock with the related carrying value of $56.2 million reclassified to common stock and additional paid-in capital.

7. PREFERRED STOCK WARRANTS

In connection with the closing of the Series B financing in August 2011, the Company issued warrants for the purchase of 574,953 shares of Series B convertible preferred stock. The exercise price of the warrants was $0.09 per share. The preferred stock warrant liability was measured at fair value on a recurring basis. Changes in fair value were recorded in change in fair value of preferred stock warrant liability in the Statements of Operations and Comprehensive Loss. As of December 31, 2013 and for the period in 2014 up to the IPO date, the Company revalued

the warrants using a hybrid of the option pricing method and the probability-weighted expected return method. The hybrid methodology was applied to reflect two exit scenarios, IPO and merger using a market approach and the income approach was used in the stay private scenario. The scenarios were weighted

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based on the Company s estimate of the probability of each scenario: 20% for IPO; 10% for merger and 70% for stay private for the year ended December 31, 2013. As of December 31, 2013, the fair value of this convertible preferred stock warrant liability amounted to $6.5 million. Just prior to the IPO close date of June 24, 2014, the preferred stock warrant liability was remeasured prior to the net exercise of the warrants using the IPO price.

8. EQUITY INCENTIVE PLANS

2008 Plan

The Company 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 nonstatutory 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 (2014 Plan) became effective on June 18, 2014, immediately prior to the time the Company s Registration Statement on Form S-1 became effective. Under the 2014 Plan, 1,419,328 shares of common stock were initially reserved for issuance pursuant to a variety of stock-based compensation awards, including stock options, stock appreciation rights, or SARs, restricted stock awards, restricted stock unit awards, deferred stock awards, deferred stock unit awards, dividend equivalent awards, stock payment awards and performance awards. In addition, 35,221 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 1,454,549. 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 1,153,279 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 10,683,053 shares of stock may be issued upon the exercise of incentive stock options. Effective January 1, 2016, the 2014 Plan share reserve was increased by 1,038, 595 shares.

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Stock Plan Activity

The following table summarizes activity under the 2008 Plan and the 2014 Plan, including grants to nonemployees and restricted stock issued:

	Shares Available for Grant	Options Issued and Outstanding			
		Number of Shares	Average Exercise Price per Share	Aggregate Intrinsic Value (in thousands)	
Balance at December 31, 2012	96,841	1,293,767	$ 0.77		
Options granted	(99,552)	99,552	3.42		
Options exercised		(223,865)	0.56		
Options canceled	6,625	(6,625)	2.23		
Balance at December 31, 2013	3,914	1,162,829	$ 1.03		
Options authorized	1,452,661				
Options granted	(188,888)	188,888	24.41		
Options exercised		(336,398)	0.71		
Options canceled	4,084	(4,084)	2.21		
Options repurchased	3,511	(3,511)	0.55		
Issuance of common stock for services	(10,000)				
Balance at December 31, 2014	1,265,282	1,007,724	$ 5.51		
Options authorized	743,569				
Options granted	(379,709)	379,709	19.60		
Options exercised		(77,784)	1.42		
Options canceled	28,563	(28,563)	12.41		
Issuance of common stock for services	(13,285)				
Balance at December 31, 2015	1,644,420	1,281,086	$ 9.78	$	13,129
Vested and expected to vest at December 31, 2015		1,259,972	$ 9.59	$	13,096
Vested at December 31, 2015		835,860	$ 4.36	$	12,075

The weighted-average grant-date estimated fair value of options granted during the years ended December 31, 2015, 2014 and 2013 was $12.91, $18.53 and $2.68 per share. The aggregate intrinsic value was calculated as the difference

between the exercise price of the options and the estimated fair value of the Company s common stock of $18.12 per share as of December 31, 2015.

The total fair value of options that vested during the years ended December 31, 2015, 2014 and 2013 was $2.4 million, $0.5 million and $0.2 million, respectively.

