

Akebia Therapeutics, Inc.
Form 10-K
March 26, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT
OF 1934
Commission File Number 001-36352

AKEBIA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	20-8756903 (I.R.S. Employer Identification No.)
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245 First Street, Cambridge, MA (Address of principal executive offices)	02142 (Zip Code)
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Registrant's telephone number, including area code: (617) 871-2098

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

Title of each class	Name of each exchange on which registered
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Common Stock, par value \$0.00001 per share	The Nasdaq Global Market
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Securities registered pursuant to Section 12(g) of the Act: None

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). YES NO

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
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Non-accelerated filer	Smaller reporting company
	Emerging growth company

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the closing price of the registrant's Common Stock on The Nasdaq Global Market on June 30, 2018, was \$534,415,547.

The number of shares of registrant's Common Stock outstanding as of March 15, 2019 was 117,122,262.

DOCUMENTS INCORPORATED BY REFERENCE

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Portions of the Proxy Statement for the registrant's 2019 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

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NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that are being made pursuant to the provisions of the U.S. Private Securities Litigation Reform Act of 1995 with the intention of obtaining the benefits of the “safe harbor” provisions of that Act. These forward-looking statements may be accompanied by words such as “anticipate,” “believe,” “build,” “can,” “contemplate,” “continue,” “could,” “should,” “designed,” “estimate,” “project,” “expect,” “forecast,” “intend,” “likely,” “may,” “plan,” “possible,” “potential,” “predict,” “strategy,” “seek,” “target,” “will,” “would,” and other words of similar meaning. These forward-looking statements include, but are not limited to, statements about:

- our expectations with respect to (i) the anticipated financial impact and potential benefits to us related to our merger with Keryx Biopharmaceuticals, Inc., or Keryx, that was completed on December 12, 2018, or the Merger, (ii) integration of the businesses subsequent to the Merger, and (iii) other matters related to the Merger;
- the potential therapeutic applications of the hypoxia inducible factor, or HIF, pathway;
- our pipeline, including its potential, and our research activities;
- the potential therapeutic benefits, safety profile, and effectiveness of our product candidates, including the potential for vadadustat to set a new standard of care in the treatment of anemia due to chronic kidney disease;
- the potential indications and market potential and acceptance of our product and product candidates, including our estimates regarding the potential market opportunity for Auryxia, vadadustat or any other product candidates and the size of eligible patient populations;
- our competitive position, including estimates, developments and projections relating to our competitors and their products and product candidates, and our industry;
- our expectations, projections and estimates regarding our costs, expenses, revenues, capital requirements, need for additional capital, financing our future cash needs, capital resources, cash flows, financial performance, profitability, tax obligations, liquidity, growth, contractual obligations, the period of time our cash resources and collaboration funding will fund our current operating plan, internal control over financial reporting, and disclosure controls and procedures;
- the timing of the availability and disclosure of clinical trial data and results;
- our and our collaborators’ strategy, plans and expectations with respect to the development, manufacturing, commercialization, launch, marketing and sale of our product candidates, and the associated timing thereof;
- the designs of our studies, and the type of information and data expected from our studies and the expected benefits thereof;
- the timing of or likelihood of regulatory filings and approvals, including labeling or other restrictions;
- our ability to maintain any marketing authorizations we currently hold or will obtain, including our marketing authorizations for Auryxia and our ability to complete post-marketing requirements with respect thereto;
- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms and processes on a timely basis, or at all, with third-party payors for Auryxia or any other product candidate that may be approved;
- the targeted timing of enrollment of our clinical trials;
- the timing of initiation of our clinical trials and plans to conduct preclinical and clinical studies in the future;
- the timing and amounts of payments from or to our collaborators and licensees, and the anticipated arrangements and benefits under our collaboration and license agreements, including with respect to milestones and royalties;
- our intellectual property position, including obtaining and maintaining patents; and the timing, outcome and impact of administrative, regulatory, legal and other proceedings relating to our patents and other proprietary and intellectual property rights;
- expected reliance on third parties, including with respect to the development, manufacturing, supply and commercialization of our product and product candidates;
- accounting standards and estimates, their impact, and their expected timing of completion;

- estimated periods of performance of key contracts;
- our facilities, lease commitments, and future availability of facilities;
- cybersecurity;
- insurance coverage;
- our employees, including our management team, employee compensation, employee relations, and our ability to attract and retain high quality employees;
- the implementation of our business model, current operating plan, and strategic plans for our business, product candidates and technology, and business development opportunities including potential collaborations, alliances, mergers, acquisitions or licensing of assets;
- the timing, outcome and impact of current and any future legal proceedings.

