ARDELYX, INC.
Form 10-K
March 14, 2018
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2017

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 ZIP CODE)

(510) 745-1700

(REGISTRANT'S TELEPHONE NUMBER, INCLUDING AREA CODE)

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

Title of Each Class:	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

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

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

Indicate by check mark whether the Registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

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

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

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

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

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

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

The aggregate market value of the 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, 2017, based on the last reported sales price of the Registrant's common stock of $5.10 per share was $168,628,611.

The number of shares of Registrant's Common Stock outstanding as of March 8, 2018, was 47,603,568.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the Registrant's Definitive Proxy Statement for its 2018 Annual Meeting of Stockholders, which will be filed with the Commission within 120 days of December 31, 2017, the close of the Registrant's 2017 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, 2017

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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,” “predict,” “positioned,” “seek,” “should,” “target,” “will,” “would,” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our expectation regarding the timing of our filing of a New Drug Application with the U.S.Federal Food and Drug Administration requesting approval to market tenapanor for patients with irritable bowel syndrome with constipation, or IBS-C;
- our expectation regarding the timing of receipt of results from our second Phase 3 clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in patients with end-stage renal disease, or ESRD, on dialysis;
- our expectations regarding our plans for and our participation in the commercialization of tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis, including our expectations regarding our plans to build our own sales and marketing organization to market and sell tenapanor for such indication;
    - our plans to seek one or more collaboration partners to commercialize tenapanor for IBS-C;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates;
- 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 the Ardelyx Primary Enterocyte and Colonocyte Culture System;
- 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;
- 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 specialized biopharmaceutical company focused on developing first-in-class, disruptive medicines for the treatment of renal diseases. Our primary therapeutic focus is on treating people with renal diseases, which affect both the heart and the kidneys. This includes patients with end-stage renal disease, or ESRD, who suffer from elevated serum phosphorus, or hyperphosphatemia; patients with chronic kidney disease, or CKD, and/or heart failure patients with elevated serum potassium, or hyperkalemia. We have also developed a number of programs directed toward treating gastrointestinal, or GI, disorders, including the treatment of irritable bowel syndrome with constipation, or IBS-C.

Our portfolio is led by the development of tenapanor, a first-in-class inhibitor of NHE3. In our renal pipeline, tenapanor is being evaluated in a second Phase 3 trial for the treatment of hyperphosphatemia in patients with ESRD who are on dialysis. This registration trial follows a successful first Phase 3 trial completed in 2017, which achieved statistical significance for the primary endpoint. We are also advancing a small molecule potassium secretagogue program, RDX013, for the potential treatment of hyperkalemia. We believe that both tenapanor and RDX013 have the potential to provide treatment options that are differentiated significantly from binders, the current standards of care in both of these markets. We believe our small molecule approach to treating these conditions could significantly reduce the pill burden for patients, leading to higher compliance, and offer completely new mechanisms of action that interact with receptors in the gut, potentially allowing improved efficacy in some patients.

In addition to the development for renal diseases, we have developed tenapanor for the treatment of patients with IBS-C. In 2017, we completed the T3MPO program for this indication, including two Phase 3 studies, both of which achieved statistical significance for the primary endpoint, and a long-term safety extension study. We believe that data from the T3MPO program collectively demonstrated the ability of tenapanor to provide sustained relief of constipation and reduced abdominal pain with a generally favorable tolerability profile. Based on the results of the T3MPO clinical program in IBS-C, we are preparing to submit our first New Drug Application, or NDA, to the United States Food and Drug Administration, or FDA, in the second half of 2018 for tenapanor for the treatment of IBS-C.

Our Commercial Strategy

We aim to build a multi-product company that commercializes its renal products in the United States. Our strategy is to leverage ex-U.S. collaborations with established industry leaders to efficiently bring our renal medicines to patients outside the United States. Additionally, our goal is to bring tenapanor for IBS-C to market by leveraging domestic and ex-U.S. collaborations.

In November 2017, we entered into a license agreement that provides Kyowa Hakko Kirin Co., Ltd., or KHK, with exclusive rights to develop and commercialize tenapanor for the treatment of cardiorenal diseases, including hyperphosphatemia, in Japan. Under the terms of the license agreement, we received a $30 million upfront payment and are eligible to receive up to $130 million in development and commercialization milestones based upon currency exchange rates as of the effective date of the license agreement, as well as high-teen royalties on net sales throughout the term of the agreement.

In December 2017, we entered into a license agreement with Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd., or Fosun Pharma, providing Fosun Pharma with the exclusive rights to develop and commercialize tenapanor in China for the treatment of patients with hyperphosphatemia related to CKD and patients with IBS-C. Under the terms of the agreement, we received an upfront payment of $12 million and are eligible to receive additional milestones of up to $113 million, as well as tiered royalties on net sales ranging from the mid-teens to 20%.