Employee Stock Purchase Plan

The Company adopted the 2014 Employee Stock Purchase Plan (ESPP) and initially reserved 202,762 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

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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 2,230,374 shares of our common stock may be issued under the ESPP. Effective January 1, 2015, the ESPP share reserve was increased by 185,892. Under the ESPP, participants are offered the option to purchase shares of the Company s common stock at a discount during a series of successive offering periods normally commencing on March 1 and September 1 of each year. The initial offering period commenced on September 1, 2014 and will end on February 27, 2015. The number of shares authorized for issuance under the ESPP as of December 31, 2015 was 388,654, of which 347,074 shares were available for future issuance.

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 employees:

	Year Ended December 31, 2015	
	2015	**2014**
Expected term (years)	0.5	0.5
Volatility	97%	73%
Risk-free interest rate	0.16%	0.05%
Dividend yield	%	%

There were no shares issued during the year ended December 31, 2014 under the ESPP. In 2015, the Company sold 41,580 shares of its common stock under the ESPP. The shares were purchased at a weighted-average purchase price of $13.25 with proceeds of approximately $0.6 million.

Modification of Stock Awards

During September 2014, the Company entered into a Transition and Separation Agreement with its Chief Scientific Officer, Dominique Charmot, under which certain restricted shares that were subject to vesting and repurchase by the Company have become fully vested as of Dr. Charmot s separation from the Company as an employee and director on December 23, 2014. This resulted in the acceleration of the vesting for 58,969 shares of restricted stock. As a result of the acceleration, the Company has recorded a stock-based compensation charge of $0.8 million during the year ended December 31, 2014 to reflect the revised service period for the restricted stock and related vesting of shares that would otherwise not have vested.

Offering of Common Stock and Warrants

In June 2015, the Company sold and issued an aggregate of 7,242,992 shares of its common stock and warrants to purchase 2,172,899 shares of common stock for aggregate gross proceeds of approximately $77.8 million or net proceeds, after deducting issuance costs, of approximately $74.3 million. The purchase price for the common stock was $10.70 per share and the purchase price for the warrants was $0.125 per warrant. The warrants are exercisable for an exercise price of $13.91 per share at any time prior to the earlier of (i) 5 years from the date of issuance or (ii) certain changes in control of the Company. The Company has determined that the warrants should be classified as equity. In July 2015, the Company filed a registration statement with the SEC with respect to the common stock and warrants.

Other than with respect to warrants issued to holders affiliated with New Enterprise Associates, the warrants contain limitations that prevent each holder of warrants from acquiring shares upon exercise of the warrants that would cause the number of shares beneficially owned by it and its affiliates to exceed 9.99% of the total number of shares of the Company s common stock then issued and outstanding. In addition, upon certain changes in control of the Company,

each holder of a warrant can elect to receive, subject to certain limitations and assumptions, securities in a successor entity. None of the warrants issued in June 2015 have been exercised during the year ended December 31, 2015.

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Stock-based Compensation

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

	Year Ended December 31,		
	2015	2014	2013
	(in thousands)		
Research and development	$ 1,327	$ 1,376	$ 200
General and administrative	1,307	316	152
Total stock-based compensation	$ 2,634	$ 1,692	$ 352

As of December 31, 2015, the Company had $5.6 million and $0.1 million of total unrecognized compensation expense, net of estimated forfeitures, related to stock option grants and purchase rights, respectively, that will be recognized over an average vesting period of 2.6 years and 0.2 years, 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 assumptions:

	Year Ended December 31,		
	2015	2014	2013
Expected term (years)	5.89	5.97	6.07
Volatility	75%	94%	98%
Risk-free interest rate	1.64%	1.79%	1.35%
Dividend yield	%	%	%

Expected Term The Company has very 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 was 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.

Expected Volatility Since the Company has limited information on the volatility of its common stock due to no significant trading history, the expected stock price volatility was calculated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle, and financial leverage to the Company.

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 the Company s stock option grants.

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

Options Granted to Nonemployees

The Company has granted options to purchase shares of common stock to consultants in exchange for services performed. The Company granted options to purchase 5,000, 10,000 and 3,333 shares with average exercise prices of $18.58, $20.77 and $3.43 per share, respectively, during the years ended December 31, 2015, 2014 and 2013, respectively. These options vest upon grant or various terms up to three years. The Company recognized non-employees stock compensation expense of $0.2 million, $0.1 million and insignificant during the years ended December 31, 2015, 2014 and 2013, respectively. The fair value of non-employees options was measured using the Black-Scholes option-pricing model reflecting the same assumptions as applied to employee options in each of the reported years, other than the expected life, which is assumed to be the remaining contractual life of the option.