These forward-looking statements involve risks and uncertainties, including those that are described in Part I, Item 1A. Risk Factors included in this Annual Report and elsewhere in this Annual Report on Form 10-K, that could cause our actual results, financial condition, performance or achievements to be materially different from those indicated in these forward-looking statements. Given these risks and uncertainties, you should not place undue reliance on these forward-looking statements. Forward-looking statements speak only as of the date of this Annual Report on Form 10-K. Except as required by law, we assume no obligation to publicly update or revise these forward-looking statements for any reason. Unless otherwise stated, our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

This Annual Report on Form 10-K also contains estimates and other information concerning our industry and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Unless otherwise expressly stated, we obtained this industry, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

In this Annual Report on Form 10-K, unless otherwise stated or the context otherwise requires, references to “Akebia,” “we,” “us,” “our,” “the Company,” and similar references refer to Akebia Therapeutics, Inc. and, where appropriate, its subsidiaries, including Keryx. The trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners. All website addresses given in this Annual Report on Form 10-K are for information only and are not intended to be an active link or to incorporate any website information into this document.

PART I

Item 1. Business

Overview

We are a biopharmaceutical company focused on the development and commercialization of therapeutics for patients with kidney disease. On December 12, 2018, we completed a merger, or the Merger, with Keryx Biopharmaceuticals, Inc., or Keryx, combining a nephrology-focused commercial organization with our robust development organization. Following the Merger, Keryx is our wholly owned subsidiary, and we are integrating our business and Keryx's business with the goal of positioning Akebia to realize the potential growth opportunities and synergies from the Merger.

We now have a commercial product and a late-stage product candidate:

• **Auryxia[®]** (ferric citrate) is approved and marketed in the United States for two indications: (1) the control of serum phosphorus levels in adult patients with chronic kidney disease, or CKD, on dialysis, or DD-CKD, or the Hyperphosphatemia Indication, and (2) the treatment of iron deficiency anemia, or IDA, in adult patients with CKD not on dialysis, or NDD-CKD, or the IDA Indication. Ferric citrate is also approved and marketed in Japan as an oral treatment for the improvement of hyperphosphatemia in patients with CKD, including DD-CKD and NDD-CKD, under the trade name Riona[®] (ferric citrate hydrate) and approved in the European Union, or the EU, for the control of hyperphosphatemia in adult patients with CKD under the trade name Fexeric[®] (ferric citrate).

• **Vadadustat** is an investigational, oral hypoxia-inducible factor prolyl hydroxylase inhibitor, or HIF-PHI, in global Phase 3 development for two indications: (1) anemia due to CKD in adult patients with DD-CKD, and (2) anemia due to CKD in adult patients with NDD-CKD. We believe vadadustat has the potential to set a new oral standard of care for patients with anemia due to CKD, subject to regulatory approval. Vadadustat's proposed mechanism of action is designed to mimic the physiologic effect of altitude on oxygen availability. At higher altitudes, the body responds to lower oxygen availability with increased production of hypoxia-inducible factor, or HIF, which coordinates the interdependent processes of iron mobilization and stimulates endogenous production of erythropoietin, or EPO, to increase red blood cell, or RBC, production and, ultimately, improve oxygen delivery.

We market Auryxia in the United States with our well-established, nephrology-focused commercial organization. Our Japanese sublicensee, Japan Tobacco, Inc., or JT, and its subsidiary, Torii Pharmaceutical Co., Ltd., or Torii, commercialize Riona in Japan. Fexeric is not currently marketed in the EU.

We plan to commercialize vadadustat, subject to U.S. Food and Drug Administration, or FDA, approval, in the United States with our commercial organization, while also leveraging our collaboration with Otsuka Pharmaceutical Co. Ltd., or Otsuka, and its U.S. commercial organization. We also granted Otsuka exclusive rights to commercialize vadadustat in Europe, China and certain other markets, subject to marketing approvals. In Japan and certain other countries in Asia, we granted Mitsubishi Tanabe Pharma Corporation, or MTPC, exclusive rights to commercialize vadadustat, subject to marketing approvals. In addition, we granted Vifor (International) Ltd., or Vifor Pharma, an exclusive license to sell vadadustat solely to Fresenius Kidney Care Group LLC, or FKC, which manages approximately 40% of the dialysis patients in the United States, at its U.S. dialysis clinics, subject to FDA approval of vadadustat, vadadustat's reimbursement under a bundled reimbursement model, and a milestone payment by Vifor Pharma.

Strategy

Our goal is to become a leading biopharmaceutical company focused on the treatment of patients with kidney disease, through the discovery, development and commercialization of innovative therapeutics. The key elements of our strategy are as follows:

• Maximize commercial opportunity for Auryxia. We aim to gain market share in Auryxia's Hyperphosphatemia Indication by leveraging Auryxia's product profile and opportunities for adoption following the release of updated clinical guidelines. We aim to gain market share and grow the market for Auryxia's IDA Indication by offering an alternative to the existing treatment approach.