OUR PROPRIETARY DRUG DISCOVERY AND DESIGN PLATFORM

In line with our overall strategy and transition to focus solely on our renal pipeline, we have shifted our research focus to support our preclinical and clinical development candidates including tenapanor and RDX013, as well as other potential renal opportunities. We intend to continue to utilize our unique discovery and design platform to help

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elucidate first-in-class mechanisms of action, as with tenapanor, and to inform preclinical experiments to help advance our product candidates. We also use our platform to further support the potential commercialization of our programs, which is valuable to us and future partners. We believe that our platform, and early pipeline, represent additional collaborative opportunities, market potential and downstream value-creation.

Using our platform, we have been able to discover targets found in the GI tract that regulate important processes in the body and design products candidates that act upon those targets to take advantage of the gut's ability to communicate with other organs. Our platform integrates two critical concepts: (i) our proprietary chemistry capabilities that enable us to design and optimize gut-restricted compounds that can provide a higher margin of safety than systemically absorbed compounds, and (ii) our stem cell-based translational technology called the Ardelyx Primary Enterocyte and Colonocyte Culture System, or APECCS, that enables us to discover targets in the GI tract which control health and disease processes, to optimize drug candidates and to understand their mechanisms of action. Our platform can be applied across the entire GI tract, allowing for the broadest evaluation of disease targets to develop medicines optimized for specific diseases. The predictive ability of our platform enables us to better assess, at a very early stage, the potential for small molecule compounds to treat specific diseases.

OUR PRODUCT PIPELINE

Tenapanor: A New Approach for Treating Hyperphosphatemia in ESRD Patients on Dialysis

The lead product candidate in our renal portfolio is tenapanor for the treatment of hyperphosphatemia, or high levels of blood phosphorus, in ESRD patients on dialysis. Hyperphosphatemia is a significant problem among dialysis patients worldwide.

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 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 kidneys and excreted in urine. In adults with functioning kidneys, normal serum phosphorus levels are 2.5 to 4.5 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 patients, 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 regulator of phosphate and vitamin D metabolism. Highly elevated levels of FGF23 is an independent risk factor for adverse cardiac clinical outcomes as well as the development of secondary hyperparathyroidism, or SHPT, marked by elevated parathyroid hormone. SHPT is associated with 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 currently prescribed medications called phosphate binders, the only interventions currently marketed for the treatment of hyperphosphatemia. Phosphate binders act by binding dietary phosphorus and commonly need to be taken 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 phosphate binders is for patients to eliminate,

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through their stool, the precipitated phosphorus that comes from the food they ingest. Phosphate binders have a number of limitations, including:

- systemic excess absorption of calcium, iron or lanthanum, resulting in side effects and other unintended consequences for ESRD patients, and
- significant challenges with patient compliance because of the large quantity and/or mass of the binders that must be taken each day.

Safety and tolerability have also been significant concerns with many approved phosphate binders, with side effects that include long-term vascular calcification with calcium-based binders and iron-overload with iron-based binders. The more common side effects of certain approved phosphate binders include GI-related adverse events such as nausea, vomiting, diarrhea, and dyspepsia as well as hypercalcemia for calcium-based binders and discolored feces for iron-based binders.

ESRD patients, who generally are severely restricted in their fluid intake, are prescribed as many as 12 or more phosphate binder pills per day, among other medications. The amount of phosphorus a binder can remove is limited by its binding capacity, and therefore, increasing the dose, and hence the pill burden, of the binder is the only way to increase the amount of phosphorus being bound and excreted. As a result of pill burden and mass, as well as a number of side effects, prescribed phosphate binder doses are intolerable for many patients, leading to a lack of treatment adherence and compliance.

We are developing tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis, as we believe it has the potential to address certain of the key limitations of current treatments and offer a completely new mechanism of action. If approved, tenapanor would be the first small molecule/non-binder approach to treating hyperphosphatemia, with a unique mechanism of action that acts by inhibiting, or blocking, the NHE3 transporter in the GI tract to reduce the absorption of dietary sodium. When tenapanor blocks the NHE3 sodium transporter in the GI tract, it reduces the absorption of dietary sodium, resulting in an increase in protons within the cells. This increase in protons causes a selective reduction in phosphate uptake by tightening junctions or pores that are involved in the regulation of phosphate homeostasis, which then limits the amount of dietary phosphate that can pass from the gut into the blood. We have not observed this impact on other ions, nutrients or macromolecules in our clinical trials. We have submitted a manuscript for publication of this mechanism in a scientific peer-reviewed journal.