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Issuance of Common Stock for Services

During the year ended December 31, 2015, the Company issued 13,285 shares of common stock in exchange for services performed. The shares issued were valued at $0.2 million based on the fair value of the common stock on the date of grant. During the year ended December 31, 2014, the Company issued 10,000 shares of common stock in exchange for services performed. The shares issued were valued at $0.2 million based on the fair value of the common stock on the date of grant.

9. INCOME TAXES

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

	December 31,		
	2015	**2014**	**2013**
Expected income tax provision at the federal statutory rate	35.0%	35.0%	35.0%
State taxes, net of federal benefit	(3.8)	4.6	(1.4)
Change in valuation allowance	(30.7)	(17.9)	(22.6)
Nondeductible expenses		(20.6)	(20.8)
Tax credits	1.3		7.3
Other	(1.7)	(3.2)	0.3
Income tax provision	0.1%	(2.1%)	(2.2%)

Significant components of the Company s deferred tax assets are as follows:

	December 31,	
	2015	**2014**
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 30,572	$ 11,262
Deferred revenue		11,099
Research credits	1,919	1,260
Other	1,582	1,201
Gross deferred tax assets	34,073	24,822
Valuation allowance	(33,845)	(24,741)
Total deferred tax assets	228	81
Deferred tax liabilities	(228)	(81)
Net deferred tax assets	$	$

Realization of deferred tax assets is dependent on future earnings, if any, the timing and amount of which are uncertain. Accordingly, the deferred tax assets have been fully offset by a valuation allowance. The valuation allowance increased by approximately $9.1 million for the year ended December 31, 2015. The valuation allowance decreased by approximately $0.3 million for the year ended December 31, 2014.

At December 31, 2015, the Company had net operating loss carryforwards for federal income tax purposes of approximately $85.2 million that expire beginning in 2030 if not utilized, and federal research and development tax credit carryforwards of approximately $2.7 million that expire beginning in 2027 if not utilized. In addition, the Company had net operating loss carryforwards for California income tax purposes of approximately $32.3 million that expire beginning in 2030 if not utilized, and state research and development tax credit carryforwards of approximately $3.0 million which can be carried forward indefinitely. Finally, the Company had approximately insignificant and $0.2 million of minimum tax credit carryovers for federal and California income tax purposes, respectively. The minimum tax credits have no expiration date.

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As a result of certain realization requirements of ASC 718, the table of deferred tax assets and liabilities does not include certain deferred tax assets as of December 31, 2015, and December 31, 2014, that arose directly from tax deductions related to equity compensation that are greater than the compensation recognized for financial reporting.

Equity will be increased by approximately $0.7 million if and when such deferred tax assets are ultimately realized. We use ASC 740 ordering when determining when excess tax benefits have been realized.

The future utilization of the 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, future changes under Sections 382 and 383 will not impact the Company s effective tax rate.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows:

	December 31,		
	2015	2014	2013
	(in thousands)		
Balance at beginning of year	$ 2,815	$ 1,411	$ 1,064
Additions (subtractions) based on tax positions related to prior year	(58)	405	
Additions based on tax positions related to current year	541	999	347
Balance at end of year	$ 3,298	$ 2,815	$ 1,411

The unrecognized tax benefits, if recognized and in absence of full valuation allowance, would impact the income tax provision by $3.3 million, $2.8 million and $1.4 million as of December 31, 2015, 2014 and 2013, respectively.

The Company has elected to include interest and penalties as a component of tax expense. During the years ended December 31, 2015, 2014 and 2013, the Company did not recognize accrued interest and penalties related to unrecognized tax benefits. Although the timing and outcome of income tax audit is highly uncertain, the Company does not anticipate that the amount of existing unrecognized tax benefits will significantly change during the next 12 months.