• Complete global development and commercialization of our late-stage product candidate, vadadustat. We believe vadadustat has the potential to address limitations of injectable erythropoiesis-stimulating agents, or ESAs, and set a new standard of care for the treatment of anemia due to CKD, subject to regulatory approval. We are conducting a global Phase 3 clinical development program for vadadustat, and our collaboration partner, MTPC, is conducting a Phase 3 clinical development program for vadadustat in Japan. We believe we are well positioned to commercialize vadadustat in the United States in partnership with Otsuka and through our agreement with Vifor Pharma, subject to FDA approval. We plan to support Otsuka's and MTPC's commercialization of vadadustat in Europe, China and certain other markets, subject to regulatory approvals. We retained full commercial rights to vadadustat in Latin America, allowing us maximum flexibility in the region.

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•Leverage portfolio synergies between our product, Auryxia, and our product candidate, vadadustat, in CKD. We believe there is an opportunity to maximize the U.S. commercial performance of Auryxia and vadadustat, subject to FDA approval and launch, by leveraging our nephrology-focused commercial organization for Auryxia and our relationships and expertise in the renal space. We also plan to explore co-development potential for Auryxia and vadadustat.

•Expand our pipeline and portfolio of renal therapeutics to advance care for patients with kidney disease. We aim to add to our pipeline and portfolio of renal therapeutics through internal discovery and development, and through strategic transactions, such as in-licenses, collaborations and acquisitions. Our pipeline and portfolio expansion efforts will be guided by our vision to improve the health of patients with kidney disease through better disease management and novel therapeutics.

Our management team has extensive experience in developing and commercializing drugs for the treatment of renal and metabolic disorders, a deep understanding of the renal space and biological pathways involved in kidney disease including HIF biology, and broad business development expertise. With this management team, fully integrated capabilities spanning research, manufacturing, development and commercialization, a growing revenue stream and a strong balance sheet, we are well positioned to execute on our strategy.

Kidney Disease

Kidney disease is an area of major unmet need globally, driving massive healthcare costs and with a generally poor prognosis: eventually many patients will progress to a stage where they are dependent on dialysis, with high morbidity and a significant increase in mortality rate.

Kidney disease can be caused by a number of distinct and concomitant factors, including cardiometabolic disorders (primarily diabetes and hypertension), genetic kidney diseases, autoimmune disorders, and aging. Given the prevalence and growth rates of these various underlying conditions, kidney disease prevalence is expected to continue to increase globally. In the United States, kidney disease significantly impacts the U.S. healthcare system, affecting more than 40 million patients and costing Medicare over \$110 billion annually in 2016 for the care provided in dialysis clinics, nephrology centers and hospitals. The U.S. Department of Health and Human Services has recognized the national pandemic and partnered with the American Society of Nephrology to found the KidneyX Innovation Accelerator, a public-private partnership to improve the lives of the 850 million people worldwide currently affected by kidney diseases by accelerating innovation in the prevention, diagnosis and treatment of kidney diseases.

Most of the conditions covered by the term “kidney disease” may ultimately lead to dependence on dialysis or kidney transplant for survival, causing renal failure, directly or indirectly, by accelerating the onset of CKD. Dependence on dialysis is associated with a significant increase in mortality and hospitalizations, and a significant reduction in quality of life for patients. It is our vision, in time, to provide or contribute to better alternatives for patients with kidney disease.

As a first step towards our vision, we aim to advance care for patients with CKD, which is the current focus of our pipeline and our FDA-approved product, Auryxia.

CKD is a condition in which the kidneys are progressively damaged to the point that they cannot properly filter the blood circulating in the body. This damage causes waste products to build up in the patient’s blood leading to other health problems, including anemia, cardiovascular disease and bone disease. As illustrated in the table below, CKD patients are categorized in one of five stages based on the degree of their loss of kidney function as measured by the glomerular filtration rate, or GFR, and the level of protein in the urine, referred to as albuminuria. CKD is estimated to affect approximately 37 million adults in the United States.

Stages and Prevalence of Chronic Kidney Disease in the United States

			Estimated Number of U.S.	
Stage	Description	GFR (mL/min/1.73m ²) ^a	U.S. Prevalence Rates ^{b, c}	Patients (millions) ^{d, e}
	Kidney damage with normal or			
1	increased GFR	≥90	4.6%	11.2
	Kidney damage with mildly			
2	decreased GFR	60-89	3.0%	7.3
3	Moderately decreased GFR	30-59	6.7%	16.4
4	Severely decreased GFR	15-29	0.4%	1.0
	Kidney failure (includes non			
5	dialysis, dialysis and transplant)	<15 (or dialysis)	0.3% (calculated)	0.7

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Sources:

^aGFR categories defined in the August 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Anemia in Chronic Kidney Disease, p. vii.