This unique mechanism of action allows tenapanor to be active in many patients at a dose of 10mg to 30mg twice daily as opposed to the multiple gram quantities per day required of the phosphate binders. Over the course of a week, the amount of tenapanor required would be less than 500mg, or a total of 14 small pills, whereas the amount of phosphate binder required, based on package inserts, would be 10 to 30 grams, or up to 64 large pills, depending on the phosphate binder. We believe this significant pill burden advantage will result in better adherence and compliance which could lead to more consistent efficacy in ESRD patients on dialysis.

Tenapanor has been specifically designed to work exclusively within the GI tract, thereby significantly reducing the amount of drug that is absorbed into the bloodstream and the potential side effects that could occur. In human studies of orally-administered tenapanor, the drug was detected in the blood in less than 1% in thousands of collected serum samples, and even in those, at very low levels (< 1.5 ng/mL). We have evaluated tenapanor across 20 clinical studies in over 2,500 individuals to date.

Clinical data supporting tenapanor in hyperphosphatemia

In February 2017, we announced data from our first Phase 3 clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis.

The Phase 3 trial was an eight-week, double-blind, randomized trial, with a four-week placebo-controlled randomized withdrawal period. We enrolled a total of 219 ESRD patients with hyperphosphatemia who are on dialysis. Enrolled patients were randomized evenly into three arms, in which all groups received tenapanor for eight weeks.

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Tenapanor was administered at doses of 3 mg or 10 mg twice-daily and in a dose-titration arm starting at 30 mg twice-daily with the option to down-titrate once a week during the first four weeks to 20, 15, 10 and 3 mg twice-daily, based on GI tolerability. After the end of the eight-week treatment period, patients were re-randomized 1:1 to either remain on their current tenapanor dose or switch to placebo for a four-week, placebo-controlled, randomized withdrawal period.

The primary endpoint of the trial was the difference in change in serum phosphorus between the pooled tenapanor-treated patients and placebo-treated patients from the end of the eight-week treatment period to the end of the four-week randomized withdrawal period, in the responder population. The responder population, which was reviewed by the FDA, is defined as patients who demonstrate a greater than or equal to 1.2 mg/dL decrease in serum phosphorus from baseline during the initial eight-week treatment period.

The study demonstrated a statistically significant difference in serum phosphorus levels from the end of the eight-week treatment period to the end of the four-week randomized withdrawal period between the tenapanor-treated group and the placebo-treated group in the responder patient population (mean -1.01 mg/dL, median of -1.3 mg/dL) and met its primary endpoint (95% confidence interval, -1.44, -0.21, LSmean -0.82 mg/dL, p=0.01). The responder population (n=80 out of 164) had a mean reduction in serum phosphorus from baseline to the end of the eight-week treatment period of 2.56 mg/dL, with a reduction of up to 5.7 mg/dL. Notably, in this group, 33% of patients had a reduction in serum phosphorus of greater than 3 mg/dL.

Tenapanor was well-tolerated in the trial. In the eight-week treatment period, the only adverse event that affected more than five percent of patients treated with tenapanor was diarrhea (39%), a patient-reported side effect of loosened stool or increased frequency in bowel movements regardless of magnitude. In the four-week randomized withdrawal period, there was a diarrhea rate of 1.2% for patients treated with tenapanor compared with 2.4% on placebo. Treatment discontinuations due to diarrhea for patients on tenapanor was 7.8% (n=17). There were no discontinuations due to diarrhea in the randomized withdrawal period.

In order to fully assess GI tolerability, patients used an eDiary to record the frequency of daily bowel habits, as well as stool form using the Bristol Stool Form Scale, or BSFS. During the eight-week treatment period, there was an average 0.4 per day increase in bowel movement frequency from baseline, and during the four-week randomized withdrawal period, there was an average 0.29 per day increase as compared to placebo. Average bowel movement frequency was within the normal range in all groups. During the eight-week treatment period, there was an average 0.87 point increase in BSFS from a baseline score of 4.2, out of a maximum of seven, where seven is liquid stool. During the four-week randomized withdrawal period, there was an average 0.7 point difference in BSFS between placebo (4.4) and tenapanor treatment (5.1).

We have initiated a second Phase 3 study of tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis. The study's design, shown in the figure, will include a 26 week open-label treatment period, with a 12-week randomized withdrawal period followed by an additional 14 week safety extension. Results from this study are expected in 2019. We currently intend to build our own sales and marketing organization to market and sell tenapanor for hyperphosphatemia in the United States.

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The hyperphosphatemia market

Phosphate binders are the only drugs marketed for the treatment of hyperphosphatemia in ESRD patients. 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)

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. Sanofi reported €922 million ($1.05 billion) in worldwide sales of sevelamer during 2016 and €802 million ($0.98 billion) in 2017. Generic sevelamer carbonate has been approved in certain jurisdictions in Europe since 2015 and in the U.S. market since June 2017.

