ARDELYX, INC.
Form 10-K
March 05, 2015
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2014

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)	(Zip Code)

Registrant's telephone number, including area code: (510) 745-1700

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

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

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

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

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

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

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

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

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

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

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

The aggregate market value of the Registrant's common stock held by non-affiliates of the Registrant as of the last business day of the Registrant's most recently completed second fiscal quarter, June 30, 2014, based on the last reported sales price of the Registrant's common stock of $15.97 per share was $96,062,968.

The number of shares of Registrant's Common Stock outstanding as of February 26, 2015 was 18,598,133.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the Registrant's Definitive Proxy Statement for its 2015 Annual Meeting of Stockholders, which will be filed with the Commission within 120 days after the close of the Registrant's 2014 fiscal year, are incorporated by reference into Part III of this Report.

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PART I

Special Note Regarding Forward-Looking Statements

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:

- AstraZeneca’s decisions with respect to its future development of tenapanor;
- the timing of data from the ongoing Phase 2a trial of tenapanor and the timing of commencement of the Phase 3 development program of tenapanor;
- our receipt of future milestone payments from our collaboration partners, and the expected timing of such payments;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use;
- the likelihood and our expectations that we elect to exercise our co-promotion rights with respect to tenapanor or an NaP2b inhibitor product, or exercise our co-fund rights with respect to the first Phase 3 clinical development program for tenapanor;
- the likelihood and potential for Sanofi to exercise its option to exclusively license our NaP2b inhibitor program;
- our ability to maintain existing and our intention to establish new collaboration partnerships;
- our ability to identify and validate targets and novel drug candidates using our proprietary drug discovery and design platform including APECCS;
- our ability to develop, acquire and advance product candidates into, and successfully complete, clinical trials;
- the timing or likelihood of regulatory filings, approvals and commercialization for our product candidates, including tenapanor and our NaP2b inhibitors;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering tenapanor and our NaP2b inhibitors;
- 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 JOBS Act;
- our financial performance; and
- developments and projections relating to our competitors and our industry.

These forward-looking statements relate to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance and achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things those listed under “Risk Factors” and elsewhere in this Annual Report on Form 10-K.

Any forward-looking statement in this Annual Report on Form 10-K reflects our current views with respect to future events and is subject to these and other risks, uncertainties and assumptions relating to our operations, results of operations, industry and future-growth. Given these uncertainties, you should not place undue reliance upon these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

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This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain drugs, including data regarding the estimated size of those markets, their projected growth rates and the incidence of certain medical conditions. Information that is based on estimates, forecasts, projections or similar methodologies is inherently subject to certain uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise specifically stated, we obtained this industry, market and other data from reports, research surveys, studies and similar data prepared by third parties, industry, medical and general publications, government data and similar sources. In some cases, we do not expressly refer to sources from which this data is derived. In that regard, when we refer to one or more sources of this type of data in any paragraph, you should assume that other data of this type appearing in the same paragraph is derived from the same sources, unless otherwise expressly stated or the context otherwise requires.

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.

ArdelyxÒ and our logo are some of our trademarks used in this Annual Report on Form 10-K. We also use trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, these trademarks and tradenames referred to appear without the ® and ™ symbol, but, in the case of our trademark and tradenames, those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, to our trademarks or tradenames.

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of innovative, minimally-systemic, small molecule therapeutics that work exclusively in the gastrointestinal, or GI, tract to treat cardio-renal, GI and metabolic diseases. We have developed a proprietary drug discovery and design platform enabling us, in a rapid and cost-efficient manner, to discover and design novel drug candidates. Utilizing our platform, we discovered and designed our lead product candidate, tenapanor, which in clinical studies has demonstrated the ability to improve the symptoms of constipation-predominant irritable bowel syndrome, or IBS-C, and to reduce the absorption of both dietary sodium and phosphorus, which are key factors in the progression of kidney disease. In 2012, we entered into a collaboration partnership with AstraZeneca AB, or AstraZeneca, for the worldwide development and commercialization of tenapanor. AstraZeneca is responsible for all development and commercialization costs for tenapanor and we have retained an option to co-promote in the United States. Together with AstraZeneca, we have completed a Phase 2b clinical trial evaluating tenapanor in patients with IBS-C. Results from the study demonstrated statistically significant and clinically meaningful improvements for IBS-C patients compared to patients receiving placebo, and at the twice daily 50 mg dose, the study met its primary endpoint. We and AstraZeneca, have also completed a Phase 2b clinical trial evaluating tenapanor in treating hyperphosphatemic patients with chronic kidney disease on dialysis, or CKD-5D, and the study met its primary endpoint of lowering serum phosphate. In this study, the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses were higher than expected based on previous clinical trials. Higher discontinuations rates due to diarrhea were observed primarily in the 30mg once daily and 30mg twice daily dose groups. We plan to announce results of a Phase 2a trial in patients with late-stage chronic kidney disease, or CKD, during the second quarter of 2015.

In February 2014, we licensed to Sanofi S.A., or Sanofi, our program evaluating small molecule NaP2b inhibitors for the treatment of hyperphosphatemia in CKD-5D. We are also independently advancing other discovery and lead development programs focused in cardio-renal, GI and metabolic diseases.

We continue to evolve our proprietary drug discovery and design platform. As part of this platform, we have developed a cell-culture system that simulates gut tissue, which we refer to as Ardelyx Primary Enterocyte and Colonocyte Culture System, or APECCS. We have ongoing work to identify human gastrointestinal tract-specific RNA transcripts and proteins and thus far have identified over 3,800 proteins on the inner surface of the gut, many of which we believe may be drug targets.

Tenapanor is a minimally-absorbed, small molecule that acts locally in the gastrointestinal tract to inhibit the sodium transporter NHE3 and reduce sodium uptake from the gut. We and AstraZeneca have evaluated or are evaluating tenapanor in fourteen human clinical studies in over 1,000 individuals to date, including the following Phase 2 studies:

- Phase 2b in IBS-C patients: We announced positive results from this study in October 2014. At the twice daily 50 mg dose of tenapanor, the study met its primary efficacy endpoint of an increase in the complete spontaneous bowel movement (CSBM) responder rate. Most secondary endpoints, including abdominal pain, the overall responder rate and other abdominal and IBS-C symptoms, demonstrated statistically significant and clinically meaningful improvements.
- Phase 2b in CKD-5D patients with hyperphosphatemia: We announced results from this clinical trial in February 2015. In the study, there was a statistically significant dose-related decrease in serum phosphate levels for tenapanor-treated patients compared to patients receiving placebo (p=0.012). It was noted, however, that the rate of diarrhea and the rate of discontinuations due to diarrhea were higher than expected based on previous clinical trials. Higher discontinuations rates due to diarrhea were observed primarily in the 30mg once daily and 30mg twice daily dose groups. The overall safety profile remains consistent with that observed in previous tenapanor trials.

- Phase 2a Stage 3 CKD patients with type 2 diabetes mellitus, albuminuria and high blood pressure: This Phase 2a randomized, double-blind, placebo-controlled clinical trial in 154 patients to evaluate the effects of tenapanor on kidney function and fluid overload has completed enrollment. The results of this clinical trial are expected in the second quarter of 2015.

We believe the market opportunity for tenapanor for these three potential patient populations is significant. We believe there are approximately 4.4 million individuals in the United States with IBS-C. Additionally, we estimate, based on the utilization of phosphate binders, the only approved therapies for hyperphosphatemia, that there are approximately 270,000 hyperphosphatemic patients with CKD-5D in the United States. The worldwide market for phosphate binders in 2011 was reported to be $1.5 billion and is projected to reach $2.3 billion by 2015. We believe there are approximately 1.8 million patients in the United States that have late-stage, or stage 3b or stage 4 CKD with type 2 diabetes, or diabetic nephropathy.

Under our agreement, AstraZeneca has the right to determine which indications it will continue to develop. AstraZeneca has the right to elect to develop one, two or all three of the indications, and AstraZeneca has the right to terminate the agreement upon written notice to us. If AstraZeneca determines that it will advance any one of the indications forward into a Phase 3 clinical trial, we would receive a royalty payment of $50.0 million. In addition, we would receive a $20.0 million development milestone if AstraZeneca determines to move forward with the development of tenapanor by commencing a Phase 2b or Phase 3 clinical study in any of the indications; provided that this milestone payment would be a $10.0 million payment if AstraZeneca decides to move forward with only the IBS-C indication.

Utilizing our proprietary drug discovery and design platform, we are pursuing other internal discovery and lead-development programs that are currently in the research phase. While we have identified molecules that exhibit attributes of the activity we are seeking in each of the following programs, we have not yet selected a lead molecule in these programs.

- NaP2b Program: We have discovered novel NaP2b inhibitors for the treatment of hyperphosphatemia in CKD-5D patients by inhibiting the active absorption of phosphorus. In February 2014, we entered into an option and license agreement with Sanofi under which we granted Sanofi an exclusive worldwide license to conduct research utilizing our small molecule NaP2b inhibitors. Sanofi has the option to obtain an exclusive license to develop, manufacture and commercialize our NaP2b inhibitors. Under our arrangement, Sanofi is responsible for all of the costs and expenses for research and preclinical activities and, should it exercise its option, for the development and commercialization efforts under the program, while we retain an option to co-promote licensed products in the United States.
- RDX009 Program: Our focus is the discovery and development of minimally-absorbed TGR5 agonists that stimulate GLP-2 and GLP-1 and have the potential when used in combination with a DPP4 inhibitor to treat inflammatory bowel disease, or IBD, short bowel syndrome or non-alcoholic steatohepatitis, or NASH.
- RDX013 Program: Our focus is the discovery and development of drug candidates to treat hyperkalemia, or elevated serum potassium, commonly seen in CKD-5D patients and in patients with less severe CKD prior to dialysis.

Our operations to date have been funded by $56.2 million in equity investments primarily from leading venture capital investment firms, $76.3 million in upfront and development milestone payments from our collaboration partners AstraZeneca and Sanofi and $61.2 million net proceeds from our IPO in June 2014.

Our Proprietary Drug Discovery and Design Platform

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

Benefits of our Platform versus Traditional Drug Discovery

Traditional small molecule drug discovery and design focuses on drugs that are rapidly absorbed in the GI tract. Once absorbed, those molecules typically need to survive the first-pass metabolism that occurs in the liver in order to arrive at the targeted cells or tissues and provide the desired benefit or effect. Compared to the traditional approach employed by the pharmaceutical industry to develop systemic drugs, we believe our proprietary drug discovery and design platform has several key benefits:

- Exploits the natural functions of the gut to affect disease. The gut is not a passive organ. It is lined with a variety of cell types that actively control the absorption of nutrients and minerals from the diet and serves to assist in the balance of those in the body. The gut also functions as an endocrine gland, causing the release of hormones in response to various stimuli. Additionally, the gut has multiple ways to communicate with the immune system and central nervous system. Our platform allows us to discover and validate targets, and to design drugs to modulate these targets and active functions of the gut in order to prevent and treat disease. With our drug candidates, we can stimulate receptors in the gut to increase the release of endogenous hormones to take advantage of their natural effect on diseases and conditions. We have identified over 3,800 human gastrointestinal tract-specific RNA transcripts and proteins on the inner surface of the gut, many of which we believe may be drug targets.
- Results in drug candidates with a superior safety profile that remain minimally-systemic. Traditional approaches to drug development require the design of molecules to elicit an effect in a particular area or tissue of the body. To do this, those molecules must be absorbed into the bloodstream thereby exposing many or all tissues to the drug and potentially to the drug's metabolites. Drug and metabolite exposure in tissues not relevant to treating the intended disease or condition increases the chance of unwanted side effects. We avoid this systemic exposure by limiting the penetration of our drug candidates through the gut and into the bloodstream or by ensuring rapid metabolism in the blood. We believe that our approach minimizes the possibility that our drugs may bind to or affect unintended targets in the body, reducing the potential for untoward side effects.
- Reduces discovery time. Because our drug candidates are designed to be minimally-systemic and work locally, we avoid the time that is dedicated in traditional drug discovery to designing molecules to achieve adequate bioavailability and avoid undesirable off-target side effects, while still providing the desired pharmacologic response. When animal studies confirm that one of our drug candidates is minimally-systemic and we observe minimal metabolism of the candidate in the gut with the use of our discovery platform tools, we have a high degree of certainty that the drug candidate will reach our intended target on the surface of the gut when administered orally.
- Promotes efficient phenotypic screens. Our platform, particularly as enhanced with APECCS, allows us to conduct efficient phenotypic screening as the cell system used for screening is a better representation of the GI as compared with other technologies. The in vitro activity of selected hits is believed to be more predictive of in vivo activity compared to more traditional approaches.

How our Proprietary Drug Discovery and Design Platform Works

Our platform allows us to identify and design novel minimally-systemic drug candidates to treat cardio-renal, GI and metabolic diseases.

- Identify: We identify and evaluate receptors and transporters on the epithelia of the GI tract that may impact diseases and we use a suite of techniques to characterize cell functions such as protein imaging and pharmacological probes in order to confirm that such targets are found on cells of the lumen, or inside surface, of the intestines. Using our scientific expertise and specialized know-how, along with traditional screening methodologies, we identify starting chemistries that have the potential to engage actively with the targeted receptor or transporter. These starting tool compounds are often absorbed into the bloodstream and have undesirable properties but serve the purpose of confirming the presence of the target we are pursuing. We use medicinal chemistry techniques to optimize potency and target engagement to eliminate or limit off-target activity and improve various drug properties of the compound.
- Minimally-systemic: We use our medicinal chemistry expertise, together with a suite of tools and capabilities we have developed to test and monitor the minimally–systemic qualities of our drugs. We then transform the optimized tool compounds into pre-lead drug candidates that have low systemic availability, low gastric and intestinal metabolism, favorable drug properties such as solubility and stability, and that affect the desired biological response in animals. These pre-lead molecules are then optimized in all respects to create lead molecules that can enter IND-enabling studies.
- APECCS: APECCS, our novel cell-based system, involves the biopsy of various segments of the gut and the growth of those cells under proprietary conditions to maintain, to the extent possible, the integrity and functionality of the various cell types and substructures. We have developed this into a miniaturized format that allows us to utilize it for cell based drug screening. In addition to using APECCS in the design of our small molecule drug candidates, we use the APECCS technology to measure epithelial transport of ions and nutrients and to screen compounds to identify potential disease modulators such as inhibitors or activators using phenotypic screening. APECCS has the potential to allow us to identify novel targets, mechanisms of action and physiology as well as provide us an early understanding of how identified compounds may interact with specific gut tissues. In addition, we believe that APECCS may also provide us with a clear path to translate cell-based observations into in vivo rodent models and ultimately into human clinical studies.