The Company files income tax returns in the U.S. federal, California and Massachusetts tax jurisdictions. Due to the Company s net operating loss and tax credit carryforwards, the income tax returns remain open to U.S. federal and California state tax examinations. The Company is not currently under examination in any tax jurisdiction.

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10. 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 share-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 the Company had net losses for the years ended December 31, 2015, 2014 and 2013, 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 share and per share amounts):

	December 31,		
	2015	2014	2013
Numerator:			
Net loss	$ (29,621)	$ (3,214)	$ (6,564)
Denominator:			
Weighted average number of shares outstanding basic and diluted	22,892,640	10,248,337	1,127,948
Net loss per share basic and diluted	$ (1.29)	$ (0.31)	$ (5.82)

Potentially dilutive securities that were not included in the diluted per share calculations because they would be anti-dilutive were as follows:

	December 31,		
	2015	2014	2013
Convertible preferred stock			11,517,222
Options to purchase common stock	1,244,442	1,007,724	1,162,829
Warrants to purchase convertible preferred stock			574,953
Warrants to purchase common stock	300,302		
Total	1,544,744	1,007,724	13,255,004

11. RELATED PARTY TRANSACTIONS

There were no related party transactions in 2015.

As part of the consulting arrangement with the spouse of an executive of the Company to provide research and development services related to clinical operations, the Company incurred expenses of $0.2 million for services rendered during each of the years ended December 31, 2014 and 2013, respectively.

12. COMMITMENTS AND CONTINGENCIES

The Company has a lease agreement for a facility in Fremont, California that was amended in December 2012 to extend the lease agreement to September 2016. In September 2014, the Company signed the second amendment to its facility lease agreement in Fremont, California to add space and to extend the lease term through September 2019. In addition, the amended lease agreement provides for a tenant improvement allowance of up to $0.6 million. The extended lease has rent escalation clauses through the lease term. Rent increases, including the impact of a rent holiday and leasehold improvement allowance from the landlord, will be recognized as deferred rent and amortized on a straight-line basis over the term of the lease.

Under the terms of the lease agreement, the Company provided the lessor with a security deposit in the amount of $0.1 million. The lessor shall be entitled to draw on the security deposit in the event of any uncured default by the Company under the terms of the lease.

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The future minimum payments under the noncancelable operating lease at December 31, 2015, are as follows (in thousands):

Year ending December 31,	Amounts
2016	868
2017	895
2018	921
2019	653
Total	$ 3,337

Rent expense under operating leases was $0.9 million, $0.6 million and $0.5 million for the years ended December 31, 2015, 2014 and 2013, respectively.

The Company entered into a series of purchase commitments at December 31, 2015 totaling $2.3 million, all of which will be due within the next year.

Guarantees and Indemnifications

The Company indemnifies 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, the Company currently holds director and officer liability insurance. This insurance allows the transfer of risk associated with our exposure and may enable the Company to recover a portion of any future amounts paid. The Company believes that the fair value of these indemnification obligations is minimal. Accordingly, the Company has not recognized any liabilities relating to these obligations for any period presented.

13. SELECTED QUARTERLY FINANCIAL DATA (UNAUDITED)

Selected quarterly financial results from operations for the years ended December 31, 2015 and 2014 are as follows (in thousands, except per share amounts):

	2015 Quarter End			
	March 31,	June 30	September 30	December 31
Total revenue	$ 5,883	$ 18,143	$	$
Operating expenses	9,373	9,087	18,079	16,876
Net (loss) income	(3,502)	9,007	(18,126)	(17,000)
Net (loss) income per share:				
Basic	(0.19)	0.43	(0.70)	(0.65)
Diluted	(0.19)	0.42	(0.70)	(0.65)

	2014 Quarter End			
	March 31,	**June 30**	**September 30**	**December 31**
Total revenue	$ 8,550	$ 9,137	$ 7,598	$ 6,338
Operating expenses	9,014	6,386	7,517	10,270
Net (loss) income	(3,071)	3,753	74	(3,970)
Net (loss) income per share:				
Basic	(2.44)	0.20		(0.21)
Diluted	(2.44)	0.18		(0.21)

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14. SUBSEQUENT EVENTS

In January 2016, the Company completed the sale and issuance of an aggregate of 8,625,000 shares of Common Stock. The Company received net proceeds from the Offering of approximately $80.4 million, after deducting the Underwriters discounts and commissions and estimated offering expenses payable by the Company.