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 3 studies being developed by Opko Health, Inc., and PT20, an iron-based binder in Phase 3 being developed by Shield Therapeutics.

According to the most recent data available from the U.S. Renal Data System, in 2015 there were 444,337 patients on hemodialysis in the United States. Additionally, according to the European ERA-EDTA Registry 2015 Annual Report and a study in 2014 by the Japanese Society for Dialysis Therapy, there were approximately 317,000 patients on hemodialysis in Europe and about 255,000 in Japan. We estimate, based on phosphate binder utilization, the only approved therapies for hyperphosphatemia, that there are approximately 310,000, 250,000 and 260,000 ESRD patients with hyperphosphatemia in the United States, countries in Europe and Japan, respectively, resulting in approximately 820,000 ESRD patients with hyperphosphatemia in such countries.

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 medical need for new agents with

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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 and mass among any currently marketed hyperphosphatemia products, with milligram rather than gram quantities. 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.

Our intention is to build a United States-focused, highly efficient, specialized sales and marketing organization focused on nephrology. The nephrology market is a concentrated market strongly influenced by key opinion leaders. There were 10,083 nephrologists in the United States in 2015 and 6,620 dialysis facilities in the United States that offer in-center dialysis. Based on the experience of our management team, we believe that a specialty salesforce is appropriate for this marketplace. We believe that tenapanor for the treatment of hyperphosphatemia could represent a market opportunity of between $500 million and $700 million in the United States.

As a first-in-class treatment, and as the first non-binder option with a well-tolerated safety profile, we believe tenapanor could address the significant pill burden challenges and intolerability that patients experience with today's binder treatments. After the second Phase 3 study readout, if successful, we intend to submit a New Drug Application to the FDA in 2019 and would plan for a potential launch 2020.

To bring tenapanor to patients outside the United States, we intend to establish strategic collaborations with industry leading pharmaceutical companies with established commercial infrastructures. In 2017, we entered into two collaboration partnerships, and the revenues recorded from those collaboration partnerships in 2017 accounted for more than 10% of total revenues recorded during the year ended December 31, 2017.

License agreement with KHK

In November 2017, we entered into a license agreement ("KHK License Agreement") with KHK under which we granted KHK an exclusive license to develop and commercialize tenapanor in Japan for the treatment of cardiorenal diseases and conditions, excluding cancer ("KHK Field"). We retained the rights to tenapanor outside of Japan, and also retained the rights to tenapanor in Japan for indications other than those in the KHK Field. Pursuant to the KHK License Agreement, KHK is responsible for all of the development and commercialization costs for tenapanor in the KHK Field in Japan.

Under the KHK License Agreement, we are responsible for supplying the tenapanor drug product for KHK's use in development and during commercialization until KHK has assumed such responsibility. Additionally, we are responsible for supplying the tenapanor drug substance for KHK's use in development and commercialization throughout the term of the KHK License Agreement, provided that KHK may exercise an option to manufacture the tenapanor drug substance under certain conditions.

Under the terms of the KHK License Agreement, we have received a $30.0 million upfront payment and are eligible to receive up to an additional $130.0 million in development and commercialization milestones, based upon currency exchange rates as of the effective date of KHK License Agreement.

We are also eligible to receive royalties based on aggregate annual net sales of the licensed products at a high teen percentage, subject to certain single digit reductions under certain circumstances described in the KHK License Agreement.

The KHK License Agreement will continue until all of KHK's applicable payment obligations under the KHK License Agreement have been performed or have expired, or the agreement is earlier terminated. Under the terms of the KHK License Agreement, we and KHK each have the right to terminate the agreement for material breach by the other

party. In addition, KHK may terminate the agreement for convenience; for certain safety reasons or if certain primary endpoints under an applicable development plan are not met despite KHK's commercially reasonable efforts and KHK reasonably determines that it cannot obtain regulatory approval. KHK may also terminate the agreement if certain pivotal clinical trials conducted by us do not meet their primary endpoints. We may terminate the KHK License Agreement if KHK challenges any patents licensed to KHK under the agreement.

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License agreement with Fosun

In December 2017, we entered into a license agreement (the "Fosun License Agreement") with Fosun Pharma under which we granted Fosun Pharma an exclusive license to develop and commercialize tenapanor in China for the treatment, diagnosis or prevention of (i) irritable bowel syndrome with constipation and chronic idiopathic constipation, (ii) hyperphosphatemia related to chronic kidney disease and (iii) other diseases or conditions for which we obtain marketing approval in either the US or China (collectively, "Fosun Field"). The Fosun Field excludes the treatment of cancer. We retained the rights to tenapanor outside of China, and also retained the rights to tenapanor in China for indications other than those in the Field. Pursuant to the terms of the Fosun License Agreement, Fosun Pharma is responsible for all of the development and commercialization costs for tenapanor in the Fosun Field in China.