Our Strategy

Our goal is to be a leader in the discovery, development and commercialization of innovative, minimally-systemic, small molecule therapeutics that work exclusively in the GI tract to treat cardio-renal, GI and metabolic diseases. Our strategy involves the following:

Advance tenapanor into late-stage and pivotal clinical trials. We are actively involved with AstraZeneca in the development efforts for tenapanor, and we participate in the strategic and operational management of the global tenapanor program. We are focused on rapidly and efficiently advancing this program.

Use non-dilutive financing from our existing collaboration partnerships and the proceeds from our initial public offering to expand our product pipeline and advance our earlier-stage product candidates into clinical trials. As of December 31, 2014, we have received $76.3 million in non-dilutive funding from our collaboration partners, AstraZeneca and Sanofi. If we achieve our milestones in these agreements, we would receive additional significant non-dilutive funding. We plan to use these payments to continue our discovery and development efforts for our clinical and preclinical product candidates and to expand our product pipeline, including through the potential acquisition or in-license of other products. In addition, we will continue to evaluate new collaboration partnerships to enhance the discovery, development or commercialization of other product candidates in our product pipeline.

Leverage our technological capabilities and drug discovery and design platform to expand our product pipeline. We have developed a unique approach to discover and develop new agents to treat diseases involving the exploitation of receptors and targets on the epithelia of the GI tract that affect related biology to treat disease. We have built a suite of tools, knowledge and capabilities around this approach and have leveraged such tools for the discovery of NHE3 inhibitors such as tenapanor, NaP2b inhibitors, TGR5 agonists and other drug candidates in our pipeline. We have developed APECCS to augment and help streamline the approach. We plan to leverage these tools, capabilities and know-how to discover, develop and commercialize new first-in-class drugs that treat cardio-renal, GI and metabolic diseases.

Develop commercial capabilities. With the co-promotion rights under the AstraZeneca and Sanofi partnerships, along with the commercial expertise of our management team, we are well-positioned to develop a commercial presence in renal and GI diseases and expect to develop U.S. commercial capabilities. Assuming that one or both of our collaboration partners continue to advance the programs into Phase 3 clinical development and assuming the receipt of positive Phase 3 results, we expect to exercise our right to co-promote one of our drug candidates with AstraZeneca or Sanofi, either of which would provide financial support that would assist us in building a specialty sales and marketing team for this purpose. We also may develop additional commercial capabilities in connection with other opportunities we choose to pursue.

Leverage our management team’s drug development and commercialization expertise to identify and secure complementary in-licensing opportunities. Our management team has significant experience in the development and commercialization of products in the cardio-renal, GI and metabolic fields in which we operate. We intend to leverage this expertise to pursue additional in-licensing opportunities that expand our product pipeline within relevant therapeutic fields.

Our Product Pipeline

The following table summarizes key information about our product candidates:

Tenapanor

Summary of tenapanor

Tenapanor has demonstrated the ability to improve the symptoms of IBS-C and to reduce the absorption of both dietary sodium and phosphorus, which are widely recognized as key factors in the progression of kidney disease. In addition to the evaluation of tenapanor for the treatment of IBS-C, we and AstraZeneca have completed a Phase 2b clinical trial evaluating the potential for tenapanor in the treatment of hyperphosphatemic patients with end-stage renal disease, or ESRD on dialysis, also known as CKD-5D. A Phase 2a clinical trial is currently being conducted in order to understand the potential impact tenapanor may have on markers of kidney disease and fluid status in CKD stage 3, or CKD-3 patients.

Tenapanor is a minimally-absorbed, small molecule that acts locally in the gastrointestinal tract to inhibit the NHE3 transporter and reduce sodium uptake from the gut. In vitro studies have shown that tenapanor is a potent inhibitor of human NHE3 and specific for NHE3 versus other transporters such as NHE1, NHE2 and NaP2b. When radiolabeled tenapanor was administered orally to rats, we demonstrated that approximately 98% of the administered dose was recovered, unchanged, in feces, indicating that no substantial metabolism occurred and that the drug was minimally-absorbed. In human studies of orally-administered tenapanor, the drug was detected in the blood in only 0.7% of more than 3,000 collected serum samples, and even in those, at very low levels (< 1.5 ng/mL). Results from a human ADME study demonstrated that tenapanor is minimally-absorbed. In such study, inactive metabolites were identified in plasma samples that were approximately 9% of the parent compound. Tenapanor is stable at room temperature and has been formulated into small tablets ranging in strength from 1 mg to 50 mg.

We have administered tenapanor to over 1,000 subjects to date including 347 healthy volunteers, 417 IBS-C subjects and about 255 patients with CKD and ESRD. Tenapanor has been administered in a single dose of up to 900 mg and for a period of up to 3 months at 100 mg/day. The most common side effects, generally observed in all clinical trials, consistent with the minimally-absorbed exaggerated GI pharmacology of the drug were loose stools and diarrhea.

In animal studies and Phase 1 studies in healthy adult volunteers where fecal sodium was measured, we observed that tenapanor has a significant effect on the diversion of dietary sodium into the stool. In addition, in IBS-C patients, we saw that tenapanor elicited the expected pharmacological effect of increased fecal fluid that results from the inhibition of sodium absorption. The sodium effect of tenapanor is related to its interaction with NHE3. NHE3 is a sodium-proton exchanger located on the epithelia or surface of the intestinal lumen. NHE3 is also located on absorptive cells of the nephrons (structural units of the kidney that filter the blood). Its role is to absorb sodium into the body from the intestine or, alternately, re-absorb it from the filtered plasma in the kidney in order to maintain sodium balance in the body. The net flow of sodium (and chloride through other means) from the intestines also results in the complementary absorption of intestinal water to maintain a constant blood sodium concentration.

In preclinical studies with tenapanor, we observed that, in addition to diverting sodium into the stool, tenapanor also inhibited the absorption of phosphorus, and in several Phase 1 studies in healthy adults, we observed that tenapanor has a significant effect on the diversion of dietary phosphorus into the stool. In in vitro studies we determined that tenapanor does not directly inhibit NaP2b or PiT1, both of which are phosphorus transporters in the gut.

Tenapanor for treating IBS-C

In October 2014, we announced the positive results of our Phase 2b clinical study evaluating tenapanor in 371 IBS-C patients. Results from this study demonstrated statistically significant and clinically meaningful improvement in IBS-C symptoms for tenapanor-treated patients compared to patients receiving placebo. At the twice daily 50 mg dose, the study met its primary efficacy endpoint of an increase in the CSBM responder rate. Most secondary endpoints, including the overall responder rate, the abdominal pain responder rate, and other abdominal and IBS-C symptoms, demonstrated statistically significant and clinically meaningful improvements. Tenapanor was well-tolerated, and the safety results were consistent with those observed in previous tenapanor trials.

IBS-C is a GI disorder in which abdominal pain or discomfort is associated with constipation, which significantly affects the health and quality of life of affected patients. It is unknown what causes IBS-C. There is no specific test or biomarker for IBS-C and therefore, its presence is diagnosed by symptoms and by eliminating other disorders. IBS-C is very similar to chronic constipation and it is clinically distinguished by a significant pain component.

Clinical data supporting tenapanor in IBS-C

We conducted a Phase 2b clinical trial in IBS-C patients and announced results from that study in October 2014. The clinical trial was a randomized, double blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of three dose levels of tenapanor in 371 subjects with IBS-C as defined by the Rome III criteria and who had active disease as determined during a two-week screening period. Subjects who qualified and who were randomized into the study received 5, 20, or 50 mg of tenapanor or placebo twice daily for 12 consecutive weeks. At the end of this treatment period, subjects were followed for an additional 4 weeks. The results were reported on an intent-to-treat basis.

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

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

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

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

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

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

Size of the IBS-C market

Based on reports in the literature regarding the prevalence of IBS in the U.S. population and the percentage of individuals who have IBS-C as opposed to other forms of IBS, we estimate that approximately 1.4% of the U.S. population has IBS-C, or about 4.4 million individuals. Of those, approximately 1.0 million patients have been diagnosed with IBS-C. Additionally, there are about 6.6 million IBS-C patients in Europe and about 3.4 million in Japan. The per-patient economic burden of IBS-C is estimated to be $1,500 to $7,500 per year in direct costs and $800 to $7,700 per year in indirect costs, implying the total burden in the United States is $2 billion to $15 billion.

Limitations of current products for IBS-C

Numerous treatments exist for the constipation component of IBS-C, many of which are over-the-counter. We are aware of two prescription products marketed for IBS-C, Linzess (linaclotide) marketed by Ironwood Pharmaceuticals and Actavis and Amitiza (lubiprostone) marketed by Sucampo and Takeda. In Phase 3 clinical trials of Linzess in IBS-C patients, up to 19.8% more patients receiving Linzess than placebo reached the primary endpoint, overall responder rate, indicating a significant response during 6 out of 12 weeks of treatment. In these studies, Linzess caused diarrhea in up to 20% more patients than placebo.

Tenapanor’s competitive advantage in IBS-C

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

In our Phase 1 clinical trials in healthy adults, we observed a consistent and gradual increase of fecal sodium when the once daily dose was increased from 3 mg to 100 mg, and we observed an approximate doubling of fecal sodium when the frequency of dosing was increased to twice daily. In all of our studies, we have seen that stool form change correlates with the amount of sodium diverted. In our Phase 2a clinical trial in IBS-C patients, we dosed up to 100 mg once daily and observed activity consistent with an IBS-C drug and an incidence of diarrhea, a significant limitation of other IBS-C drugs that was similar to placebo. Our phase 2b clinical trial demonstrated a stronger efficacy signal than the Phase 2a with a low to moderate rate of diarrhea of 11.2% versus placebo. Given that we have observed a gradual dose response of sodium with increased dose and dose frequency of tenapanor and that diarrhea represents an exaggerated pharmacological response to the drug, we believe it may be possible to start dosing at once daily and/or a low dose. Those who do not respond would receive a higher dose or increased dose frequency. This ability to titrate

the dose of tenapanor, if proven in subsequent clinical trials in IBS-C patients, would represent a significant differentiation of tenapanor versus currently commercialized products, and may allow optimization of dose response while limiting diarrhea.

Tenapanor for treating hyperphosphatemia in CKD-5D patients

In February 2015, we announced that our Phase 2b clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in CKD-5D patients, or ESRD patients on dialysis, met its primary endpoint of lowering serum phosphate. In this study, the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses were higher than expected based on previous clinical trials. Higher discontinuations rates due to diarrhea were observed primarily in the 30mg once daily and 30mg twice daily dose groups.

CKD is the progressive deterioration of renal function that can occur over several months or years. The symptoms of worsening kidney function are nonspecific, and can include having less energy, reduced appetite, dry itchy skin, swollen feet and ankles, or generally just not feeling well. If the deterioration continues and is not halted by either changes in life-style 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 CKD-5D 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.

Hyperphosphatemia in CKD-5D

Phosphorus, a vital element required for most cellular processes, is present in almost every food in the Western diet, and, in individuals with normal kidney function, any excess dietary phosphorus is efficiently removed by the kidney and excreted in urine. In adults with functioning kidneys, normal serum phosphorus levels are 2.6 to 3.8 mg/dL. With kidney failure, elevated phosphorus becomes a toxin and is diagnosed as hyperphosphatemia when serum phosphorus levels are greater than 5.0 mg/dL. Although patients with CKD-5D rely on dialysis to eliminate toxins, phosphorus is not readily removed by the procedure and other means of managing phosphorus levels must be employed.

In CKD-5D, excess levels of phosphorus have been shown to lead to an increase in cardiovascular disease risk, as well as increases in serum FGF-23, an important serum endocrine hormone that regulates phosphorus metabolism, and elevated parathyroid hormone, also known as secondary hyperparathyroidism. These endocrine changes in CKD-5D patients are a concern as elevated parathyroid hormone leads to the development of renal osteodystrophy, a condition of abnormal bone growth characterized by brittle bones.

Elevated levels of FGF-23 are strongly associated with an increased risk of cardiovascular mortality. With concurrent elevated calcium levels common in these patients, particularly when calcium is used as a means of controlling phosphorus, deposits containing calcium and phosphate develop in arteries, joints, skin, soft tissue and other organs. Increased coronary artery calcification is associated with an increased risk of heart disease, stroke and death.

Clinical data supporting tenapanor in hyperphosphatemia

We and AstraZeneca conducted a Phase 2b clinical study evaluating tenapanor in CKD-5D patients with hyperphosphatemia. We announced results of this study in February 2015. This Phase 2b trial (ClinicalTrials.gov identifier NCT02081534) was a randomized, double blind, placebo-controlled, multi-center, international study evaluating the safety and efficacy of six dose levels of tenapanor (3 and 30 mg once daily, and 1, 3, 10, and 30 mg twice daily) in 161 hyperphosphatemic CKD-5D patients. The primary efficacy endpoint was the change from baseline of S-phosphate levels to the end of treatment and the endpoint was analyzed using an analysis of covariance

model (ANCOVA). The study met its primary endpoint by demonstrating a statistically significant dose-related decrease in serum phosphate levels for tenapanor-treated patients compared to patients receiving placebo (p=0.012).

The Effect of Tenapanor on Serum Phosphate in Hyperphosphatemic CKD-5D Patients

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

*LSMean = least square mean

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

As expected, due to its pharmacological actions, the most frequent adverse event was diarrhea. The rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses were higher than expected based on previous clinical trials. Higher discontinuations rates due to diarrhea were observed primarily in the 30mg once daily and 30mg twice daily dose groups. There were no other notable gastrointestinal adverse events that appeared to be tenapanor related. The overall safety profile remains consistent with that observed in previous tenapanor trials in this patient population.

Phase 2b CKD-5D Hyperphosphatemia Adverse Events: Gastrointestinal Disorders*

Preferred Term	1 mg BID	3 mg BID	10 mg BID	30 mg BID	3 mg QD	30 mg QD	Placebo
n/group	23	21	23	25	22	21	26
Abdominal Distension		1					
Abdominal Pain				2	1		1
Abdominal Pain Upper			1				
Diarrhea	6	6	11	17	4	11	3
Diverticulum	1						
Dyspepsia		1					
Fecal Incontinence		1	2				2
Feces Soft		1					
GI Hypermotility					1		
GI Sounds Abnormal			1				
Hemorrhoids						1	
Nausea		1	1	1	2	1	1
Rectal Prolapse				1			
Steatorrhea			1				
Vomiting		1			1	2	

*Number of patients who had at least 1 AE in system organ class of gastrointestinal disorders; in these tables QD refers to once daily dosing and BID refers to twice daily dosing.