^bU.S. Prevalence Rates for Stages 1-4 based on averages of data from 2011-2012 and 2013-2014, CDC CKD Surveillance System, National Health and Nutrition Examination Survey, or NHANES.

^cU.S. Prevalence Rate for Stage 5 is based on a calculation using estimated number of U.S. patients with Stage 5 CKD from 2017 U.S. Renal Data System Annual Report, as set forth in this table, and U.S. population data for people 20 years and older from www.census.gov.

^dEstimated Number of U.S. Patients for Stages 1-4 based on the 2017 U.S. Prevalence rates, as set forth in this table, as applied by Akebia to U.S. population data for people 20 years and older from www.census.gov.

^eEstimated Number of U.S. End-Stage Renal Disease Patients from 2017 U.S. Renal Data System Annual Report. The prevalence and incidence of CKD is increasing in all segments of the United States population. Risk factors for the development of CKD include concomitant diseases such as hypertension, diabetes mellitus and cardiovascular disease, lifestyle factors such as tobacco use and inactivity, family history, aging and prenatal factors such as maternal diabetes mellitus, low birth weight and small-for-gestational-age status. According to an article in *The Lancet* published in May 2013, projected worldwide population changes suggest that the potential number of cases of CKD, specifically end-stage, will increase disproportionately in countries such as Japan, China and India where the number of elderly people is increasing. This effect will be accelerated further if the growth in the prevalence of hypertension and diabetes persists, along with the associated increased risk of stroke and cardiovascular disease, and access to treatment does not improve.

The progression of CKD towards renal failure is complicated by multiple conditions which further deteriorate kidney function and the general health of patients if left untreated. Typically the prevalence of these conditions increases as CKD progresses. For instance, anemia is characterized by low hemoglobin levels and is typically associated with a worsening quality of life, increased hospitalizations and increased mortality. The prevalence of anemia increases with the severity of CKD from an estimated 20% in patients with Stage 3 NDD-CKD to an estimated 95% in patients with Stage 5 DD-CKD.

Anemia, or low hemoglobin/red blood count, in patients with CKD most commonly arises from two etiologies:

1. IDA: results from low levels of iron due to abnormal iron absorption and utilization in patients with CKD.
2. Anemia due to CKD: results from inadequate levels of EPO, a protein hormone synthesized by specialized cells in the kidney that stimulates production of red blood cells in the bone marrow. As renal function declines, the body progressively loses the ability to produce endogenous EPO.

IDA in adult patients with NDD-CKD is an FDA-approved indication for Auryxia, and anemia due to CKD in NDD-CKD and DD-CKD patients are the two indications being investigated in Phase 3 clinical trials for vadadustat.

Hyperphosphatemia is another condition associated with CKD that is characterized by elevated serum phosphorus levels and is also typically associated with a worsening of health including increased cardiovascular risk and increased mortality. Hyperphosphatemia in DD-CKD patients is also an FDA-approved indication for Auryxia.

In addition to these conditions that are the current focus of our pipeline and portfolio of approved indications, there are several other disorders that have deleterious consequences on patient's health, including hypercalcemia, hyperkalemia, hyponatremia, hypernatremia, and hyperparathyroidism. These conditions are generally not well controlled, particularly in the later stages of CKD and as patients transition to dialysis.

We are considering opportunities for further development and co-development of Auryxia and vadadustat in CKD patients, including in patients with later stage NDD-CKD.

When considering the clinical and commercial opportunities in CKD, it is important to take note of the contrasting market dynamics between DD-CKD and NDD-CKD.

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DD-CKD patients receive treatment for the various complications of CKD including anemia and hyperphosphatemia. Given the concentration of dialysis clinics in large networks, with DaVita and Fresenius Kidney Care accounting for nearly 80% of the dialysis population in the United States, treatment is usually driven by medical protocols that are rolled out across the entire network of clinics. These protocols are informed by very large data sets and when updated, result in rapid change applicable to large segments of the patient population. This is particularly true of medications covered under the End Stage Renal Disease, or ESRD, Prospective Payment System, or PPS, in Medicare, or the ESRD Bundle, a payment structure with a flat base rate per dialysis session adjusted for individual patient and facility characteristics. Dialysis-related drugs are included in the ESRD Bundle if they fall into functional categories such as anemia management and bone and mineral metabolism, except that oral-only drugs are exempted from inclusion until 2025. In a final ESRD PPS rule published in November 2018, CMS confirmed that it will expand the Transitional Drug Add-On Payment Adjustment, or TDAPA, to all new dialysis drugs approved by the FDA after January 1, 2020. The TDAPA will provide separate payment for new drugs for two years based on the drug's Average Sales Price, ASP, that will be added to the base rate in order to facilitate the adoption of innovative therapies. Although there are several details that need clarification, the rule provides support for our assumption that new anemia treatments, including the HIF-PHI class, will be included in the ESRD Bundle and will be eligible for separate payment initially under TDAPA.