Under the terms of the Fosun License Agreement, we are responsible for supplying the tenapanor drug product for Fosun Pharma's use in development and during commercialization until Fosun Pharma has assumed such responsibility. Additionally, we are responsible for supplying the tenapanor drug substance for Fosun Pharma's use in development and commercialization throughout the term of the Fosun License Agreement.

Under the terms of the Fosun License Agreement, we received an upfront payment of $12 million and are eligible to receive additional milestones of up to $113 million in the aggregate, as well as tiered royalty payments on aggregate net sales ranging from the mid-teen percent to twenty percent, subject to certain reductions under certain circumstances, as described in the Fosun License Agreement.

The Fosun License Agreement will continue until all of Fosun Pharma's applicable payment obligations under the License Agreement have been performed or have expired, or the agreement is earlier terminated. Under the terms of the Fosun License Agreement, we and Fosun Pharma each have the right to terminate the agreement for material breach by the other party or in the event of insolvency by the other party. In addition, Fosun Pharma may terminate the agreement for convenience and we may terminate the agreement if Fosun Pharma challenges any patents licensed to it under the agreement.

RDX013 Program: Small Molecule for Treating Hyperkalemia

RDX013 is our novel, small molecule program for the potential treatment of hyperkalemia. Our RDX013 approach works by tapping into the GI tract's natural ability to secrete potassium into the lumen of the gut to reduce serum potassium levels. This mechanism differs significantly from the potassium binders currently on or approaching the market. For a potassium binder to work, it must be present when dietary potassium is ingested so that the agent can bind the potassium and prevent its absorption in the gut. This results in the need for large quantities of binder in order to bind the large amounts of potassium in the diets of most individuals. In contrast, we observed in our preclinical models that a small amount of RDX013 could cause potassium to be secreted into the lumen of the gut. In this way, we believe that RDX013 may have the potential to lower serum potassium whether or not potassium is present in the diet and could result in a very low pill burden, potentially allowing better patient compliance, longer-term use and potentially better efficacy than potassium binders. As described below, certain medications commonly administered to patients with CKD and/or heart failure can also cause hyperkalemia. With the successful development of an effective potassium secretagogue to treat hyperkalemia in a small, convenient pill format, we believe our RDX013 approach may allow nephrologists and cardiologists with an opportunity to treat hyperkalemia chronically without reducing the dose of these medications.

Hyperkalemia is generally defined as the presence of blood potassium levels greater than 5.0 mEq/L. Normal levels are 3.5 to 5.0 mEq/L. When hyperkalemia is severe, above 7.0 mEq/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 issues. Kidney disease can result in the elevation of potassium in the blood. Certain drugs such as the common hypertension medications known as RAAS inhibitors, which inhibit the renin-angiotensin-aldosterone system, can cause hyperkalemia. As a result, the dosage of RAAS inhibitors must often be significantly reduced in patients whose potassium levels are elevated (such as in those with CKD and heart failure). Because of the risk of hyperkalemia, several published guidelines have suggested that physicians should reduce and

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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 less effective than RAAS inhibitors, particularly in patients with failing kidneys and severe hypertension. According to the 2015 publication Market Dynamix: Hyperkalemia, 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. 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 clearly a strong medical need for new medications that control hyperkalemia in order to allow for optimal use of RAAS inhibitors to control hypertension in these patient populations.

The hyperkalemia market

Of the people with CKD and/or heart failure in the United States, we estimate that there are approximately 2.1 million people who also have occurrences of hyperkalemia. According to a retrospective study conducted in 2005 of a national cohort of 246,000 patients 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 to control hypertension and to slow the course of CKD.

Additionally, the number of adults in the U.S. living with heart failure is about 6.5 million, based on data collected in the National Health and Nutrition Examination Survey, which is taken in stages over multiple years. Our proprietary research suggests that up to 16%, or approximately 1,000,000, of these patients had hyperkalemia during a 12-month period. Over half of heart failure patients are prescribed RAAS inhibitors. Our proprietary research also suggests that up to 200,000 patients with ESRD in the U.S. 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 commercially launched by Relypsa, which was acquired by Galenica AG for $1.5 billion in September 2016. However, according to a 2017 survey of more than 200 nephrologists and cardiologists, conducted by Spherix Global Insights, about half of those surveyed note that, even with Veltassa available, there remains a high unmet need for new treatments for hyperkalemia.

Additionally, ZS Pharma submitted an NDA in June 2015 for ZS-9, a sodium zirconium cyclosilicate-based oral potassium binder. ZS Pharma was acquired by AstraZeneca in December 2015 for $2.7 billion.