Phase 2b CKD-5D Hyperphosphatemia Discontinuations Due to Adverse Events

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

*There may be multiple reasons for a single discontinuation

**The term “diarrhea” also includes similar changes in stool form or bowel habits

Size of the hyperphosphatemia market

According to the most recent data available from the U.S. Renal Data System, in 2012 there were 408,711 patients on hemodialysis in the United States. Additionally, according to the European ERA-EDTA Registry 2012 Annual Report and a study in 2010 by the Japanese Society for Dialysis Therapy, there were approximately 280,000 patients on hemodialysis in Europe and about 250,000 in Japan. We estimate, based on phosphate binder utilization, the only approved therapies for hyperphosphatemia, that there are approximately 280,000, 225,000 and 220,000 CKD-5D patients with hyperphosphatemia in the United States, Europe and Japan, respectively.

Limitations of current products for hyperphosphatemia

Since dialysis is unable to efficiently eliminate excess phosphorus, CKD-5D patients are put on restrictive low phosphorus diets and are prescribed medications called phosphate binders, the only pharmacologic interventions currently marketed for the treatment of hyperphosphatemia. Phosphate binders are a collection of drugs whose function is to bind, or absorb, dietary phosphorus and are taken in conjunction with meals and snacks. They include calcium, iron or lanthanum, a rare-earth metal, which bind to and precipitate with dietary phosphate in the GI tract. The goal is for patients to eliminate the precipitated phosphorus in their stool. A limitation of this approach is the systemic excess absorption of calcium, iron or lanthanum, resulting in side effects and other unintended consequence for CKD-5D patients. In an effort to eliminate these unwanted side effects, non-absorbed exchange resins, such as sevelamer were developed to bind to phosphate in the GI tract and to be eliminated in stool.

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

CKD-5D patients take on average 10-14 oral medications each day, and they are severely restricted in their fluid intake. In addition, to control their serum phosphorus, their phosphate binder-related pill burden is significant, typically consisting of nine or more pills a day. The amount of phosphate a binder can remove is limited by its binding capacity, and therefore, increasing the dose, and the pill burden, of the binder is the only way to increase the amount of phosphate being bound and excreted. As a result, prescribed binder doses are intolerable for many patients.

The effectiveness of current treatment with phosphate binders is limited. For example, in a 2012 study conducted by Amgen in 1,430 ESRD patients on hemodialysis in the United States in which 89% of the patients in the study had previously been prescribed phosphate binders, the average baseline serum phosphorus level was 6.4 mg/dL, significantly above the target for dialysis patients of 5.5 mg/dL and far above normal serum phosphorus levels of 2.6 to 3.8 mg/dL. Other studies suggest that this lack of efficacy is due primarily to poor patient compliance associated with significant pill burden and other tolerability issues.

Tenapanor’s competitive advantage in hyperphosphatemia

Given that the objective is to lower serum phosphorus levels to below 5.5 mg/dL in dialysis patients, and that many of these patients are unable to accomplish this goal with currently marketed phosphate binders, there is a clear medical need for new treatments for hyperphosphatemia. We believe that there is a significant opportunity for new agents with new mechanisms, demonstrated efficacy, a strong safety profile, and significantly lower pill burden. We believe that tenapanor, if approved, has the potential to have the lowest pill burden among any of the marketed hyperphosphatemia drugs, with milligram rather than gram quantities dosed once or twice daily.

Tenapanor for treating CKD: potential long-term benefit of sodium control

In an ongoing Phase 2a trial, we and AstraZeneca are exploring the potential benefit of tenapanor in treating patients with CKD who still have some renal function and are not yet on dialysis. In order to explore the benefits of tenapanor in this population, we are initially evaluating tenapanor for its effect on markers of kidney disease and fluid status. We expect results from this trial in the second quarter 2015.

The decline in renal function in patients with CKD is initially asymptomatic and the rate of disease progression varies based on genetics, ethnicity, the underlying cause, such as cardiovascular disease, diabetes, and many other factors. As the disease progresses, signs and symptoms of CKD become more apparent and include fluid overload, hyperkalemia, metabolic acidosis, hypertension, anemia, and mineral and bone disorders. Therapy to delay progression of the disease focuses on blood pressure control and reduction in urinary protein excretion.

Sodium and fluid overload in CKD

In CKD patients, failing kidneys are less efficient at blood filtration and sodium elimination resulting in fluid and sodium overload. This fluid overload correlates with the rapid decline of kidney function and the eventual requirement for renal replacement therapy including hemodialysis. The effects of fluid overload include high blood pressure, worsening kidney and heart disease, fluid in the lungs, or edema, causing dyspnea, or shortness of breath, and ultimately poor survival. Fluid overload has been shown to be an independent predictor of mortality in both hemodialysis patients and in CKD patients.

In a study of CKD patients where sodium intake was restricted, the investigators demonstrated that lower sodium intake corresponded to reduced blood pressure and albuminuria in those patients. Those two measures are indicators that kidney function may be improving. Although generally acknowledged that excess sodium intake should be curtailed in this population, it is also recognized that the majority of people who are told to restrict sodium intake are non-compliant. We believe that the pharmacologic approach we are taking with tenapanor may have the same impact as a low sodium diet, but may improve compliance.

We believe that, if we are successful in demonstrating an improvement in UACR with a reasonable tolerability profile particularly related to rate of diarrhea at effective doses, our ongoing Phase 2a clinical trial of tenapanor in CKD patients will provide data to allow for further investment in larger trials evaluating tenapanor’s ability to delay CKD disease progression. We expect to receive results from the ongoing Phase 2a study in the second quarter of 2015.

Limitations of current approaches to delay CKD progression

In an effort to preserve renal function, physicians often suggest a number of interventions and life-style modifications; however, most of them are quite cumbersome and lead to poor patient compliance. Although low sodium diets are generally required for all CKD patients, most patients are generally poorly compliant for a variety of reasons, including cost, lack of availability of low sodium foods and the unwillingness to change eating habits.

Most CKD patients are also treated with a combination of therapies designed to delay progression of kidney disease by controlling diabetes, blood pressure and decreasing fluid retention. Diuretics are often prescribed to inhibit sodium re-uptake in the kidney and increase urinary sodium and water excretion. However, diuretics lose efficacy as kidney function declines, and are known to cause electrolyte disorders such as hypokalemia (low potassium) and metabolic alkalosis (high bicarbonate level in the blood). Hypertension medications referred to as ACE inhibitors, ARBs and mineral corticoid receptor blockers also reduce blood pressure associated with fluid overload, which in turn can delay the rate of progression of CKD. In addition, these agents, particularly mineral corticoid receptor blockers, can result in hyperkalemia (high potassium), preventing their widespread use in CKD patients.

Size of late-stage CKD market

Worldwide, there are about 64.6 million patients with stage 3 or 4 CKD all of which are at significant risk of kidney disease progression, heart disease caused by vascular calcification and premature death. There are approximately 3.6 million patients in the United States with stage 3b and 4 CKD. There are about 8.5 million and 2.3 million patients with stage 3b or 4 CKD in Europe and Japan, respectively. Of these, there are about 1.8 million, 1.7 million and 0.6 million patients in the United States, Europe and Japan, respectively that have both CKD and type 2 diabetes, the patient population currently studied in the ongoing Phase 2a CKD clinical trial.

Preclinical and clinical data supporting tenapanor for CKD

In preclinical models, rats with CKD that were fed a high salt diet and exhibited hypervolemia, cardiac hypertrophy and arterial stiffening, had improved measures of cardio-renal function including a dose-dependent reduction of extracellular fluid volume, left ventricular hypertrophy, albuminuria, and blood pressure in a dose-dependent manner with administration of tenapanor. We observed these effects whether tenapanor was administered prophylactically or after disease was established. In these studies, tenapanor also prevented increases in glomerular area and urinary KIM-1, both markers of renal injury. In addition, rats dosed with a combination of tenapanor and the blood pressure medication enalapril showed improvement in cardiac diastolic dysfunction and arterial pulse wave velocity relative to those animals dosed with enalapril alone.

In human studies, tenapanor reduced urinary sodium excretion by 20 to 50 mmol/day and led to an increase of similar magnitude in stool sodium. The results of these preclinical and clinical studies suggest that therapeutic alteration of sodium transport with tenapanor in the gastrointestinal tract could lead to improvements in CKD and has informed the design of our development plan.

We and AstraZeneca are conducting an exploratory Phase 2a, randomized, double-blind, placebo- controlled study to evaluate pharmacodynamics of tenapanor in patients with stage 3 CKD, type 2 diabetes mellitus with albuminuria and elevated systolic blood pressure. One-hundred and fifty-four subjects have been randomized and enrollment is closed. The study consists of a 4-week run-in period, 12 weeks of blinded treatment with tenapanor 5, 15, 30, or 60 mg BID or placebo, and a 2-week follow-up period.

Pharmacodynamic assessments, or assessments of biological effects of tenapanor, include the following measures: Urine albumin-to-creatinine ratio, or UACR and eGFR (s-creatinine, and s-cystatin-c) which are indications of kidney function, blood pressure, bioimpedance a measure of excess body fluid, mean weekly stool consistency and stool frequency and urinary and blood markers associated with kidney disease. Safety assessments are performed at regular intervals and include physical examinations, vital signs, body weights, electrocardiograms, and laboratory results from blood and urine tests.

If the results of the ongoing Phase 2a study demonstrate that tenapanor offers a benefit by decreasing elevated UACR, a measure that roughly correlates with kidney disease severity and which has a significant component that may be independent of any blood pressure effect, and if the agent can demonstrate a reasonable tolerability profile particularly related to rate of diarrhea, we believe this may give us insight into the potential long-term benefit of tenapanor on delaying the progression of kidney disease.

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Other Development Programs

Utilizing our proprietary drug discovery and design platform, we are pursuing other internal discovery and lead-development programs that are currently in the research phase, including our RDX002 program partnered with Sanofi, and the two internal programs that we have announced, RDX009 and RDX013. While we have identified molecules that exhibit certain of the activity we are seeking in each of these programs, we have not yet selected a lead molecule in these programs.

RDX002 NaP2b Inhibitor for Hyperphosphatemia

RDX002 refers to our program aimed at discovering and evaluating small molecule inhibitors of the intestinal phosphate transporter NaP2b (also known as NaPi2b, Npt2b and SLC34A2). Our RDX002 program includes a portfolio of minimally-absorbed NaP2b inhibitors in the discovery and preclinical stage of development. We have licensed this program to Sanofi, and under the terms of the agreement, Sanofi is responsible for completing discovery and preclinical work and, if it exercises its option, developing and commercializing at least one NaP2b inhibitor resulting from the program.

NaP2b is an intestinal phosphate transporter whose activity is believed to account for a significant portion of dietary phosphate absorption in humans. We believe the inhibition of NaP2b would provide utility for the treatment of hyperphosphatemia in CKD-5D patients.

We have identified several NaP2b inhibitors that showed activity in vitro and in animal models. In rats with normal renal function certain NaP2b compounds were able to reduce urinary excretion of phosphorus better than commercial phosphate binders such as sevelamer or colestilan, even when these compounds were dosed at approximately 1/10 of the dose of the commercial binders. In addition, our NaP2b compounds had additive effects when administered with sevelamer or colestilan. In a rat model designed to emulate CKD (5/6 nephrectomized rats where one full kidney and 2/3 of the second kidney are removed) one of our NaP2b inhibitors significantly reduced serum phosphorus and was additive or synergistic with sevelamer. This agent also significantly improved animal survival in the same model.

Our identified NaP2b inhibitors work through a mechanism distinct from those employed by binders. Our NaP2b inhibitors are designed to inhibit NaP2b, one of the primary phosphate transporters in the gut. We have shown that our inhibitors are able to inhibit phosphate regardless of the amount of phosphate in the diet. We believe this mechanism would have a significant advantage over phosphate binders, and may allow us to significantly decrease pill burden while retaining a similar phosphorus effect. Additionally, we believe that the use of a NaP2b inhibitor in combination with a phosphate binder may allow the dose of the phosphate binder to be reduced. We cannot predict whether or not these effects will be seen until the appropriate clinical trials are conducted.

RDX009 TGR5 agonists for IBD, Short Bowel Syndrome and NASH

Our RDX009 program is aimed at discovering and evaluating small molecule, orally-administered drug candidates that stimulate TGR5. We believe the stimulation of TGR5 may have utility in several conditions, including inflammatory bowel disease, or IBD, short bowel syndrome, and possibly type 2 diabetes and NASH.

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

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

Historically one of the limitations for the development of TGR5 agonists has been the observation with systemic compounds that stimulation of TGR5 in the gallbladder results in excess gallbladder filling, potentially increasing the risk of gallstones. Utilizing our approach to design small molecules, we have created novel TGR5 agonist candidates that have extremely low systemic exposure and we have shown that these agents do not result in excess gallbladder filling in preclinical animal models. These TGR5 agonists, in combination with certain DPP4 inhibitors, also demonstrated significant activity in several different animal models of disease.

RDX013 for hyperkalemia

Our RDX013 program is aimed at discovering and evaluating small molecule, orally-administered drug candidates that modulate the transport of potassium in the GI tract.

Our agents will be designed to enhance potassium secretion or prevent potassium absorption in the colon and correct hyperkalemia disorders in CKD patients. We believe that specific potassium transporters in the intestines may serve as useful targets for our program. We are also using APECCS to identify novel pathways to activate potassium flux from the interior of the GI epithelium cells to the GI lumen. We believe that such agents may be used as stand-alone agents or used in combination with potassium binders to boost efficacy or to reduce the pill burden of the potassium binders. Several agents we have developed have demonstrated significant activity in animals.

Collaboration Partnerships

Collaboration partnership with AstraZeneca

Overview

In October 2012, we entered into a collaboration partnership with AstraZeneca for the development and commercialization of our small molecule NHE3 inhibitors, including tenapanor as well as back-up compounds. Additionally, as part of the collaboration partnership, we agreed to provide development support related to the licensed compounds subject to reimbursement by AstraZeneca for our internal and external expenses incurred in providing such efforts, subject to an agreed upon cap on AstraZeneca's obligation to reimburse our costs for the Phase 2b clinical trial of tenapanor for IBS-C.

Under the terms of the agreement, we received a $35.0 million upfront payment and we are eligible to receive up to $237.5 million in development milestones, of which we have received $40.0 million. In addition to the $237.5 million in total development milestones, we are also eligible to receive up to $597.5 million in sales and launch milestones which, when combined with the $35.0 million upfront payment, provides for potential payments of up to $870.0 million. Through December 31, 2014, we also received $34.2 million in reimbursement for our development efforts provided under the agreement. We are also eligible to receive incremental tiered royalties based on aggregate annual net sales of each licensed product starting in the high single digits and increasing to high teen percentages as annual net sales increase. If we exercise our right to co-fund the first Phase 3 development program for tenapanor, we could acquire an increase in our royalties by 1%, 2% or 3%, as described below under the heading "—Right to co-fund/royalty buy-up."