In contrast, NDD-CKD is characterized by larger patient populations with lower treatment rates for CKD-related conditions. In addition to improving cardiovascular risk and quality of life, unmet need includes delaying the progression of CKD and therefore the transition to dialysis. Reimbursement in the non-dialysis setting aligns with traditional commercial and government payer reimbursement for outpatient drugs.

Our Commercial Product: Auryxia

Overview

Auryxia (ferric citrate) is a non-calcium, non-chewable, orally-administered tablet that was approved for marketing by the FDA in September 2014 as a phosphate binder for the Hyperphosphatemia Indication and was commercially launched in the United States shortly thereafter. In November 2017, Auryxia received marketing approval from the FDA for a second indication, the IDA Indication, and was commercially launched for this indication in the United States shortly thereafter.

In January 2014, our Japanese sublicensee, JT, received approval from the Japanese Ministry of Health, Labour and Welfare to market ferric citrate in Japan under the trade name Riona as an oral treatment for the improvement of hyperphosphatemia in patients with CKD, including DD-CKD and NDD-CKD, and was commercially launched in Japan shortly thereafter. In September 2015, we received approval to market ferric citrate in the EU under the trade name Fexeric for the control of hyperphosphatemia in adult patients with CKD. Fexeric was also approved in the EU as a New Active Substance, or NAS, which provides 10 years of data and marketing exclusivity in the EU. Fexeric is not currently marketed in the EU, and our EU marketing authorization for Fexeric will cease to be valid on December 23, 2019 unless we commence marketing Fexeric in the EU by that date. We are exploring commercialization opportunities with third parties for Fexeric.

We have licensed and sublicensed certain intellectual property rights covering Auryxia from Panion & BF Biotech, Inc., or Panion. For more information regarding our intellectual property rights to Auryxia and our license agreement with Panion see Part I, Item 1. Business – Intellectual Property – Auryxia and Part I, Item 1. Business - License, Collaboration and Other Strategic Agreements – License Agreement with Panion & BF Biotech, Inc. We have received

four Paragraph IV certification notice letters regarding Abbreviated New Drug Applications, or ANDAs, submitted to the FDA, with the first having been received on October 31, 2018. For more information about these Paragraph IV certification notice letters and any related litigation, see Part I, Item 3. Legal Proceedings.

Market Opportunity

Hyperphosphatemia

Hyperphosphatemia is a metabolic disorder characterized by elevated serum phosphorus levels. Phosphorus is a vital element required for most cellular processes and, in individuals with normal kidney function, excess dietary phosphorus is removed by the kidneys and excreted in urine. In adults with functioning kidneys, normal serum phosphorus levels are 2.5 to 4.5 mg/dL. In adults with DD-CKD, elevated phosphorus levels, or hyperphosphatemia, can be associated with adverse effects, including increased risk for cardiovascular disease, bone disease and death.

Phosphate binders are the only interventions marketed for the treatment of hyperphosphatemia. According to the U.S. Renal Data System, or USRDS, 2018 Annual Data Report, there are approximately 511,000 adult patients in the United States with DD-CKD in 2016, of which approximately 85% were treated with a phosphate binder. Phosphate binders need to be taken with meals and snacks, and it is not uncommon for DD-CKD patients to be prescribed as many as 12 or more phosphate binder pills per day, among other medications. Patients taking phosphate binders also experience gastrointestinal tolerability issues. As a result of the pill burden and tolerability issues associated with phosphate binders, prescribed phosphate binders are often intolerable for many patients, leading to lack of treatment adherence and compliance.

In addition, in 2016 approximately 55% of patients treated with a phosphate binder were treated with a calcium-based binder, which can lead to side effects such as increased cardiovascular risk, hypercalcemia and gastrointestinal-related adverse events. Due to the risks associated with calcium-based binders, in 2017 Kidney Disease: Improving Global Outcomes, or KDIGO, recommended that clinicians limit the use of calcium-based binders. A third party market research survey of 195 nephrologists conducted in the fourth quarter of 2018 after the release of the 2017 KDIGO guidelines indicated that 51% of those surveyed anticipate decreasing their use of calcium-based binders in patients with DD-CKD.

Lanthanum-based phosphate binders are another alternative. Lanthanum is a rare earth element and is minimally absorbed in the gastrointestinal tract. Lower level tissue deposition, particularly in bone and liver, has been observed in animals, however, the long-term, potentially harmful, effects due to the accumulation of lanthanum in these tissues have not been clearly determined.