We believe that, unlike these agents which require large amounts of drug for the desired effect, RDX013 may have the potential to lower serum potassium whether or not potassium is present in the diet and could result in very low pill burden, allowing better compliance, longer-term use and potentially better efficacy than potassium binders.

If we are successful in developing RDX013 and obtaining marketing authorization from the FDA, we would expect to leverage the renal sales and marketing organization that we intend to build to support commercialization in the United States of tenapanor for treating hyperphosphatemia in dialysis patients.

Tenapanor: NHE3 Inhibitor for Treating IBS-C

In addition to its development for hyperphosphatemia, we have completed development of tenapanor for the treatment of IBS-C and are pursuing strategic collaborations to bring it to market in this indication. We have completed two Phase 3 clinical trials in patients with IBS-C (T3MPO-1 and T3MPO-2) along with a long-term safety study

(T3MPO-3) and expect to submit an NDA to the FDA in the second half of 2018.

IBS-C is a GI disorder in which abdominal pain or discomfort is associated with constipation, and which significantly impacts the health and quality of life of affected patients. A study published in the American Journal of Gastroenterology in 2015, showed that over 50% of IBS-C patients rated their pain, constipation and straining as being

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“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. 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 is clinically distinguished by a significant abdominal pain component.

Tenapanor is a minimally-systemic small molecule that acts locally in the GI tract to inhibit the sodium transporter NHE3 and reduce sodium uptake from the gut. Part of its mechanism to treat constipation caused by IBS-C is an osmotic effect in the intestines – water follows salt and stool is gently loosened by the body’s own fluids. In addition to this mechanism, data from nonclinical studies, which were presented in November 2017 at the American Society of Nephrology Annual Meeting, suggest that tenapanor reduced abdominal pain caused by IBS-C through the inhibition of TRPV-1 dependent signaling. TRPV-1, better known as the "hot chili pepper receptor," is a well-established pain target known for transmitting painful stimuli from a variety of sources including heat, protons and inflammatory molecules. Using an established rodent model of IBS-like colonic hypersensitivity, preclinical data showed that tenapanor treatment reduced visceral hypersensitivity (pain in the internal organs) and normalized colonic sensory neuronal excitability and TRPV-1 currents. Treatment with tenapanor also increased stool excretion and stool water content. In these nonclinical studies, tenapanor had a superior effect on visceral hypersensitivity than placebo or PEG, a well-known laxative not known to have an analgesic effect.

Phase 3 clinical data supporting tenapanor in IBS-C

At the end of 2017, we completed our Phase 3 program, the T3MPO program, for tenapanor for the treatment of IBS-C. This included two Phase 3 studies, T3MPO-1 and T3MPO-2, and a long-term safety extension study, T3MPO-3. In the discussion below, statistical significance is denoted by p-values. The p-value is the probability that the reported result was achieved purely by chance (e.g., a p-value <0.001 means that there is a less than a 0.1% probability that the observed change was purely due to chance). Generally, a p-value less than 0.05 is considered statistically significant.

In May 2017, we reported data from the first Phase 3 study, T3MPO-1. T3MPO-1 was a 12-week, double-blind, placebo-controlled, multi-center, randomized trial with a four-week, randomized withdrawal period conducted in a total of 610 patients meeting the ROME III criteria for the diagnosis of IBS-C. Patients were randomized one to one to receive either 50 mg of tenapanor or placebo twice-daily. The trial included a two-week screening period, during which patients with active disease, based on bowel movement frequency and abdominal pain score recorded in a daily phone diary, were randomized into the trial.

The study achieved statistical significance for the primary endpoint and seven of eight secondary endpoints. The primary endpoint, the combined responder rate for six of 12 weeks, showed that a greater proportion of tenapanor-treated patients compared to placebo-treated patients (27.0% vs 18.7%, p=0.02) had at least a 30% reduction in abdominal pain and an increase of one or more complete spontaneous bowel movements, or CSBM, in the same week for at least six of the 12 weeks of the treatment period. The CSBM responder rate in the six of 12 weeks (defined as having an increase of at least one CSBM from baseline during a week for six of 12 weeks) did not reach statistical significance (33.9% vs. 29.4%, p=0.27); however, the abdominal pain responder rate in the six of 12 weeks (defined as having at least a 30% decrease in abdominal pain from baseline during a week for six of 12 weeks) did achieve statistical significance (44.0% vs. 33.1%, p=0.008). In the nine of 12 treatment weeks, the study achieved statistical significance for the combined responder rate (13.7% vs. 3.3%, p<0.001), in which patients must have had an increase of at least one CSBM from baseline and at least three CSBMs during a week for nine of 12 weeks as well as a 30% or greater reduction in abdominal pain for nine of the 12 weeks. In addition, for the nine of 12 weeks, the study achieved statistical significance for the individual CSBM responder rate (16.9% vs. 5%, p<0.001) and the abdominal pain responder rate (30.3% vs. 19.4%, p=0.003).