AstraZeneca solely funds all development and commercialization costs for licensed compounds and licensed products, except for costs that we elect to undertake if we exercise our right to co-fund certain development efforts in exchange for an increase in the royalty percentage, as described below under the heading "—Right to co-fund/royalty buy-up."

AstraZeneca may choose to develop tenapanor for any indication. Provided that it is pursuing development for at least one indication, AstraZeneca may choose not to develop tenapanor for any other indications. AstraZeneca must use

commercially reasonable efforts to develop, manufacture, seek regulatory approval for and commercialize a licensed product in each of certain specified major markets.

Right to co-fund/royalty buy-up

We may elect to participate in the funding of the first Phase 3 development program for the first indication for the first licensed product by paying a co-funding amount of $20.0 million, $30.0 million or $40.0 million. We may exercise this right within a specified time period after the decision to proceed to Phase 3 clinical development for the first indication for the first licensed product. If we elect to co-fund the Phase 3 development program for the specific indication for the relevant licensed product, we will receive a 1%, 2% or 3% increase in the royalty payable on net sales of the licensed product for all indications, depending upon the level of co-funding that we elect. We may exercise this right only for a period of 60 days following AstraZeneca's determination to proceed to the first Phase 3 clinical development program for tenapanor for a specific indication. An election to participate in the co-fund will be based, in part, on our analysis as to the likelihood of success of the Phase 3 clinical development program and the potential for regulatory approval to commercialize tenapanor. The selected co-funding amount would be paid ratably over the estimated period of the Phase 3 clinical development program.

Right to co-promote in the United States

We may elect to co-promote in the United States the first licensed product for the first indication for which Phase 3 clinical development is completed. If we make such an election, we may also elect to co-promote the same licensed product for additional indications for which Phase 3 clinical development is completed in the specified period. After we make a co-promotion election, we must enter into a separate co-promotion agreement on terms and conditions set out in our agreement with AstraZeneca, which includes, among other rights and obligations, a requirement for Ardelyx to provide a trained sales force for promoting the licensed product, which may not also promote products that compete with the licensed product or other products then promoted by AstraZeneca or its affiliates and AstraZeneca must reimburse us for our agreed-upon co-promotion efforts other than for general training of our sales force. We will continue to have a right to receive royalties on net sales of licensed products as set forth in the agreement even if we elect to co-promote the licensed product in the United States.

Other terms

For periods specified in the agreement, neither we nor AstraZeneca can research, develop or commercialize NHE3 inhibitors, other than pursuant to the agreement.

The agreement will expire in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries, and the satisfaction or expiration of all other payment obligations under the agreement. The royalty term for each licensed product in each country is the period commencing with the first commercial sale of the applicable licensed product in the applicable country and ending on the later of expiration of specified patent coverage or 10 years after the first commercial sale in the applicable country. AstraZeneca has the right to terminate the agreement at any time in its entirety, upon specified prior written notice to us, and is deemed to have so terminated the agreement if it ceases all exploitation of licensed products for a specified continuous time period and does not provide a plan to recommence such exploitation within a particular time period thereafter. AstraZeneca may also terminate the agreement on a country by country basis upon a specified prior written notice if there are third party patents that may be infringed in particular countries by the development, manufacture or commercialization of licensed products, subject to certain conditions. The agreement may also be terminated by us in the event that AstraZeneca actively assists in a legal challenge of any of the patents exclusively licensed to AstraZeneca under the agreement, and it may be terminated by us or by AstraZeneca for a material breach by or insolvency of the other party.

Collaboration partnership with Sanofi

Overview

In February 2014, we entered into a license option and license agreement with Sanofi under which we granted Sanofi an exclusive worldwide license to conduct research utilizing our small molecule NaP2b inhibitors solely for the purpose of completing activities under a preclinical development plan. Under the terms of this agreement, Sanofi has the option to obtain an exclusive license to develop, manufacture and commercialize our NaP2b inhibitors. Sanofi may exercise this option at any time following the effective date of the agreement and ending 45 days after the filing of an IND, subject to certain exceptions, and if Sanofi does not file an IND on or before the 40 month anniversary at the completion of the technology transfer phase, the agreement will terminate.

Sanofi is responsible for conducting and funding all research, development and commercialization of licensed products under the agreement. If Sanofi exercises its option, it must use commercially reasonable efforts to develop, seek regulatory approval for, manufacture and commercialize a licensed product for any indication in each of certain specified major markets.

We received a $1.25 million upfront payment, and we are eligible to receive up to $196.75 million in development and regulatory milestone payments. We are also eligible to receive incremental tiered royalties based on aggregate annual net sales of any licensed product starting in the mid-single digits and increasing to low teen percentages as annual net sales increase, subject to reduction in specified circumstances.

Right to co-promote in the United States

We may elect to co-promote in the United States for each licensed product for which Phase 3 clinical development is completed. We may elect to provide a level of co-promotion support within a range specified in our agreement with Sanofi. If we make such an election to co-promote, we have additional rights to elect to co-promote other licensed products under this agreement. After we make a co-promotion election, we must enter into a separate co-promotion agreement on terms and conditions set out in our agreement with Sanofi. Such co-promotion agreement must provide reasonable terms and conditions under which we will co-promote the relevant licensed products, and will require Sanofi to compensate us for performing our co-promotion obligations. We will continue to have a right to receive royalties on net sales of licensed products as set forth in the agreement even if we elect to co-promote the licensed product in the United States.

Other terms

During the term of the agreement, and in certain circumstances for a specified period following termination of the agreement, neither we nor Sanofi can, subject to certain exceptions described in the agreement, research, develop or commercialize a NaP2b inhibitor other than pursuant to the agreement.

The agreement will expire if Sanofi does not exercise its option by the earlier of (i) 45 days after the filing of an IND for a NaP2b inhibitor (subject to certain extensions for regulatory actions) and (ii) the expiration or termination of the agreement. If Sanofi does exercise its option, the agreement will expire in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries, and the satisfaction or expiration of all other payment obligations under the agreement. The royalty term for each licensed product in each country is the period commencing with the first commercial sale of the applicable licensed product in the applicable country and ending on the later of expiration of specified patent coverage or 10 years after the first commercial sale in the applicable country. Sanofi has the right to terminate the agreement at any time in its entirety or on a country-by-country basis upon specified prior written notice to us, and is deemed to have so terminated the agreement if it has not filed an IND for a licensed compound within a specified period of time, if it fails to exercise its option within a specified period of time, or if, after exercising its option, it ceases all exploitation of licensed products for a specified continuous time period and does not provide a plan to recommence such exploitation within a particular time period thereafter. The agreement may also be terminated by us in the event that Sanofi actively assists in a legal challenge of one of the patents exclusively licensed to Sanofi under the agreement, and it may be terminated by us or by Sanofi for a material breach by or insolvency of the other party.

Commercialization of our Products

We retain co-promotion rights with our collaboration partners, AstraZeneca and Sanofi, in the United States, and under the terms of our agreements, our commercialization costs will be funded by the collaboration partner. We expect, subject to certain conditions set forth in the AstraZeneca agreement, to take advantage of these opportunities to co-promote our licensed products. We intend to build a focused, specialized sales force in the United States to effectively support the commercialization of these and future products.

If we co-promote our licensed products, we would develop a sales capability to target key prescribing physicians in nephrology, gastroenterology, endocrinology or cardiology, depending on the product. We currently do not have any

sales or marketing activities or personnel. Within the time required under our agreements with AstraZeneca and Sanofi, if we exercise our co-promotion right we will establish the required capabilities in advance of any product approval and commencement of commercialization to prepare for product launch. If we are not able to establish these sales and marketing capabilities, either on our own or through collaboration with AstraZeneca and Sanofi, any revenue from our future products that we commercialize may be materially adversely affected.

Competition

Competition for management of IBS-C

Numerous treatments exist for constipation and the constipation component of IBS-C, many of which are over-the-counter. These include psyllium husk (such as Metamucil), methylcellulose (such as Citrucel), calcium polycarbophil (such as FiberCon), lactulose (such as Cephulac), polyethylene glycol (such as MiraLax), sennosides (such as Exlax), bisacodyl (such as Ducolax), docusate sodium (such as Colace), magnesium hydroxide (such as Milk of Magnesia), saline enemas (such as Fleet) and sorbitol. These agents are generally inexpensive and work well to relieve temporary constipation.

We are aware of two prescription drugs currently on the U.S. market that are approved to treat IBS-C:

- Linzess (linaclotide): Linzess is a drug developed by Ironwood Pharmaceuticals, Inc., approved in 2012 and 2013 for IBS-C and chronic constipation in both the United States and in Europe. Linzess is based on the heat stable enterotoxin produced in E. coli that causes traveler's diarrhea. Linzess targets guanylate cyclase C in the intestines and, by doing so, induces intestinal chloride and fluid secretion, which results in the outpouring of water into the intestine. Linzess in a meta-analysis was deemed "moderately effective compared with placebo for improving typical symptoms of IBS-C". In two IBS-C phase 3 studies, Linzess had a 12.6% and 19.8% overall responder rate compared to the placebo. In these studies, the most common side effect was diarrhea which occurred in 20% of the patients, and led to discontinuation of 5% of the patients.
- Amitiza (lubiprostone): Amitiza was first approved in the United States in 2006 and is currently marketed by Sucampo Pharmaceuticals, Inc. and Takeda Pharmaceutical Company Limited for treatment of chronic idiopathic constipation, or CIC, IBS-C and opioid-induced constipation, or OIC. Amitiza binds selectively to and activates the type-2 chloride channel in the intestine releasing chloride and water into the intestine. In two IBS-C phase 3 studies, Amitiza's overall response rate (global relief of IBS-C symptoms) was about 6% greater than placebo. The primary adverse events were nausea and diarrhea, which occurred in 8% and 7% of patients, respectively.

We are aware of several products in development targeting IBS-C and/or CIC. These include Ferring Pharmaceuticals, Inc./Albireo AB's elobixibat, an IBAT inhibitor in Phase 3 for CIC and in Phase 2 for IBS-C and Synergy Pharmaceuticals, Inc.'s plecanatide, a GC-C agonist similar to linaclotide in Phase 3 for CIC and in Phase 2 for CIC and OIC as well, Synergy Pharmaceuticals, Inc. has SP-333 in Phase 2 for OIC.

Competition for hyperphosphatemia

Phosphate binders are the only pharmacologic interventions currently marketed for the treatment of hyperphosphatemia. Calcium-based binders are the least expensive option to treat hyperphosphatemia. In hemodialysis patients, sevelamer has a 40% patient share versus 44% for calcium-based binders, 16% for lanthanum and 5% for iron-based binders. The various types of phosphate binders commercialized in the United States include the following:

- Calcium carbonate (many over-the-counter brands including Tums and Caltrate)
- Calcium acetate (several prescription brands including PhosLo and Phoslyra)
- Lanthanum carbonate (Fosrenol marketed by Shire)
- Sevelamer hydrochloride (Renagel, marketed by Sanofi)
- Sevelamer carbonate (Renvela, marketed by Sanofi)
- Sucroferric oxyhydroxide (Velphoro, marketed by Vifor Fresenius)
- Ferric citrate (Auryxia, marketed by Keryx)

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

jurisdictions in Europe in 2015.

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

Ferric citrate (Auryxia), an iron-based phosphate binder, was approved by FDA in September 2014. While iron is often deficient in CKD-5D patients because of CKD-associated anemia and lack of sufficient dietary iron, the FDA has required Auryxia to add a warning of iron-overload in the label.

The hydrochloride form of sevelamer, Renagel, was launched in the United States by Genzyme Corporation in 1998 prior to its acquisition by Sanofi, and the carbonate form, Renvela, was launched in 2008. Renvela is currently priced in the United States at a cost of more than $10,000 per patient per year, Fosrenol (lanthanum carbonate) is priced at about $7,500 and calcium-based binders are approximately $900. Despite its higher price, sevelamer is the leading phosphate binder product in the hemodialysis market with 36% patient share (versus 51% split among several calcium-based binders). Sanofi booked €684 million ($770 million) in worldwide sales of sevelamer during 2013. The U.S. patents for sevelamer expired in February 2014 and generic launch was allowed in March 2014. Synthon announced the successful completion of a Phase 3 multicenter, randomized, double-blind, multiple-dose, crossover trial in Europe to compare safety and demonstrate equivalence of serum phosphate control of Synthon sevelamer carbonate tablets to Renvela tablets in chronic kidney disease patients on hemodialysis in April 2014. Currently, several pharmaceutical companies are distributing Synthon manufactured sevelamer carbonate tablets in multiple European countries including, but not limited to, the UK, Spain, Sweden and Denmark.

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

Competition for long-term management of CKD

There are no treatments for CKD that have been proven to reverse the disease. Additionally, various interventions, such as improved diet, blood pressure control, and blood glucose control have had only moderate success in delaying the progression of the disease. CKD patients are currently treated with a combination of diuretics and inhibitors of the renin-angiotensin aldosterone system, or RAAS, to decrease fluid retention and improve hypertension.

There are several dozen generic and branded products that interfere with the RAAS pathway, or act as diuretics. Some of these agents, such as furosemide and thiazide diuretics, were first used in the late 1950s. We are aware of a few new products being developed for treatment of hypertension such as Novartis AG's LCZ696, a dual inhibitor of angiotensin ll receptor and neutral endopeptidase that is in Phase 3, and Palatin Technology, Inc.'s PL-3994, a long-acting natriuretic peptide receptor A agonist in Phase 2.

We are aware of certain investigational drugs that were being developed for delaying kidney decline as measured by eGFR. Among other products, Concert Pharmaceuticals, Inc. is developing CTP-499 which showed protective effects on kidney function at 48 weeks in a Phase 2 clinical trial in patients with CKD and type 2 diabetes. We are aware of several drugs in Phase 2 clinical trials being evaluated for diabetic nephropathy (excluding drugs for blood pressure) including ChemoCentryx, Inc.'s CCR antagonist CCX140, Eli Lilly and Company's TGF-beta monoclonal antibody LY2382770, Genkyotex S.A.'s dual NOX1/NOX4 inhibitor GKT137831, Fibrogen, Inc.'s CTGF inhibitor FG-3019, Pfizer, Inc.'s long-acting PDE5 inhibitor PF-489791, and Noxxon Pharma AG's aptamer inhibitor of MCP-1/CCR2

NOX-E36. To our knowledge, none of these drugs has clinical data showing a delay in the progression of CKD.