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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, 2015, 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, 2015, 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, 2015, the end 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, 2015, our internal control over financial reporting was effective.

Internal control over financial reporting has inherent limitations. Internal control over financial reporting is a process that involves human diligence and compliance and is subject to lapses in judgment and breakdowns resulting from human failures. Internal control over financial reporting also can be circumvented by collusion or improper management override. Because of such limitations, there is a risk that material misstatements will not be prevented or detected on a timely basis by internal control over financial reporting. However, these inherent limitations are known features of the financial reporting process. Therefore, it is possible to design into the process safeguards to reduce, though not eliminate, this risk.

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Attestation Report of the Registered Public Accounting Firm

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

Changes in Internal Control over Financial Reporting

There were no changes in our internal controls over financial reporting during the quarter ended December 31, 2015 identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

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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 2016 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, 2015, 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.

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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 the signature page of this Annual Report on Form 10-K.

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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: March 4, 2016

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 Mark Kaufmann, 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	President, Chief Executive Officer and Director	March 4, 2016
Michael Raab	*(Principal Executive Officer)*	
/s/ Mark Kaufmann	Chief Financial Officer	March 4, 2016
Mark Kaufmann	*(Principal Financial Officer)*	
/s/ Narani Arasaratnam	VP, Corporate Controller	March 4, 2016
Narani Arasaratnam	*(Principal Accounting Officer)*	
/s/ David Mott	Chairman of the Board of Directors	March 4, 2016
David Mott		
/s/ William Bertrand, Jr.	Director	March 4, 2016

William Bertrand, Jr.		
/s/ Annalisa Jenkins, MBBS, MRCP	Director	March 4, 2016
Annalisa Jenkins, MBBS, MRCP		
/s/ Gordon Ringold, Ph.D.	Director	March 4, 2016
Gordon Ringold, Ph.D.		
/s/ Richard Rodgers	Director	March 4, 2016
Richard Rodgers		

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Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference Form	Date	Number	Filed Herewith
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	
4.3	Form of Warrant issued pursuant to the Securities Purchase Agreement by and among Ardelyx, Inc. and the purchasers signatory thereto, dated June 2, 2015	S-3	7/13/2015	4.3	
10.1(a)	License Agreement, dated as of October 4, 2012, by and among AstraZeneca AB and Ardelyx, Inc.	S-1/A	6/5/2014	10.1(a)	
10.1(b)	Amendment Number One to License Agreement, dated as of December 23, 2013, by and between AstraZeneca AB and Ardelyx, Inc.	S-1/A	6/5/2014	10.1(b)	
10.1(c)	Termination Agreement, dated June 2, 2015, by and between AstraZeneca AB and Ardelyx, Inc.	10-Q	8/12/2015	10.1	
10.1(d)	Amendment No. 1 to Termination Agreement and to Manufacturing and Supply Agreement, dated November 2, 2015 by and between AstraZeneca AB and Ardelyx, Inc.				X
10.2	License and Option Agreement, dated February 21, 2014, by and between Sanofi and Ardelyx, Inc.	S-1/A	6/5/2014	10.2	
10.3	Amended and Restated Investor s Rights Agreement dated June 23, 2011, by and among Ardelyx, Inc. and the investors listed therein.	S-1	5/19/2014	10.3	
10.4(a)	Lease, dated August 8, 2008, by and between 34175 Ardenwood Venture, LLC and Ardelyx, Inc.	S-1	5/19/2014	10.4(a)	
10.4(b)	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)	
10.4(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	
10.5(a)#	Ardelyx, Inc. 2008 Stock Incentive Plan, as amended.	S-1	5/19/2014	10.5(a)	
10.5(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)	
10.5(c)#		S-1	5/19/2014	10.5(c)	