Tenapanor was well-tolerated in the study. The only adverse events observed in more than two percent of patients treated with tenapanor, as compared with placebo, were diarrhea (14.6% vs 1.7%) and nausea (2.6% vs 1.7%). The placebo adjusted discontinuation rate due to diarrhea was 5.3%.

In October 2017, we reported results from the second Phase 3 study of tenapanor for the treatment of IBS-C, T3MPO-2, a 26-week, double-blind, placebo-controlled, multi-center, randomized trial in 593 patients. Patients were

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randomized one to one to receive either 50 mg of tenapanor or placebo twice-daily. The trial included a two-week screening period, during which patients with active disease, based on bowel movement frequency and abdominal pain score recorded in a daily phone diary, were randomized into the trial.

The study achieved statistical significance for the primary endpoint and all secondary endpoints evaluated for the topline results and demonstrated the ability to normalize bowel movements. The primary endpoint, the combined responder rate for six of 12 weeks, showed that a greater proportion of tenapanor-treated patients compared to placebo-treated patients (36.5% vs. 23.7%, p<0.001) had at least a 30% reduction in abdominal pain and an increase of one or more CSBMs in the same week for at least six of the 12 weeks of the treatment period. The study achieved statistical significance for the CSBM and abdominal pain responder rates in the six of 12 weeks (47.4% vs. 33.3%, p<0.001; 49.8% vs. 38.3%, p=0.004). In the nine of 12 treatment weeks, the study achieved statistical significance for the combined responder rate (18.4% vs. 5.3%, p<0.001), in which patients must have had an increase of at least one bowel movement from baseline and at least three per week and a 30% reduction in abdominal pain for nine of the 12 weeks. In addition, for the nine of 12 weeks, the study achieved statistical significant for the individual CSBM responder rate (22.2% vs. 6.0%, p<0.001) and the abdominal pain responder rate (35.8% vs. 26.7%, p=0.015). The study also achieved statistical significance for all three durable responder endpoints, the combined responder rate (18.1% vs. 5.0%, p<0.001), CSBM responder rate (21.2% vs. 5.7%, p<0.001) and abdominal pain responder rate (34.8% vs. 26.7%, p=0.028), which are identical to the nine of 12-week responder endpoints, except the response must also occur in three of the last four treatment period weeks.

Tenapanor was well-tolerated in the T3MPO-2 study. The only adverse events observed in more than two percent of patients in the tenapanor-treated group that were also greater than placebo were diarrhea (16.0% vs. 3.7%), flatulence (3.1% vs. 1.0%), nasopharyngitis (4.4% vs. 3.7%) and abdominal distension (3.4% vs. 0.3%). The placebo adjusted discontinuation rate due to diarrhea was 5.8%.

Patients who completed T3MPO-1 and T3MPO-2 were eligible to enter T3MPO-3, our open-label, long-term safety trial where patients could continue to receive tenapanor for up to one year. In late 2017, we completed T3MPO-3 and have reported results that tenapanor had a mean compliance rate of approximately 98%, and that tenapanor was well-tolerated among the 240 patients treated. Of patients treated, 9.2% reported experiencing diarrhea, with 1.7% of patients discontinuing treatment due to diarrhea. The overall discontinuation rate in the study was 2.1%.

Based on the positive results from the T3MPO program, we are preparing to submit an NDA to the FDA to request marketing approval of tenapanor for the treatment of IBS-C in the United States.

To support the global commercialization of tenapanor for IBS-C, we are pursuing strategic collaborations to bring tenapanor to patients. In December 2017, we entered into a license agreement to provide Fosun Pharma with the exclusive rights to develop and commercialize tenapanor in China for the treatment of patients with IBS-C and hyperphosphatemia related to chronic kidney disease.

The IBS-C market

Numerous treatments exist for the constipation component of IBS-C, many of which are over-the-counter. There are three prescription products marketed for IBS-C: (i) Linzess (linaclotide), marketed by Ironwood Pharmaceuticals and Allergan, (ii) Amitiza (lubiprostone), marketed by Takeda and Sucampo, a wholly-owned subsidiary of Mallinckrodt, and (iii) Trulance (plecanatide), marketed by Synergy Pharmaceuticals.

We believe that tenapanor may offer a significant benefit over currently marketed drugs like Amitiza, Linzess and Trulance in part because of the profile demonstrated in our Phase 3 program, which showed best-in-class efficacy results for the 9-of-12 week combined responder rates. Within the United States, there are approximately 11 million

patients that suffer that suffer from IBS-C. There is significant unmet need for prescription medications, where, according a 2015 American Gastroenterological Association report, only 1 in 4 treated patients are very satisfied with the current FDA approved treatments in IBS-C.