Intellectual Property

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

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

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of our issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we, or our collaboration partners, 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 or our collaboration partners, 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. With respect to tenapanor, our collaboration partner, AstraZeneca, and with respect to our NaP2b portfolio, under certain circumstances, our collaboration partner, Sanofi, will be responsible for and have the right to control, with input from us, the selection of the appropriate issued patent for filing to obtain any patent term extension that may be available under applicable laws.

We may rely, in some circumstances, on trade secrets to protect our technology. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaboration partners, sponsored

researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning the business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during the normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

NHE3 patents

Our NHE3 patent portfolio is wholly owned by us and exclusively licensed to AstraZeneca. This portfolio includes one issued U.S. patent, U.S. Patent No. 8,541,448, covering the composition of tenapanor, and one issued Japanese patent, Japanese Patent No. 5502106 covering the composition of tenapanor. Both of these issued patents are predicted to expire in 2029. Five additional patent applications are pending in the United States covering the composition of or methods of using tenapanor. 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 to expire in 2029. An additional application that is eligible for worldwide filing is also pending, and we expect that AstraZeneca will file national patent applications in Europe, Japan, China, India, Israel and a number of other countries at the time when the PCT is converted to national filings.

NaP2b Patents

Our NaP2b portfolio is wholly owned by us, exclusively licensed to Sanofi, and includes four issued U.S. patents and three pending U.S. applications covering the composition of or methods of using our NaP2b inhibitor compounds. The issued patents, and if issued, the pending applications are predicted to expire in 2031. Related national patent applications are pending in Europe and Japan. Any patents resulting from these patent applications, if issued, are also predicted to expire in 2031.

Manufacturing

AstraZeneca is responsible for the manufacture of all future clinical trial and commercial supplies of tenapanor, and should Sanofi exercise its option to develop and commercialize NaP2b inhibitor compounds under our agreement, Sanofi will be responsible for the manufacture of all clinical trial and commercial supplies.

To date, we have relied upon third-party contract manufacturing organizations, or CMOs, to manufacture both the active pharmaceutical ingredient and final drug product dosage forms of our potential drug candidates used as clinical trial material. We expect that we will continue to rely upon CMOs for the manufacture of our clinical trial materials for our own internal programs.

Government Regulation/FDA

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

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

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

completion of extensive preclinical laboratory tests, preclinical animal studies and formulation studies, some performed in accordance with the FDA's current Good Laboratory Practice, or GLP, regulations;
submission to the FDA of an Investigational New Drug, or IND, application which must become effective before human clinical trials in the United States may begin;
approval by an independent institutional review board, or IRB, or ethics committee at each clinical trial site before each trial may be initiated;
performance of adequate and well-controlled human clinical trials in accordance with Good Clinical Practice, or GCP, regulations to establish the safety and efficacy of the drug candidate for each proposed indication;
submission to the FDA of a new drug application, or NDA;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current Good Manufacturing Practice, or cGMP, regulations;
satisfactory completion of a potential review by an FDA advisory committee, if applicable; and
FDA review and approval of the NDA prior to any commercial marketing, sale or commercial shipment of the drug.

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

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

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

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

Clinical trials

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

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, FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials after NDA approval. In other cases, a sponsor may voluntarily conduct additional clinical trials post approval to gain more information about the drug. Such post approval trials are typically referred to as Phase 4 clinical trials.
Concurrent with clinical trials, companies usually complete additional preclinical studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the drug in commercial quantities in accordance with GMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

The FDA, the IRB or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate.

New drug applications

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

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

committee, but it generally follows such recommendations.

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

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

Drugs may be marketed only for the FDA approved indications and in accordance with the provisions of the approved labeling. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the applicant to develop additional data or conduct additional preclinical studies and clinical trials.

The testing and approval processes require substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. Even if we believe a clinical trial has demonstrated safety and efficacy of one of our drug candidates for the proposed indication, the results may not be satisfactory to the FDA. Nonclinical and clinical data may be interpreted by the FDA in different ways, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals which could delay or preclude us from marketing drugs. The FDA may limit the indications for use or place other conditions on any approvals that could restrict the commercial application of the drugs. After approval, certain changes to the approved drug, such as adding new indications, manufacturing changes, or additional labeling claims are subject to further FDA review and approval. Depending on the nature of the change proposed, an NDA supplement must be filed and approved before the change may be implemented. For many proposed post-approval changes to an NDA, but excluding efficacy supplements to an NDA, the FDA has up to 180 days to review the application. As with new NDAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

Other regulatory requirements

Any drugs manufactured or distributed by us or our collaboration partners pursuant to FDA approvals would be subject to continuing regulation by the FDA, including recordkeeping requirements and reporting of adverse experiences associated with the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic announced and unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP, which impose certain procedural and documentation requirements upon us and our third party manufacturers. Failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as warning letters, suspension of manufacturing, seizure of product, injunctive action or possible civil penalties. We cannot be certain that we or our present or future third party manufacturers or suppliers

will be able to comply with the cGMP regulations and other ongoing FDA regulatory requirements. If we or our present or future third party manufacturers or suppliers are not able to comply with these requirements, the FDA may, among other things, halt our clinical trials, require us to recall a drug from distribution or withdraw approval of the NDA for that drug.

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

Fraud and abuse laws

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

The Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchase, order, or prescription of a particular drug, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, the Affordable Care Act, among other things, amends the intent requirement of the federal Anti-Kickback Statute and federal criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. Moreover, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

The federal False Claims Act prohibits anyone from knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. For example, pharmaceutical companies have been prosecuted under the federal False Claims Act in connection with their off-label promotion of drugs. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between $5,500 and $11,000 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. If the government were to allege that we were, or convict us of, violating these false claims laws, we could be subject to a substantial fine and may suffer a decline in our stock price. In addition, private individuals have the ability to bring actions under the federal False Claims Act and certain states have enacted laws modeled after the federal False Claims Act.

In addition to the laws described above, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively known as the Affordable Care Act, also imposed new reporting requirements on drug manufacturers for payments made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. The period between August 1, 2013 and December 31, 2013 was the first reporting period and manufacturers were required to report aggregate payment data by March 31, 2014, and will be required to report detailed payment data and submit legal attestation to the accuracy of such data during Phase 2 of the program (which begins in May 2014 and extends for at least 30 days). Thereafter,

manufacturers must submit reports by the 90th day of each subsequent calendar year.

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

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

Third-party coverage and reimbursement

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

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

Healthcare reform

In March 2010, President Obama signed one of the most significant healthcare reform measures in decades. The Affordable Care Act substantially changes the way healthcare will be financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry.

The Affordable Care Act contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement changes and fraud and abuse, which will impact existing government healthcare programs and will result in the development of new programs, including Medicare payment for performance initiatives and improvements to the physician quality reporting system and feedback program. Additionally, the Affordable Care Act:

- increases the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1%;
- requires collection of rebates for drugs paid by Medicaid managed care organizations;
- expands eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expands access to commercial health insurance coverage through new state-based health insurance marketplaces, or exchanges;
- requires manufacturers to participate in a coverage gap discount program, under which they must agree to offer 50 percent point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D, beginning January 2011; and
- imposes a non-deductible annual fee on pharmaceutical manufacturers or importers who sell "branded prescription drugs" to specified federal government programs.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011 among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of 2 percent per fiscal year, which went into effect on April 1, 2013. In January 2013, the ATRA was enacted, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers. These new laws and the regulations and policies implementing them, as well as other healthcare reform measures that may be adopted in the future, may have a material adverse effect on our industry generally and on our ability to successfully develop and commercialize our products.

Other regulations

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

Employees

As of December 31, 2014, we had 34 full-time employees, including a total of 13 employees with Ph.D. degrees. Within our workforce, 27 employees are engaged in research and development and the remaining 7 in general management and administration, including finance, legal, and business development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We believe that we maintain good

relations with our employees.

Research and Development

The costs were $25.9 million, $28.1 million and $10.2 million in research and development in the years 2014, 2013 and 2012, 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.

About Ardelyx

We commenced operations in 2007. 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. The information contained in, or that can be accessed through, our website is not part of this Annual Report on Form 10-K.

Financial Information about Segments

We operate only in one business segment. See Note 1 to our financial statements included in this Annual Report on Form 10-K.

Available Information

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. The information in or accessible through the SEC and our website are not incorporated into, and are not considered part of, this filing. Further, our references to the URLs for these websites are intended to be inactive textual references only.

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. We have only one product candidate in clinical trials and no product sales, which, together with our limited operating history, makes it difficult to assess our future viability.

We are a clinical-stage biopharmaceutical company with a limited operating history. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. To date, we have focused substantially all of our efforts on our research and development activities, including developing our lead product candidate, 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. Our net loss for the years ended December 31, 2014, 2013 and 2012 was $3.2 million, $6.6 million and $9.8 million, respectively. As of December 31, 2014, we had an accumulated deficit of $71.9 million.

If we do not receive anticipated milestone payments from our collaboration partners, AstraZeneca AB, or AstraZeneca and Sanofi S.A., or Sanofi, our operating losses will substantially increase for the foreseeable future as we continue our discovery, research, development, manufacturing and commercialization activities. There can be no assurance that we will receive any potential milestones under our agreements with AstraZeneca and/or Sanofi. For a discussion of the risks associated with our preclinical and clinical development programs with, and potential for milestone payments from, AstraZeneca and Sanofi, see below under "—Risks Related to Our Business."

Even if we receive the anticipated milestone payments or receive royalty payments from our collaboration partners, we may not be able to achieve or sustain profitability. For example, we may choose to exercise our right to co-fund a portion of the first Phase 3 clinical development program for tenapanor, incurring expenses of up to $40.0 million, and we would likely incur continued operating losses during the period we are co-funding the program. In addition, our receipt of milestone payments from our collaboration partners may not result in the recognition of revenue in the period received, as we may be required to amortize the milestone payment over a period of time. Depending upon such requirement and the period of amortization, we may continue to incur losses even after the receipt of such milestone payments. Therefore, there can be no assurance that our losses will not increase into the future. Our prior losses, combined with possible future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

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

We have no products approved for sale and have never generated any revenue from product sales. Our ability to generate revenue from product sales and achieve profitability depends on our ability, and the ability of our collaboration partners, to successfully complete the development of and obtain the regulatory and marketing approvals necessary to commercialize one or more of our product candidates. We do not anticipate generating revenue from product sales for the foreseeable future. Our ability to generate future revenue from product sales or pursuant to milestone payments depends heavily on many factors, including but not limited to:

- the completion of research and preclinical and clinical development of our product candidates;
- together with our collaboration partners, obtaining regulatory approvals for our product candidates;
- the ability of our collaboration partners to successfully commercialize and/or our ability to commercialize or co-promote, if we so choose, our product candidates;
- developing a sustainable and scalable manufacturing process for any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products to support clinical development and the market demand for our product candidates, if approved;
- obtaining market acceptance of our product candidates, if approved, as viable treatment options;
- addressing any competing technological and market developments;
- identifying, assessing, acquiring, in-licensing and/or developing new product candidates;
- negotiating favorable terms in any collaboration partnership, licensing or other arrangements into which we may enter;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how, and our ability to develop, manufacture and commercialize our product candidates and products without infringing intellectual property rights of others; and
- attracting, hiring, and retaining qualified personnel.

In cases where we, or our collaboration partners, are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which regulatory approval is granted, the accepted price for the product, the ability to get reimbursement at any price and whether we have royalty and/or co-promotion rights for that territory. If the number of patients suitable for our product candidates is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from the sale of such products, even if approved. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our failure to generate revenue from product sales would likely depress our market value and could impair our ability to raise capital, expand our business, discover or develop other product candidates or continue our operations. A decline in the value of our common stock could cause our stockholders to lose all or part of their investment.

We may require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our product development or other operations.

Since our inception, most of our resources have been dedicated to our research and development activities, including developing our lead product candidate, tenapanor, and developing our proprietary drug discovery and design platform. As of December 31, 2014, we had working capital of $89.5 million, including capital resources consisting of cash and cash equivalents of $107.3 million. We believe that we will continue to expend substantial resources for the foreseeable future, including costs associated with research and development, conducting preclinical studies and clinical trials, obtaining regulatory approvals, and sales and marketing. Because the outcome of any clinical trial and/or regulatory approval process is highly uncertain, we cannot reasonably estimate the actual amounts necessary to

successfully complete the development, regulatory approval process and commercialization or co-promotion of any of our product candidates.

Based on our current operating plan, we believe that our existing capital resources will allow us to fund our operating plan through at least the next 12 months. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including, but not limited to:

the decision of AstraZeneca whether or not to continue the development of tenapanor or exercise its right of termination under the agreement to return the program to us;

the achievement of development and regulatory milestones resulting in the payment to us from our collaboration partners of contractual milestone payments and the timing of receipt of such payments, if any;

our decision whether or not to exercise our right to co-fund the first Phase 3 clinical development program for tenapanor, in which case we may invest $20.0 million, $30.0 million or $40.0 million to acquire an increase of 1%, 2% or 3%, respectively, in the royalties payable to us by AstraZeneca on net sales of tenapanor;

the progress, timing, scope, results and costs of our preclinical studies and clinical trials for our product candidates that have not been licensed, including the ability to enroll patients in a timely manner for clinical trials;

the time and cost necessary to obtain regulatory approvals for our product candidates that have not been licensed and the costs of post-marketing studies that could be required by regulatory authorities;

our ability and the ability of our collaboration partners to successfully commercialize and/or co-promote our product candidates;

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

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

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

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

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

the number and scope of preclinical and discovery programs that we decide to pursue or initiate;

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

the costs of filing, prosecuting, maintaining, defending and enforcing any patent claims and other intellectual property rights, including litigation costs and the outcome of such litigation, including costs of defending any claims of infringement brought by others in connection with the development, manufacture or commercialization of our product candidates.

Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate our research and development activities, preclinical and clinical trials for our product candidates for which we retain such responsibility and our establishment and maintenance of sales and marketing capabilities or other activities that may be necessary to commercialize or co-promote our product candidates.

Risks Related to Our Business

If AstraZeneca exercises its right to terminate its collaboration partnership with us, we would not receive any additional milestone payments or revenue from this collaboration partnership, and our results of operations and financial condition will be materially and adversely affected.