Aluminum-type phosphate binders were widely used in the past. However, the systemic absorption of aluminum from these agents and the potential toxicity associated with their use no longer make this type of binder a viable long-term treatment option.

Iron Deficiency Anemia

Anemia is a condition characterized by abnormally low levels of hemoglobin. Hemoglobin is contained within RBCs and carries oxygen to other parts of the body. If there are too few RBCs or if hemoglobin levels are low, the cells in the body will not get enough oxygen. IDA is a common form of anemia that is caused by patients not having enough iron to manufacture healthy RBCs. Although anyone can develop IDA, IDA is particularly common in patients with NDD-CKD. IDA is associated with fatigue, lethargy, decrease quality of life, cardiovascular complications, hospitalizations and increased mortality.

We estimate that there are more than 500,000 adult patients in the United States with NDD-CKD diagnosed with IDA. Currently, there are two forms of iron therapy used to treat IDA: oral iron supplements and iron delivered via intravenous infusion, or IV iron. Oral iron is currently the first-line iron replacement therapy for most physicians; however, oral iron supplements are poorly absorbed by many patients, which may adversely impact their effectiveness, and are associated with certain side effects, such as constipation, diarrhea and cramping, that may adversely affect patient compliance. IV iron is viewed as an effective treatment; however, like other intravenous medicines, it is logistically difficult to administer in an office setting, where NDD-CKD patients are more often treated.

Commercialization

We are marketing Auryxia in the United States through our well-established, nephrology-focused sales force and commercial organization. In 2018, our sales force called on approximately 7,300 nephrologists, who represented 82% of prescriptions written for phosphate binders by nephrologists.

Auryxia, as an oral drug, is covered by Medicare only under Part D. We have gained broad access for Auryxia in the United States in both Medicare Part D and commercial channels. Auryxia is currently covered for the Hyperphosphatemia Indication in nine of the ten largest Medicare Part D plans, which provide coverage for approximately 33.6 million people, and the ten largest commercial plans and pharmacy benefit managers in the United States, which provide coverage for approximately 131.7 million people. In September 2018, the Centers for Medicare & Medicaid Services, or CMS, decided that Auryxia would not be covered by Medicare for the IDA Indication. While this decision does not impact CMS coverage of the Hyperphosphatemia Indication, it requires all prescriptions for Auryxia for Medicare patients to undergo a prior authorization to ensure their use in the Hyperphosphatemia Indication. We are engaged in discussions with CMS and Medicare Part D sponsors on this matter as we believe that Auryxia should qualify for coverage under Medicare Part D of the CMS regulations for the IDA Indication.

JT, and its subsidiary, Torii, market Riona in Japan. We receive tiered double-digit royalties from JT and Torii based on their sales in Japan. Fexeric is not currently marketed in the EU, and our current marketing authorization for Fexeric in the EU ceases to be valid on December 23, 2019 unless we commence marketing Fexeric in the EU by that date. We are exploring commercialization opportunities with third parties for Fexeric.

Our Late-Stage Product Candidate: Vadadustat

Overview

Vadadustat is an investigational oral HIF-PHI product candidate, in global Phase 3 development for two indications: anemia due to CKD in adult patients with DD-CKD, and anemia due to CKD in adult patients with NDD-CKD. We believe vadadustat has the potential to set a new oral standard of care for patients with anemia due to CKD.

Vadadustat's proposed mechanism of action is designed to mimic the physiologic effect of altitude on oxygen availability. At higher altitudes, the body responds to lower oxygen availability with increased production of HIF, which coordinates the interdependent processes of iron mobilization and EPO production to increase RBC production and, ultimately, improve oxygen delivery. The significance of the HIF pathway was recognized by the 2016 Albert Lasker Basic Medical Research Award, which honored the three physician-scientists who discovered the HIF pathway and elucidated this primary oxygen sensing mechanism that is essential for survival.

Market Opportunity

Anemia due to Chronic Kidney Disease

Anemia is common in patients with CKD, and its prevalence increases with disease progression. Anemia due to CKD results from inadequate EPO levels, which negatively affect RBC production. Left untreated, anemia accelerates overall deterioration of patient health with increased morbidity and mortality. Based on third party prevalence data and company estimates, approximately 37 million people in the United States have CKD and approximately 5.7 million of these individuals suffer from anemia. Anemia due to CKD is currently treated by injectable recombinant human ESAs, such as EPOGEN® (epoetin alfa) and Aranesp® (darbepoetin alfa), or blood transfusion. Based on publicly available information on ESA sales and market data compiled by a third-party vendor, global sales of injectable ESAs for all uses were estimated to be approximately \$6.1 billion in 2018. The vast majority of these sales were for the treatment of anemia due to CKD.