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Other GI Programs

In addition to tenapanor for IBS-C, we have an early GI pipeline comprised of RDX8940, a minimally absorbed, oral TGR5 agonist for which we submitted an investigational new drug application, or IND, in late 2016; RDX011, our second-generation NHE3 inhibitor; and our RDX023 program for the development of gut-biased farnesoid X receptor, or FXR, agonists. While we are not currently actively developing these programs, they represent potential collaboration opportunities to support their continued development.

INTELLECTUAL PROPERTY

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

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

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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 four issued U.S. patents, two issued Japanese patents, two issued Korean patents and one issued patent in each of the following territories: Australia, China, the European Union, Mexico, and Israel. 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 U.S. and international patent applications are pending covering additional methods of using tenapanor, and composition of matter and methods of using compounds that we believe may be follow on compounds to tenapanor.

Other program patents

We have patent applications pending in the United States and internationally that cover the compositions and methods of using our TGR5 agonists, our FXR agonists and compounds in our RDX013 program.

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 and for our commercial product requirements, when and if regulatory approval is received. Our license agreements with KHK and Fosun Pharma require us to supply active pharmaceutical ingredient and final drug product dosage forms of tenapanor for their use in the development of tenapanor in each of their respective territories, and we are further obligated to continue to supply active pharmaceutical ingredient to support their commercialization of tenapanor in each of their territories. We expect that we will use CMOs to satisfy our supply obligations to our collaboration partners.

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.

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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 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

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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 drug. Phase 3 clinical trials are generally undertaken with large numbers of patients, such as groups of several hundred to several thousand, to further evaluate dosage, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse patient population at multiple, geographically-dispersed clinical trial sites.
- Phase 4: In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor’s agreement to conduct additional clinical trials after NDA approval. In other cases, a sponsor may voluntarily conduct additional clinical trials post approval to gain more information about the drug. Such post approval trials are typically referred to as Phase 4 clinical trials.

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

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

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

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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, 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.

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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 differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use.

Hatch-Waxman Act

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

turn, be cited by potential competitors in support of approval of an ANDA or 505(b)(2) NDA.

Upon submission of an ANDA or a 505(b)(2) NDA, an applicant must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. Generally, the ANDA or

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505(b)(2) NDA cannot be approved until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through the last type of certification, also known as a paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all of the listed patents claiming the referenced product have expired.

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

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

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

Fraud and abuse laws

In the 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 Payments Sunshine Act, and other state and federal laws and

regulations.

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

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by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. 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 $11,181 and $22,363 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 $165,786 per year (or up to an aggregate of $1.105 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. Manufacturers must submit reports by the 90th day of each subsequent calendar year.

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

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.

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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, due to subsequent legislative amendments, CMS provided that such inclusion will remain delayed until January 1, 2025. Unless additional Congressional action is taken, beginning in 2025 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 that bundling may have on drugs for the treatment of hyperphosphatemia, 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 is 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 measures, which have impacted existing government healthcare programs and have resulted in the development of new programs, including Medicare payment for performance initiatives and improvements to the physician quality reporting system and feedback program.

Additionally, the 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;

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- 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.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. We expect that the new presidential administration and U.S. Congress will likely continue to seek to modify, repeal, or otherwise invalidate all or certain provisions of, the Affordable Care Act. There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the Affordable Care Act.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, included aggregate reductions to Medicare payments to providers of 2 percent per fiscal year, which went into effect on April 1, 2013, and, due to subsequent legislative amendments, will remain in effect through 2025 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, individual states have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and to encourage importation from other countries and bulk purchasing. Recently, there has also been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. 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.

EMPLOYEES

As of December 31, 2017, we had 75 full-time employees, including a total of 15 employees with Ph.D. degrees. Within our workforce, 54 employees are engaged in research and development and the remaining 21 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

Our research and development costs were $75.5 million, $94.2 million and $39.9 million in the years ended December 31, 2017, 2016 and 2015, 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.

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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 tenapanor and developing our proprietary drug discovery and design platform. To date, we have not commercialized any products or generated any revenue from the sale of products.

We are not profitable and have incurred losses in each year since our inception in October 2007, and we do not know whether or when we will become profitable. We 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, 2017, we had an accumulated deficit of $278.2 million.

We expect that our operating losses will substantially increase for the foreseeable future as we prepare for the potential commercialization of, and incur manufacturing and development costs for, tenapanor, including costs associated with completing the ongoing Phase 3 development of tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis, preparing the new drug application, or NDA, for submission to the U.S. Food and Drug Administration, or FDA, to request marketing authorization for tenapanor for the treatment of patients with IBS-C, and continuing our discovery and research 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 w