In October 2012, we entered into a license agreement with AstraZeneca granting it an exclusive worldwide license to our small molecule NHE3 inhibitor program, which includes our lead product candidate, tenapanor, for all indications. Under this agreement, AstraZeneca has responsibility for completing all nonclinical and clinical development and obtaining and maintaining regulatory approval for tenapanor from the FDA and regulatory agencies outside of the United States. Ultimately, if tenapanor is advanced through clinical trials and receives marketing approval from the FDA or comparable foreign regulatory agencies, AstraZeneca will be responsible for the commercialization of tenapanor, subject to our right to elect to participate in certain co-promotion activities in the United States. AstraZeneca has the right to terminate this collaborative partnership at any time for any reason upon written notice to us. If AstraZeneca elects to terminate the collaborative partnership with us, our business would be materially and adversely harmed and depending on the timing of such event:

- we would not be eligible to receive any of the remaining development or regulatory milestone payments or royalties on product sales of tenapanor;
- the development of tenanapor may be significantly delayed as a result of the need to transition the program back to us;
- we would bear all of the risks and costs related to the further development and commercialization of tenapanor;
- we may not be able to obtain a sufficient supply of clinical trial material from AstraZeneca to support the continued development of tenapanor, and as a result the development of tenapanor may be significantly delayed;
- we may encounter difficulty and delay associated with the transfer of the manufacturing process from AstraZeneca to a third party contract manufacturer, and such third party contract manufacturer may not be able to manufacture clinical or commercial supplies of tenapanor in the time frame, at the scale or to the specifications required;
- in order to fund further development and commercialization of tenanapor, we would need to raise substantial additional capital in order to internally pursue the development of the program, and even if we raise additional capital, we may need to seek out and establish alternative collaboration partnerships with third-party collaboration partners for the program, which may not be possible, or we may not be able to do so on terms which are acceptable to us, in which case it may be necessary for us to limit the size or scope of the program or delay the program, in either case, in a manner that would adversely impact our ability to realize value from the program; and
- our cash expenditures would increase significantly if it is necessary for us to hire a significant number of additional employees and allocate limited resources to the development and commercialization of tenapanor.

Any of these events would have a material adverse effect on our results of operations and financial condition.

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

To date, we have invested a significant amount of our efforts and financial resources in the research and development of tenapanor, which is currently our lead product candidate and only product candidate in clinical trials. Our near-term prospects, including our ability to finance our operations through the receipt of milestone payments and generate revenue from product sales, will depend heavily on AstraZeneca's decision whether or not to continue the development of tenapanor, and should it determine to continue development, on the successful development and AstraZeneca's commercialization of tenapanor, if approved. The clinical and commercial success of tenapanor will depend on a number of factors, including the following:

- whether tenapanor's safety and efficacy profile is satisfactory to the U.S. Food and Drug Administration, or FDA, and foreign regulatory authorities to warrant marketing approval;
- whether FDA or foreign regulatory authorities require additional clinical trials prior to approval to market tenapanor;
- the prevalence and severity of adverse side effects of tenapanor;
- the results of a long-term rat carcinogenicity study required for approval of tenapanor, which will not be known for at least one and half years, and which may be delayed for a significant period of time for reasons outside of the control of AstraZeneca, particularly if AstraZeneca is required to restart or modify the study for any reason;
- whether, as a result of the observation of the absorption of inactive metabolites of tenapanor seen in our radiolabeled human ADME study, the FDA or foreign regulatory authorities require additional nonclinical studies prior to the commencement of Phase 3 activities, which, if required, could delay the development of tenapanor;
- the timely receipt of necessary marketing approvals from the FDA and foreign regulatory authorities;
- the ability of AstraZeneca and us through our co-promotion rights, if we choose to exercise such rights and are not precluded from doing so under the terms of our agreement with AstraZeneca or any subsequent co-promotion agreements, to successfully commercialize tenapanor, if approved for marketing and sale by the FDA or foreign regulatory authorities, including educating physicians and patients about the benefits, administration and use of tenapanor;
- achieving and maintaining compliance with all regulatory requirements applicable to tenapanor;
- acceptance of tenapanor as safe, effective and well-tolerated by patients and the medical community;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of alternative and competing treatments;
- obtaining and sustaining an adequate level of coverage and reimbursement for tenapanor by third-party payors;
- the effectiveness of AstraZeneca's marketing, sales and distribution strategy and operations;
- the ability of AstraZeneca, or any third-party manufacturer it contracts with, to successfully scale up the manufacturing process for tenapanor, which has not yet been demonstrated, and to manufacture supplies of tenapanor and to develop, validate and maintain a commercially viable manufacturing process that is compliant with current good manufacturing practice, or cGMP, requirements;
- enforcing intellectual property rights in and to tenapanor;
- avoiding third-party interference, opposition, derivation or similar proceedings with respect to our patent rights, and avoiding other challenges to our patent rights and patent infringement claims; and
- a continued acceptable safety and tolerability profile of tenapanor following approval.

Most of these factors are beyond our control, including clinical development, the regulatory submission process, manufacturing, marketing and sales efforts of AstraZeneca.

As a first-in-class drug, tenapanor, has not been extensively studied in humans and the nonclinical and clinical data on its effect in the human body is limited to the trials and studies that we and AstraZeneca have completed. As a first-in-class drug, there is a higher likelihood that approval may not be attained as compared to a class of drugs with approved products. We cannot be certain that tenapanor will be successful in preclinical studies, clinical trials or receive regulatory approval. Further, it may not be possible or practicable to demonstrate, or if approved, to market on the basis of, certain of the benefits we believe tenapanor possesses, including the reduction of sodium absorption in patients with CKD, which is unlikely to be an endpoint to be considered for approval in CKD patients. Additionally, the reduction of serum phosphorus is currently an approvable endpoint in CKD-5D patients, but not in the broader CKD patient population in the United States. If the number of patients in the market for tenapanor or the price that the market can bear is not as significant as we estimate, we may not generate significant revenue from sales of tenapanor, if approved. Accordingly, there can be no assurance that tenapanor will ever be successfully commercialized or that we will ever generate revenue from sales of tenapanor. If we and AstraZeneca are not successful in completing the development of, obtaining approval for, and commercializing tenapanor, or are significantly delayed in doing so, our business will be materially harmed.

We are dependent on AstraZeneca for the development, regulatory approval, manufacture and commercialization of our small molecule NHE3 inhibitor program, which includes tenapanor, and if AstraZeneca exercises its right to terminate the agreement, does not elect to continue development of one or more indications for tenapanor, fails to perform as expected, or is unable to obtain the required regulatory approvals for tenapanor, the potential for us to generate future revenue from milestone and royalty payments from tenapanor would be significantly reduced and our business would be materially and adversely harmed.

The potential for us to obtain future development milestone payments and, ultimately, generate revenue from royalties from tenapanor depends entirely on the successful development, regulatory approval, marketing and commercialization of tenapanor by AstraZeneca. In addition to the risks inherent in the development of a drug product candidate, our collaboration partnership with AstraZeneca may not be successful due to a number of important factors, including the following:

prior to the 175th day after the database lock for the Phase 2b clinical trial in hyperphosphatemic ESRD patients, AstraZeneca may terminate the license for any reason with 30-days' prior written notice and thereafter AstraZeneca may terminate the license with 120-days' prior written notice;

- if our agreement with AstraZeneca terminates, we will no longer have rights to receive potential revenue under the agreement with AstraZeneca for future milestones or royalties, in which case we would need to identify alternative means to continue the development, manufacture and commercialization of tenapanor, alone or with others.

AstraZeneca has the unilateral ability to choose not to develop tenapanor for one or more indications for which it has been or is currently being evaluated, including the IBS-C indication and the hyperphosphatemia indication, provided it pursues at least one indication,

AstraZeneca may choose to pursue an indication that is not in our strategic best interest or to delay the pursuit of, or forego an indication, even if clinical data is supportive of further development for such indication;

AstraZeneca's strategic withdrawal from selling gastrointestinal, or GI, products and the differing treatment of the IBS-C indication in our agreement implies that AstraZeneca may choose not to develop the IBS-C indication even though our recently announced Phase 2b clinical data in IBS-C patients indicated that at the 50 mg twice daily dose, the study met its primary efficacy endpoint; AstraZeneca may choose not to develop and commercialize tenapanor in all relevant markets;

AstraZeneca may take considerably more time advancing tenapanor through the clinical and regulatory process than we currently anticipate, which could materially delay the achievement of milestones and, consequently the receipt of milestone payments from AstraZeneca;

AstraZeneca's obligation to use "commercially reasonable efforts" with regard to the development, regulatory approval, manufacture and commercialization of tenapanor under our agreement leaves AstraZeneca with discretion in determining the efforts and resources that it will apply to the development, regulatory approval, manufacture and commercialization of tenapanor;

subject to our right to elect to participate in co-promotion activities in the United States, AstraZeneca controls all aspects of the commercialization of tenapanor;

AstraZeneca may change the focus of its development and commercialization efforts or pursue higher-priority programs and, accordingly, reduce the efforts and resources allocated to tenapanor, which will have the direct effect of reducing our co-promotion activities as our level of co-promotion is limited to a percentage of the overall commercialization activities;

AstraZeneca may fail to develop a commercially viable formulation or manufacturing process for tenapanor, and may fail to manufacture or supply sufficient drug substance of tenapanor for commercial use, if approved, which could result in lost revenue;

AstraZeneca may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
AstraZeneca may sublicense its rights with respect to tenapanor to one or more third parties without our consent;
AstraZeneca may not dedicate the resources that would be necessary to carry tenapanor through clinical development or may not obtain the necessary regulatory approvals; and
if AstraZeneca is acquired during the term of our collaboration partnership, the acquiror may have different strategic priorities that could cause it to terminate our agreement or reduce its commitment to our collaboration partnership.

The timing and amount of any milestone and royalty payments we may receive under our agreement will depend on, among other things, the efforts, allocation of resources, and successful development and commercialization of tenapanor by AstraZeneca under our agreement. There can be no assurance that any of the development and regulatory milestones will be achieved or that we will receive any future milestone payments under the agreement. In addition, in certain circumstances we may believe that we have achieved a particular milestone and AstraZeneca may disagree with our belief. In that case, receipt of that milestone payment may be delayed or may never be received, which may require us to adjust our operating plans.

If AstraZeneca does not perform in the manner we expect or fulfill its responsibilities in a timely manner, or at all, the clinical development, regulatory approval and commercialization efforts related to tenapanor could be delayed or terminated and it could become necessary for us to assume the responsibility at our own expense for the clinical development of tenapanor. In that event, we would likely be required to substantially limit the size and scope of the development and commercialization of tenapanor or seek additional financing to fund further development, or to identify alternative collaboration partners for tenapanor, and our potential to generate future revenue from royalties and milestone payments from tenapanor would be significantly reduced or delayed and our business would be materially and adversely harmed.

Our election to co-fund the first Phase 3 clinical development program for tenapanor must be made in a limited time period following AstraZeneca's determination to proceed to the first Phase 3 clinical development program for tenapanor and, as a result, we may make a substantial capital investment for a product candidate based on limited clinical data.

Under our agreement with AstraZeneca, we may elect to participate in the funding of the first Phase 3 clinical development program for the first indication of tenapanor by investing a co-funding amount of $20.0 million, $30.0 million or $40.0 million to acquire an increase of 1%, 2% or 3%, respectively, in the royalties payable to us by AstraZeneca on net sales of tenapanor. We may exercise this right only for a limited period of 60 days following AstraZeneca's determination to proceed to the first Phase 3 clinical development program for tenapanor for a specific indication. An election to participate in the co-fund will be based, in part, on our analysis as to the likelihood of success of the Phase 3 clinical development program and the potential for regulatory approval to commercialize tenapanor, as well as on an analysis of the capital requirements to advance our other programs. As a result, we will be required to make a substantial capital investment in tenapanor prior to the initiation of the first pivotal clinical trial and if tenapanor is unsuccessful in its pivotal trial or if it never receives regulatory approval, we will not receive any financial return on this capital investment.

We have not yet negotiated our agreement with AstraZeneca specifying all of the terms of our co-promotion right.

Pursuant to our license agreement with AstraZeneca, we have retained a co-promotion right with respect to tenapanor in the United States. While the license agreement includes the material terms of our co-promotion right, we and AstraZeneca mutually agreed to negotiate a separate agreement specifying the detailed activities and responsibilities in respect of the marketing and co-promotion of tenapanor following our election to exercise our co-promotion rights. If we elect to exercise our co-promotion rights, the separate agreement we negotiated with AstraZeneca may place restrictions or additional obligations on us, including financial obligations. Any restrictions or additional obligations

may restrict our co-promotion activities or involve more significant financial obligations than we currently anticipate.

Exercising our co-promotion right under our license agreement with AstraZeneca may restrict our future commercialization and/or co-promotion activities.

Our agreement with AstraZeneca prohibits us from using the same sales force to co-promote tenapanor as we do to promote other products that compete with tenapanor or with any other products that are then being actively promoted by AstraZeneca or its affiliates. If we elect to co-promote tenapanor, we may therefore be required to have a separate sales forces to promote other products we may elect to co-promote under our agreement with Sanofi, or other products we develop and commercialize on our own, should any of such products be competitive with tenapanor or with any other products promoted by AstraZeneca or its affiliates. The exercise of the co-promotion right under our agreement with AstraZeneca, could adversely affect the efficiency and cost of our promotion efforts for our products and, effectively, may prohibit us from exercising our co-promotion rights under our agreement with Sanofi or with respect to other co-promotion rights with future collaboration partners.

If Sanofi does not exercise its option to obtain an exclusive license to develop, manufacture and commercialize our NaP2b inhibitors or if it exercises the option and subsequently terminates any development program under its collaboration partnership with us, any potential milestone payments or revenue from product sales under this collaboration partnership will be significantly reduced or non-existent, and our results of operations and financial condition will be materially and adversely affected.

In February 2014, we entered into a License Option and License Agreement with Sanofi under which we granted Sanofi an exclusive worldwide license to conduct research utilizing our small molecule NaP2b inhibitors, which we refer to as our RDX002 program, solely for the purpose of completing activities under a preclinical development plan. We believe the inhibition of NaP2b, an intestinal phosphate transporter, would provide utility for the treatment of hyperphosphatemia in CKD-5D patients, which is also the lead indication for which we and AstraZeneca are developing tenapanor.

Under the terms of this agreement, Sanofi has the option to obtain an exclusive license to develop, manufacture and commercialize our NaP2b inhibitors. Sanofi may exercise this option at any time following the effective date of the agreement and ending 45 days after the filing of an investigational new drug application, or IND, subject to certain exceptions, and if Sanofi does not file an IND on or before the 40th month anniversary of the completion of the technology transfer phase, the agreement will terminate.