When administered to a patient, injectable ESAs provide supraphysiological levels of exogenous EPO to stimulate production of RBCs. While injectable ESAs can be effective in raising hemoglobin levels, they have the potential to cause significant side effects, and need to be injected subcutaneously or intravenously. In particular, injectable ESAs may lead to thrombosis, stroke, myocardial infarction and death. These safety concerns, which became evident starting in 2006, have led to a significant reduction in the use of injectable ESAs. Data from the USRDS 2015 Annual Data Report indicate that the collective injectable ESA treatment rate in NDD-CKD patients in the United States decreased by approximately half from 2009 to 2013. Today, anemia is either not treated or inadequately treated in the majority of NDD-CKD patients.

According to the USRDS 2018 Annual Data Report, there were approximately 511,000 patients in the United States on dialysis in 2016, of which 88% were on in-center hemodialysis and the remainder on peritoneal or home hemodialysis. ESAs are given to approximately 90% of in-center hemodialysis patients and 75% of peritoneal dialysis patients. There is an unmet need for treatment options for patients with anemia due to CKD that offer an improved safety profile, and such agents would have significant market potential.

Vadadustat Has the Potential to Set a New Standard of Care

We believe that, based on the HIF-PHI mechanism of action and clinical data to date, vadadustat has the potential to set a new standard of care for the treatment of anemia due to CKD. Below is a summary of the key clinical findings;

further details are included below.

•Vadadustat stimulated endogenous EPO production. In two Phase 1 studies in normal healthy volunteers and one Phase 2 study in CKD patients, vadadustat increased serum EPO levels in a dose-dependent manner. Pre-dose EPO levels returned to baseline levels prior to subsequent daily dose. In these studies, vadadustat stimulated endogenous EPO production while avoiding supraphysiologic EPO levels.

•Vadadustat significantly increased and maintained hemoglobin levels. Our Phase 2 studies in CKD subjects with anemia demonstrated that vadadustat significantly increased and/or maintained hemoglobin levels.

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•Vadadustat was dosed orally once daily and three times weekly. Our Phase 2 studies showed that vadadustat can be orally dosed once daily in NDD-CKD subjects with up to 20 weeks of dosing. In addition, our Phase 2 clinical study in DD-CKD subjects demonstrated that in subjects who remained on therapy, once daily oral dosing of vadadustat maintained stable hemoglobin levels in subjects converting from injectable ESA therapy over 16 weeks. This study also showed the potential for three-times weekly dosing of vadadustat in DD-CKD.

•Vadadustat resulted in favorable changes in iron parameters. In three Phase 2 clinical studies, treatment with vadadustat was associated with decreases in ferritin and hepcidin and increases in total iron binding capacity. These changes are consistent with improved iron mobilization and utilization for erythropoiesis in NDD-CKD and DD-CKD subjects.

Vadadustat has the potential to stimulate erythropoiesis, avoid supraphysiologic EPO levels, and possibly reduce risk of cardiovascular and thrombotic events associated with injectable ESAs. The efficacy of vadadustat in raising/maintaining hemoglobin levels and the cardiovascular safety of vadadustat as compared with darbepoetin alfa, an injectable ESA, is being assessed in the global Phase 3 clinical program for vadadustat.

Vadadustat Clinical Development – Phase 1 and Phase 2

We have completed twenty-two Phase 1 and Phase 2 studies of vadadustat. These studies included healthy volunteers, NDD-CKD and DD-CKD patients, and support continued development of vadadustat.

Findings from three Phase 2 studies demonstrated that vadadustat administered daily raised and/or maintained hemoglobin levels and improved markers of iron mobilization to support erythropoiesis in CKD patients. The range of doses used in these Phase 2 studies had been previously shown, in Phase 1 studies of healthy volunteers, to stimulate endogenous EPO production while avoiding supraphysiologic EPO levels. The results from one completed Phase 1 and two Phase 2 of these studies are summarized below.

Phase 1 Study in Normal Healthy Volunteers (CI-0002)

We completed a Phase 1 randomized, double-blind, placebo-controlled, multiple-ascending dose study to evaluate the safety, tolerability, pharmacodynamics response, and pharmacokinetics of vadadustat administered for 10 days to healthy male volunteers. Dose responsive increases in reticulocytes, or immature RBCs, and hemoglobin levels were demonstrated in the study. Mean serum EPO levels increased by 36%, 48%, and 89% over baseline, at 8 to 16 hours after dosing in the vadadustat 500 mg/day, 700 mg/day, and 900 mg/day dosing groups, respectively, and returned to baseline by 24 hours after dosing. The incidence of adverse events, or AEs, was generally similar between the combined vadadustat dosing groups, which was 76.5%, and the placebo group, which was 78%. Gastrointestinal AEs occurred in 26.5% of subjects in the vadadustat groups and in no subjects on placebo, of which mild to moderate diarrhea was the most frequent AE (24%), with evidence of a dose-related effect. No serious adverse events, or SAEs, or deaths were reported in this study.