	Form of Restricted Stock Purchase Grant Notice and Restricted Stock Purchase Agreement under the 2008 Stock Incentive Plan, as amended.			
10.6(a)#	Ardelyx, Inc. 2014 Equity Incentive Award Plan.	S-8	7/14/2014	99.3

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Exhibit Number	Exhibit Description	Incorporated by Reference Form	Date	Number	Filed Herewith
10.6(b)#	Form of Stock Option Grant Notice and Stock Option Agreement under the 2014 Equity Incentive Award Plan.	S-1/A	6/18/2014	10.6(b)	
10.6(c)#	Form of Restricted Stock Award Agreement and Restricted Stock Unit Award Grant Notice under the 2014 Equity Incentive Award Plan.	S-1/A	6/18/2014	10.6(c)	
10.7#	Form of Indemnification Agreement for directors and officers.	S-1/A	6/9/2014	10.7	
10.8#	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	
10.9#	Amended and Restated Change in Control Severance Agreement, dated June 6, 2014, by and between Ardelyx, Inc. and Mark Kaufmann.	S-1/A	6/9/2014	10.15	
10.10#	Amended and Restated Change in Control Severance Agreement, dated June 6, 2014, by and between Ardelyx, Inc. and Elizabeth Grammer, Esq.	S-1/A	6/9/2014	10.16	
10.11#	Amended and Restated Change in Control Severance Agreement, dated June 6, 2014, by and between Ardelyx, Inc. and Jeffrey Jacobs, Ph.D.	S-1/A	6/9/2014	10.17	
10.12#	Amended and Restated Change in Control Severance Agreement, dated June 6, 2014, by and between Ardelyx, Inc. and David Rosenbaum, Ph.D.	S-1/A	6/9/2014	10.19	
10.13#	Offer Letter, dated August 11, 2011, by and between Ardelyx, Inc. and Mark Kaufmann.	S-1/A	6/9/2014	10.10	
10.14#	Offer Letter, dated May 2, 2008, by and between Ardelyx, Inc. and Jeff Jacobs, Ph.D.	S-1/A	6/9/2014	10.12	
10.15#	Offer Letter, dated December 28, 2009, by and between Ardelyx, Inc. and David Rosenbaum, Ph.D.	S-1/A	6/9/2014	10.13	
10.16#	Offer Letter, dated November 21, 2012, by and between Ardelyx, Inc. and Elizabeth Grammer, Esq.	S-1/A	6/9/2014	10.14	
10.17#	Offer Letter, dated October 15, 2014, by and between Ardelyx, Inc. and Narani Arasaratnam.	10-K	3/5/2015	10.20	
10.18#	Change in Control Severance Agreement, dated November 26, 2014, by and Between Ardelyx, Inc. and Narani Arasaratnam.	10-K	3/5/2015	10.21	
10.19#	Offer Letter, dated November 21, 2014, by and between Ardelyx, Inc. and Jeremy S. Caldwell, Ph.D.	10-K	3/5/2015	10.22	
10.20#		10-K	3/5/2015	10.23	

	Change in Control Severance Agreement, dated December 19, 2014, by and between Ardelyx, Inc. and Jeremy S. Caldwell, Ph.D.	
10.21#	Offer Letter, dated December 12, 2015, by and between Ardelyx, Inc. and Paul Korner, MD, MBA	X

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Exhibit		Incorporated by Reference			Filed
Number	Exhibit Description	Form	Date	Number	Herewith
10.22#	Ardelyx, Inc. 2014 Employee Stock Purchase Plan.	S-8	7/14/2014	99.6	
10.23#	Non-Employee Director Compensation Program.	S-1/A	6/9/2014	10.21	
10.24	Securities Purchase Agreement by and among Ardelyx, Inc. and the purchasers signatory thereto, dated June 2, 2015	10-Q	8/12/15	10.2	
10.25	Registration Rights Agreement by and among Ardelyx, Inc. and the investors signatory thereto, dated June 2, 2015	S-3	7/13/15	99.1	
12.1	Statement Regarding the Computation of Ratio of Earnings to Fixed Charges				X
23.1	Consent of Ernst & Young LLP, 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.INS	XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document				X
101.PRE	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.

# Indicates management contract or compensatory plan.