If Sanofi does not exercise its option under its agreement with us, or terminates its rights and obligations with respect to the development program or the entire agreement, then depending on the timing of such event:

- the development of our NaP2b inhibitor program may be terminated or significantly delayed;
- we would bear all of the risks and costs related to the further development and commercialization of product candidates that were previously the subject of the agreement if we decided to continue work under the NaP2b inhibitor program independently;
- we would not be eligible to receive any of the remaining development or regulatory milestone payments or royalties on product sales;
- in order to fund further development and commercialization of the NaP2b program, we may need to raise additional capital if we choose to internally pursue the development of the program, or we may need to seek out and establish alternative collaboration partnerships with third-party collaboration partners for the program, which may not be possible, or we may not be able to do so on terms which are acceptable to us, in which case it may be necessary for us to limit the size or scope of the programs or increase our expenditures and seek additional funding by other means; and
- our cash expenditures could increase significantly if it is necessary for us to hire additional employees and allocate scarce resources to the development and commercialization of the NaP2b program.

Any of these events would have a material adverse effect on our results of operations and financial condition.

In addition, we may be effectively prohibited from co-promoting any product candidates arising from the NaP2b program if we have previously exercised our co-promotion right under our agreement with AstraZeneca. For additional information regarding the effect of exercising our co-promotion right with AstraZeneca, see the risk factor above titled “Exercising our co-promotion right under our license agreement with AstraZeneca may restrict our future commercialization and/or co-promotion activities.”

Clinical drug development involves a lengthy and expensive process with an uncertain outcome, and we may encounter substantial delays in our clinical studies. Furthermore, results of earlier studies and trials may not be predictive of future trial results.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we, or our collaboration partners, must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. For example, in a Phase 2a study evaluating tenapanor in ESRD patients with fluid overload, while pharmacological activity of tenapanor was confirmed, the study failed to meet the primary endpoint of a statistically significant difference between tenapanor and placebo in change in interdialytic weight gain from baseline to week 4. The results of preclinical and clinical studies of our product candidates may not be predictive of the results of later-stage clinical trials. For example, the positive results generated to date in preclinical and clinical studies for tenapanor do not ensure that the ongoing clinical trial, or future clinical trials, will demonstrate similar results. An unacceptable adverse event profile may present challenges for the future development and commercialization of a product candidate for a particular condition despite receipt of positive efficacy data in a clinical study. For example, in a Phase 2b study evaluating tenapanor for the treatment of hyperphosphatemia in CKD-5D patients, or ESRD patients on dialysis, we observed that the study met its primary endpoint by demonstrating a statistically significant dose-related decrease in serum phosphate levels for tenapanor-treated patients compared to patients receiving placebo, while also observing that the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses were higher than expected based upon previous clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy despite having progressed through preclinical studies and initial clinical trials. A number of companies in the pharmaceutical, biopharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials for similar indications that we are pursuing due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier studies, and we cannot be certain that we will not face similar setbacks. Even if our clinical trials are completed, the results may not be sufficient to obtain regulatory approval for our product candidates.

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

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

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

We could also encounter delays if a clinical trial is suspended or terminated by us, our collaboration partner for the product candidate, by the IRBs of the institutions in which such trials are being conducted, by an independent data safety monitoring board, or DSMB, for such trial or by the FDA or other regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

Further, conducting clinical trials in foreign countries presents additional risks that may delay completion of clinical trials. These risks include the failure of physicians or enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes and political and economic risks relevant to such foreign countries. In addition, the FDA may determine that the clinical trial results obtained in foreign subjects do not represent the safety and efficacy of a product candidate when administered in U.S. patients and are thus not supportive of an NDA approval in the United States.

If there are delays in the completion of, or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates may be harmed, and our ability to generate revenue from product sales from any of these product candidates will be delayed. In addition, any delays in completing the clinical trials will increase costs, slow down our product candidate development and approval process and jeopardize the ability to commence product sales and generate revenue from product sales. Any of these occurrences may significantly harm our business, financial condition and prospects. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Our unlicensed product candidates are at an early stage of development and we may not be successful in our efforts to develop these products or expand our pipeline of product candidates.

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

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

the research methodology used and our drug discovery and design platform may not be successful in identifying potential product candidates;
competitors may develop alternatives that render our product candidates obsolete or less attractive;
product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
the market for a product candidate may change during our program so that the continued development of that product candidate is no longer reasonable;
a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective, well-tolerated or otherwise does not meet applicable regulatory criteria;
a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
a product candidate may not be accepted as safe, effective and well-tolerated by patients, the medical community or third-party payors, if applicable.

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

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

We have developed a proprietary drug discovery and design platform to enable the identification, screening, testing, design and development of new product candidates, and we recently enhanced this platform with the addition of APECCS. We plan to utilize APECCS to identify new and potentially novel targets in the GI tract. We have also identified over 3,800 human gastrointestinal tract-specific RNA transcripts and proteins on the inner surface of the gut, many of which we believe may be drug targets. However, there can be no assurance that APECCS will be able to identify new targets in the GI tract or that any of these potential targets or other aspects of our proprietary drug discovery and design platform will yield product candidates that could enter clinical development and, ultimately, be commercially valuable.

Although we expect to continue to enhance the capabilities of our APECCS system by advancing the cell culture and screening process and/or acquiring new technologies to broaden the scope of APECCS, we may not be successful in any of our enhancement and development efforts. For example, we may not be able to enter into agreements on suitable terms to obtain technologies required to develop certain capabilities of APECCS. In addition, we may not be successful in developing the conditions necessary to grow multiple segments of intestine or from multiple species, or otherwise develop assays or cell cultures necessary to expand these capabilities. If our enhancement or development efforts are unsuccessful, we may not be able to advance our drug discovery capabilities as quickly as we expect or identify as many potential drugable targets as we desire.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we have focused on research programs and product candidates that relate to discovery and development of non-systemic drugs that work in the GI tract. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration partnerships, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

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

We do not have the ability to independently conduct clinical trials and, in some cases, preclinical or nonclinical studies. We rely on medical institutions, clinical investigators, contract laboratories, collaboration partners and other third parties, such as CROs, to conduct clinical trials on our product candidates. The third parties with whom we contract for execution of the clinical trials we are conducting with AstraZeneca, as well as those third parties with whom we will contract for execution of clinical trials for our internal programs, play a significant role in the conduct of these trials and the subsequent collection and analysis of data. However, these third parties are not our employees, and except for contractual duties and obligations, we control only certain aspects of their activities and have limited ability to control the amount or timing of resources that they devote to our programs. Although we rely, and will continue to rely, on these third parties to conduct some of our preclinical and nonclinical studies and all of our clinical trials, we remain responsible for ensuring that each of our studies and clinical trials is conducted in accordance with

the applicable protocol, legal, regulatory and scientific standards and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with current good laboratory practices, or GLPs, for preclinical and nonclinical studies, and good clinical practices, or GCPs, for clinical studies. GLPs and GCPs are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our products in preclinical and clinical development, respectively. Regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our third party contractors fail to comply with applicable regulatory requirements, including GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the European Medicines Agency, or EMA, or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. There can be no assurance that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practices or cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

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

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

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

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

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

Undesirable side effects caused by our product candidates could cause us, our collaboration partners, or regulatory authorities to interrupt, delay or halt clinical trials, result in the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authorities or limit the commercial profile of an approved label. To date, patients treated with tenapanor have experienced drug-related side effects including diarrhea, nausea, flatulence, abdominal discomfort, abdominal pain, abdominal distention and changes in electrolytes, and in the Phase 2b evaluating tenapanor for the treatment of hyperphosphatemia in CKD-5D patients, we observed that the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses was higher than expected based upon the results of previous clinical trials. In the event that trials conducted by us or AstraZeneca with tenapanor, or trials we conduct with our other product candidates, reveal an unacceptable severity and prevalence of these or other side effects, such trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order AstraZeneca or us to cease further development of or deny approval of tenapanor, or any such other product candidate, for any or all targeted indications. Additionally, despite a positive efficacy profile, the prevalence and/or severity of these or other side effects could cause us or AstraZeneca to cease further development of a product candidate for a particular indication, or entirely. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

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

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or our collaboration partners, may be required to recall the product;
- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof, including the imposition of a Risk Evaluation and Mitigation Strategies, or REMS, plan that may require creation of a Medication Guide outlining the risks of such side effects for distribution to patients, as well as elements to assure safe use of the product, such as a patient registry and training and certification of prescribers;
- we, or our collaboration partners, may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer

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

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

The biotechnology and pharmaceutical industries are highly competitive, and we face significant competition from companies in the biotechnology, pharmaceutical and other related markets that are researching and marketing products designed to address diseases that we are currently developing products to treat. If approved for marketing by the FDA or other regulatory agencies, tenapanor, or our other product candidates, would compete against existing treatments. For example, tenapanor will, if approved, compete directly with phosphate binders for the treatment of hyperphosphatemia in patients with CKD-5D, including sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela), which were launched by Genzyme. Synthon announced the successful completion of a Phase 3 multicenter, randomized, double-blind, multiple-dose, crossover trial in Europe to compare safety and demonstrate equivalence of serum phosphate control of Synthon sevelamer carbonate tablets to Renvela tablets in chronic kidney disease patients on hemodialysis in April 2014. Currently, several pharmaceutical companies are distributing Synthon manufactured sevelamer carbonate tablets in multiple European countries including, but not limited to, the UK, Spain, Sweden and Denmark. In addition to the currently marketed phosphate binders, Keryx has received FDA approval for ferric citrate (Auryxia), an iron-based binder, that is also approved in Japan and we are aware of fermagate (Alpharen), an iron-based binder in Phase 2 being developed by Opko Health.

While there are no treatments for CKD that have been proven to reverse the disease we are aware of certain investigational drugs that were being developed for delaying kidney decline as measured by estimated glomerular filtration rate, or eGFR. Among other products, Concert Pharmaceuticals is developing CTP-499 which showed protective effects on kidney function at 48 weeks in a Phase 2 clinical trial in patients with CKD and type 2 diabetes.

Numerous treatments exist for constipation and the constipation component of IBS-C, many of which are over-the-counter. These include psyllium husk (such as Metamucil), methylcellulose (such as Citrucel), calcium polycarbophil (such as FiberCon), lactulose (such as Cephulac), polyethylene glycol (such as MiraLax), sennosides (such as Exlax), bisacodyl (such as Ducolax), docusate sodium (such as Colace), magnesium hydroxide (such as Milk

of Magnesia), saline enemas (such as Fleet) and sorbitol. These agents are generally inexpensive and work well to relieve temporary constipation. We are also aware of two prescription drugs currently on the U.S. market that are approved to treat IBS-C, Linzess (linaclotide), which was developed by Ironwood Pharmaceuticals and was approved in 2012 and 2013 for IBS-C and chronic constipation in both the United States and in Europe, and Amitiza (lubiprostone), which was first approved in the United States in 2006 and is currently marketed by Sucampo and Takeda for treatment of chronic idiopathic constipation, or CIC, IBS-C and opioid induced constipation, or OIC.

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

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

We currently have no sales organization. If we are unable to establish sales capabilities on our own or through third parties, we may not be able to co-promote tenapanor, if approved, or commercialize or co-promote any of our other product candidates.

We currently do not have a sales organization. In order to co-promote tenapanor or commercialize or co-promote any of our other product candidates, we must build our marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If one or more of our product candidates receives regulatory approval, we expect to establish a specialty sales organization with technical expertise and supporting distribution capabilities to co-promote and/or commercialize our product candidates, which will be expensive and time consuming. As a company, we have no prior experience in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain, and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, comply with regulatory requirements applicable to the marketing and sale of drug products and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products.

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

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

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

dependent on our contract manufacturing partners for compliance with the regulatory requirements, known as cGMPs, for manufacture of both active drug substances and finished drug products. Under our agreement with AstraZeneca, the manufacturing of tenapanor is the responsibility of AstraZeneca. We are entirely dependent on AstraZeneca for all aspects of the manufacturing and validation process, as well as providing all commercial supply of tenapanor. For additional information regarding the risks of our dependence on AstraZeneca, see the risk factors above titled “We are substantially dependent on the success of our lead product candidate, tenapanor, which may not be successful in nonclinical studies or clinical trials, receive regulatory approval or be successfully commercialized” and “We are dependent on AstraZeneca for the development, regulatory approval, manufacture and commercialization of our small molecule NHE3 inhibitor program, which includes tenapanor, and if AstraZeneca fails to perform as expected, or is unable to obtain the required regulatory approvals for tenapanor, the potential for us to generate future revenue from milestone and royalty payments from tenapanor would be significantly reduced and our business would be materially and adversely harmed.”

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

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

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

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

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

In July 2010, CMS released its final rule to implement a bundled prospective payment system for the treatment of ESRD patients as required by the Medicare Improvements for Patients and Providers Act, or MIPPA. The bundled payment covers a bundle of items and services routinely required for dialysis treatments furnished to Medicare beneficiaries in Medicare-certified ESRD facilities or at their home, including the cost of certain routine drugs. The final rule delayed the inclusion of oral medications without intravenous equivalents in the bundled payment until

January 1, 2014 and in April 2014, President Obama signed the Protecting Access to Medicare Act of 2014, which further extends this implementation date to January 1, 2024. As a result of the recent legislation, beginning in 2024, ESRD-related drugs will be included in the bundle and separate Medicare reimbursement will no longer be available for such drugs, as it is today under Medicare Part D. While it is too early to project the full impact bundling may have on the industry, the impact could potentially cause dramatic price reductions for tenapanor, if approved. We and AstraZeneca may be unable to sell tenapanor, if approved, to dialysis providers on a profitable basis if third-party payors reduce their current levels of payment, or if our costs of production increase faster than increases in reimbursement levels.

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

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

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

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

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

Our inability to obtain and maintain sufficient product liability insurance at an acceptable cost and scope of coverage to protect against potential product liability claims could prevent or inhibit the commercialization of any products we develop. We currently carry product liability insurance covering use in our clinical trials in the amount of $10.0 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions and deductibles, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not

covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses.

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

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

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

As of December 31, 2014, we had 34 full-time employees. We will need to continue to expand our managerial, operational, finance and other resources in order to manage our operations, preclinical and clinical trials, research and development activities, regulatory filings, manufacturing and supply activities, and any marketing and commercialization activities, including co-promotion activities. Our management, personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively execute our growth strategy requires that we:

- expand our general and administrative functions;
- establish and build a marketing and commercial organization;
- identify, recruit, retain, incentivize and integrate additional employees;
- manage our internal development efforts effectively while carrying out our contractual obligations to third parties; and
- continue to improve our operational, legal, financial and management controls, reporting systems and procedures.

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

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

We incur significant legal, accounting and other expenses as a public company, including costs resulting from public company reporting obligations under the Securities Exchange Act of 1934, as amended, or the Exchange Act, and regulations regarding corporate governance practices. The listing requirements of The NASDAQ Global Market require that we satisfy certain corporate governance requirements relating to director independence, distributing annual and interim reports, stockholder meetings, approvals and voting, soliciting proxies, conflicts of interest and a

code of conduct. Our management and other personnel will need to devote a substantial amount of time to ensure that we comply with all of these requirements. Moreover, the reporting requirements, rules and regulations will increase our legal and financial compliance costs and will make some activities more time consuming and costly. Any changes we make to comply with these obligations may not be sufficient to allow us to satisfy our obligations as a public company on a timely basis, or at all. These reporting requirements, rules and regulations, coupled with the increase in potential litigation exposure associated with being a public company, could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or board committees or to serve as executive officers, or to obtain certain types of insurance, including directors' and officers' insurance, on acceptable terms.

In addition, we are in the process of implementing enterprise resource planning, or ERP, system for our company. An ERP system is intended to combine and streamline the management of our financial, accounting, human resources, sales and marketing and other functions, enabling us to manage operations and track performance more effectively. However, an ERP system will require us to complete many processes and procedures for the effective use of the system or to run our business using the system, which may result in substantial costs. Additionally, during the conversion process, we may be limited in our ability to convert any business that we acquire to the ERP. Any disruptions or difficulties in implementing or using an ERP system could adversely affect our controls and harm our business, including our ability to forecast or make sales and collect our receivables. Moreover, such disruption or difficulties could result in unanticipated costs and diversion of management attention.

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

To date, we have not conducted any other review of our internal control for the purpose of providing the reports required by Section 404 and the related SEC rules. During the course of our review and testing, we may identify deficiencies and be unable to remediate them before we must provide the required reports. Furthermore, if we have a material weakness in our internal controls over financial reporting, we may not detect errors on a timely basis and our financial statements may be materially misstated. We or our independent registered public accounting firm may not be able to conclude on an ongoing basis that we have effective internal control over financial reporting, which could harm our operating results, cause investors to lose confidence in our reported financial information and cause the trading price of our stock to fall. In addition, as a public company we are required to file accurate and timely quarterly and annual reports with the SEC under the Exchange Act. Any failure to report our financial results on an accurate and timely basis could result in sanctions, lawsuits, delisting of our shares from The NASDAQ Global Market or other adverse consequences that would materially harm our business.

We may form additional collaboration partnerships in the future with respect to our independent programs, and we may not realize the benefits of such collaborations.

We may form collaboration partnerships, create joint ventures or enter into licensing arrangements with third parties with respect to our independent programs that we believe will complement or augment our existing business. We have historically engaged, and intend to continue to engage, in partnering discussions with a range of pharmaceutical and biotechnology companies and could enter into new collaboration partnerships at any time. We face significant competition in seeking appropriate collaboration partners, and the negotiation process to secure appropriate terms is time-consuming and complex. Any delays in identifying suitable collaboration partners and entering into agreements

to develop our product candidates could also delay the commercialization of our product candidates, which may reduce their competitiveness even if they reach the market. Moreover, we may not be successful in our efforts to establish such a collaboration partnership for any future product candidates and programs on terms that are acceptable to us, or at all. This may be because our product candidates and programs may be deemed to be at too early of a stage of development for collaborative effort, our research and development pipeline may be viewed as insufficient, and/or third parties may not view our product candidates and programs as having sufficient potential for commercialization, including the likelihood of an adequate safety and efficacy profile. Even if we are successful in entering into a collaboration partnership or license arrangement, there is no guarantee that the collaboration partnership will be successful, or that any future collaboration partner will commit sufficient resources to the development, regulatory approval, and commercialization effort for such products, or that such alliances will result in us achieving revenues that justify such transactions.

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

We intend to consider strategic transactions, such as acquisitions of companies, asset purchases, and or in-licensing of products, product candidates or technologies. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, collaboration partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near- and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including:

- up-front, milestone and royalty payments, equity investments and financial support of new research and development candidates including increase of personnel, all of which may be substantial;
- exposure to unknown liabilities;
- disruption of our business and diversion of our management's time and attention in order to develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- higher-than-expected acquisition and integration costs;
- write-downs of assets or goodwill or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain key employees of any acquired businesses.

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

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

We may decide to seek marketing approval for certain of our product candidates outside the United States or otherwise engage in business outside the United States, including entering into contractual agreements with third-parties. We expect that we will be subject to additional risks related to entering into these international business markets and relationships, including:

different regulatory requirements for drug approvals in foreign countries;
differing United States and foreign drug import and export rules;
reduced protection for intellectual property rights in foreign countries;
unexpected changes in tariffs, trade barriers and regulatory requirements;
different reimbursement systems, and different competitive drugs;
economic weakness, including inflation, or political instability in particular foreign economies and markets;
compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
foreign taxes, including withholding of payroll taxes;
foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
workforce uncertainty in countries where labor unrest is more common than in the United States;
production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
potential liability resulting from development work conducted by these distributors; and
business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters.

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

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

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

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such system failure,

accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data from completed or ongoing clinical trials for any of our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

We may be adversely affected by the current global economic environment.

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

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

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

Our corporate headquarters and other facilities are located in the San Francisco Bay Area, which in the past has experienced severe earthquakes. We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects.

If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our enterprise financial systems or manufacturing resource planning and enterprise quality systems, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Risks Related to Government Regulation

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

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

warning letters;
civil and criminal penalties;
injunctions;
withdrawal of regulatory approval of products;
product seizure or detention;
product recalls;
total or partial suspension of production; and
refusal to approve pending NDAs or supplements to approved NDAs.

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

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable, typically takes many years following the commencement of clinical studies, and depends upon numerous factors. The FDA and comparable foreign authorities have substantial discretion in the approval process and we may encounter matters with the FDA or such comparable authorities that requires us to expend additional time and resources and delay or prevent the approval of our product candidates. For example, the FDA may require us to conduct additional studies or trials for drug product either prior to or post-approval, such as additional drug-drug interaction studies or safety or efficacy studies or trials, or it may object to elements of our clinical development program such as the number of subjects in our current clinical trials from the United States. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate’s clinical development and may vary among jurisdictions, which may cause delays in the approval or result in a decision not to approve an application for regulatory approval. Despite the time and expense exerted, failure can occur at any stage. Applications for our product candidates could fail to receive regulatory approval for many reasons, including but not limited to the following:

the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our, or our collaboration partners', clinical studies;
the population studied in the clinical program may not be sufficiently broad or representative to assure safety in the full population for which approval is sought;
the FDA or comparable foreign regulatory authorities may disagree with the interpretation of data from preclinical studies or clinical studies;
the data collected from clinical studies of our product candidates may not be sufficient to support the submission of a NDA or other submission or to obtain regulatory approval in the United States or elsewhere;
we or our collaboration partners may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;

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

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

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

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

Even if we receive regulatory approval for a product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, any product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

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

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

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

warning letters, fines or holds on clinical trials;

restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market or voluntary or mandatory product recalls;

injunctions or the imposition of civil or criminal penalties;
suspension or revocation of existing regulatory approvals;
suspension of any of our ongoing clinical trials;
refusal to approve pending applications or supplements to approved applications submitted by us;
restrictions on our or our contract manufacturers' operations; or
product seizure or detention, or refusal to permit the import or export of products.

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

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

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

All entities involved in the preparation of product candidates for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates and AstraZeneca, and those contract manufacturers it may rely upon with respect to the manufacture of tenapanor, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We, our collaboration partners, or our contract manufacturers must supply all necessary documentation in support of an NDA or comparable regulatory filing on a timely basis and must adhere to cGMP regulations enforced by the FDA and other regulatory agencies through their facilities inspection programs. Some of our contract manufacturers have never produced a commercially approved pharmaceutical product and therefore have not obtained the requisite regulatory authority approvals to do so. The facilities and quality systems of some or all of our collaboration partners and third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. Although we oversee the contract manufacturers, we cannot control the manufacturing process of, and are completely dependent on, other than with respect to tenapanor, our contract manufacturing partners for compliance with the regulatory requirements. AstraZeneca is fully responsible for the manufacture of tenapanor, and we are entirely dependent upon AstraZeneca for compliance with the regulatory requirements. If these facilities do not pass a pre-approval plant inspection, regulatory approval of the products may not be granted or may be substantially delayed until any violations are corrected to the satisfaction of the regulatory authority, if ever. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel.

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

materially harm our business.

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

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

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

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

The regulations relating to the promotion of products for unapproved uses are complex and subject to substantial interpretation by the FDA and other government agencies. If tenapanor, or our other product candidates, receives marketing approval, we and our collaborating partners will be restricted from marketing the product outside of its approved labeling, also referred to as off-label promotion. However, physicians may nevertheless prescribe an approved product to their patients in a manner that is inconsistent with the approved label, which is an off-label use. We intend to implement compliance and training programs designed to ensure that our sales and marketing practices comply with applicable regulations regarding off-label promotion. Notwithstanding these programs, the FDA or other government agencies may allege or find that our practices constitute prohibited promotion of our product candidates for unapproved uses. We also cannot be sure that our employees will comply with company policies and applicable regulations regarding the promotion of products for unapproved uses.

Over the past several years, a significant number of pharmaceutical and biotechnology companies have been the target of inquiries and investigations by various federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U.S. Attorneys' Offices, the Office of Inspector General of the Department of Health and Human Services, the FDA, the Federal Trade Commission and various state Attorneys General offices. These investigations have alleged violations of various federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, the False Claims Act, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. Many of these investigations originate as "qui tam" actions under the False Claims Act. Under the False Claims Act, any individual can bring a claim on behalf of the government alleging that a person or entity has presented a false claim, or caused a false claim to be submitted, to the government for payment. The person bringing a qui tam suit is entitled to a share of any recovery or settlement. Qui tam suits, also commonly referred to as "whistleblower suits," are often brought by current or former employees. In a qui tam suit, the government must decide whether to intervene and prosecute the case. If it declines, the individual may pursue the case alone.

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

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

Some participants in clinical studies of tenapanor have reported adverse effects after being treated with tenapanor, including diarrhea, nausea, flatulence, abdominal discomfort, abdominal pain, abdominal distention and changes in

electrolytes and in the Phase 2b evaluating tenapanor for the treatment of hyperphosphatemia in CKD-5D patients, we observed that the rate of diarrhea and the discontinuation rate due to diarrhea at the highest doses was higher than expected based upon the results of previous clinical trials. If we are successful in commercializing any products, FDA and foreign regulatory agency regulations require that we report certain information about adverse medical events if those products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We may fail to report adverse events we become aware of within the prescribed timeframe. We may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. If we fail to comply with our reporting obligations, the FDA or a foreign regulatory agency could take action, including criminal prosecution, the imposition of civil monetary penalties, seizure of our products or delay in approval or clearance of future products.

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

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, collaboration partners, consultants and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate: (1) FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA; (2) manufacturing standards; (3) federal and state healthcare fraud and abuse laws and regulations; or (4) laws that require the reporting of true and accurate financial information and data. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. These activities also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

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

In order to market any product in the EEA (which is composed of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), and many other foreign jurisdictions, separate regulatory approvals are required. In the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. Before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

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

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

Although we do not currently have any products on the market, once we begin commercializing our products, we and our collaboration partners may be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. The laws that may affect our ability to operate as a commercial organization include:

the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;
federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;
the federal physician sunshine requirements under the Affordable Care Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the CMS information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;
state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers;
state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources;
state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts; and
European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Further, the Affordable Care Act, among other things, amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims statutes. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal

and state healthcare programs and imprisonment, any of which could adversely affect our ability to market our products and adversely impact our financial results.

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

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

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

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

In addition, the full impact of recent healthcare reform and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model. In the United States, the Affordable Care Act was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The Affordable Care Act, among other things, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D.

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

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

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Risks Related to Intellectual Property

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

There have been many lawsuits and other proceedings asserting infringement or misappropriation of patents and other intellectual property rights in the pharmaceutical and biotechnology industries. There can be no assurances that we will not be subject to claims alleging that the manufacture, use or sale of tenapanor or any other product candidates nor that any activities conducted by us, infringes existing or future third-party patents, or that such claims, if any, will not be successful. Because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of tenapanor or other product candidates or by the operation of our business. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our own patent portfolio may thus have no deterrent effect. We may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of tenapanor or our other product candidates.

We may be subject to third-party patent infringement claims in the future against us or our collaboration partners that would cause us to incur substantial expenses and, if successful against us, could cause us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing a third party's patents. We may be required to indemnify future collaboration partners against such claims. We are not aware of any threatened or pending claims related to these matters, but in the future litigation may be necessary to defend against such claims. If a patent infringement suit were brought against us or our collaboration partners, we or they could be forced to stop or delay research, development, manufacturing or sales of the product or product candidate that is the subject of the suit. As a result of patent infringement claims, or in order to avoid potential claims, we or our collaboration partners may choose to seek, or be required to seek, a license from the third party and would most likely be required to pay license fees or royalties or both. These licenses may not be available on acceptable terms, or at all. Even if we or our collaboration partners were able to obtain a license, the rights may be nonexclusive, which would give our competitors access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or forced to redesign it, or to cease some aspect of our business operations if, as a result of actual or threatened patent infringement claims, we or our collaboration partners are unable to enter into licenses on acceptable terms. Even if we are successful in defending against such claims, such litigation can be expensive and time consuming to litigate and would divert management's attention from our core business. Any of these events could harm our business significantly.

In addition to infringement claims against us, if third parties prepare and file patent applications in the United States that also claim technology similar or identical to ours, we may have to participate in interference or derivation proceedings in the United States Patent and Trademark Office, or the USPTO, to determine which party is entitled to a patent on the disputed invention. We may also become involved in similar opposition proceedings in the European Patent Office or similar offices in other jurisdictions regarding our intellectual property rights with respect to our products and technology. Since patent applications are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates.

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

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates, our drug discovery and development platform and our

development programs. Any disclosure to or misappropriation by third parties of our confidential or proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position in our market.

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

Even where laws provide protection, costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and the outcome of such litigation would be uncertain. If we or one of our collaboration partners were to initiate legal proceedings against a third party to enforce a patent covering the product candidate, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability against our intellectual property related to a product candidate, we would lose at least part, and perhaps all, of the patent protection on such product candidate. Such a loss of patent protection would have a material adverse impact on our business. Moreover, our competitors could counterclaim that we infringe their intellectual property, and some of our competitors have substantially greater intellectual property portfolios than we do.

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

successful in prohibiting the continued breach of such agreements, our business could be negatively impacted. We cannot guarantee that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.