Phase 2b Study in Non-Dialysis CKD Subjects (CI-0007)

We completed a multi-center Phase 2b study of vadadustat in non-dialysis subjects with anemia due to CKD. This double-blind, randomized, placebo-controlled study evaluated the efficacy and safety of vadadustat over 20 weeks of dosing in 210 subjects (138 vadadustat and 72 placebo) with CKD Stages 3 to 5. Subjects were enrolled into one of three groups: (1) injectable ESA naïve with hemoglobin ≤ 10.5 g/dL, (2) previously treated with injectable ESA with hemoglobin ≤ 10.5 g/dL, or (3) actively treated with injectable ESA with hemoglobin ≥ 9.5 and ≤ 12.0 g/dL, and were randomized at a ratio of 2 to 1 to once daily vadadustat or placebo. The primary endpoint was the percentage of subjects with either a mean hemoglobin of ≥ 11.0 g/dL or an increase in hemoglobin by ≥ 1.2 g/dL from baseline. A

protocol-defined dose adjustment algorithm was used to achieve the primary endpoint and to minimize hemoglobin excursions ≥ 13 g/dL.

The average age of subjects was 66 years; 78% of subjects had diabetes mellitus; and the mean estimated GFR was 25 mL/min/1.73m². 54.9% of vadadustat treated subjects compared to 10.3% of placebo treated subjects met the primary endpoint ($p=0.0001$). Only 4.3% of subjects in the vadadustat group had any hemoglobin excursion ≥ 13.0 g/dL. Between Groups 1 and 2 (the two correction cohorts; ESA-naïve and ESA previously treated), mean Hb increased significantly in the vadadustat group from pre-dose average to end-of-study average (Week 19/20). In Group 3 (conversion cohorts; ESA actively treated), placebo treated subjects experienced a decline in the mean hemoglobin within the first two weeks, whereas subjects randomized to vadadustat maintained a stable hemoglobin throughout the study.

Increases in hemoglobin in the vadadustat group were preceded by an increase in reticulocytes and accompanied by an increase in total iron binding capacity and a decrease in serum hepcidin and ferritin. There was no difference between the vadadustat and placebo groups in vascular endothelial growth factor, or VEGF, levels during the study.

A similar percentage of subjects experienced an AE in the vadadustat and placebo treatment groups (vadadustat 74.6% vs. placebo 73.6%); however, the frequency of certain AEs - diarrhea, nausea, hypertension and hyperkalemia - was greater in the vadadustat arm compared to placebo. In the vadadustat arm, a higher number of subjects reported SAEs of acute and chronic renal failure compared to placebo (9.4% vs. 2.8%, respectively); however, none was considered drug-related by the investigator. The percentage of subjects who had an SAE resulting in dialysis initiation, considered to be a more objective measure of the severity of renal disease, was comparable between vadadustat and placebo groups (8.0% versus 9.7%, respectively) and the number of subjects who discontinued from the study due to AEs of worsening CKD requiring dialysis was also comparable between the vadadustat (4.3%) and placebo (5.6%) groups. One subject with multiple co-morbidities and concomitant medications, including chlorthalidone, had an SAE of liver function test, or LFT, abnormal, considered a case of drug-induced liver injury meeting the biochemical criteria of Hy's Law, which was assessed as probably related to vadadustat. This subject made a complete recovery after vadadustat was discontinued. There were three deaths in vadadustat-treated subjects of which two cardiovascular deaths were considered to be unrelated to vadadustat and one death was attributed to myocardial ischemic and considered by the investigator to be possibly related to vadadustat; no autopsy was performed. There were no deaths in the placebo group.

In summary, vadadustat achieved the desired outcomes of raising and maintaining hemoglobin and increasing iron mobilization, while minimizing hemoglobin excursions ≥ 13 g/dL. Pergola et al published the results of this study in *Kidney International* 2016.

Phase 2 Study in Dialysis-Dependent CKD Subjects (CI-0011)

We completed a multi-center, open-label, 16-week study to assess the hemoglobin response, safety, and tolerability of vadadustat in DD-CKD subjects. The study enrolled 94 hemodialysis subjects with baseline hemoglobin levels of 9-12 g/dL, who were maintained on injectable ESAs prior to study entry. Subjects were converted from injectable ESA to vadadustat, and assigned to one of three dose cohorts: 300 mg once daily; 450 mg once daily; or 450 mg three-times weekly. For each dose cohort, the average hemoglobin level at study entry was compared to the average hemoglobin level at weeks 7 and 8, and to the average hemoglobin level at weeks 15 and 16. To evaluate hemoglobin response to each of the dose regimens, during the first eight weeks of this study, subjects were to remain on the prescribed starting dose, or decreased if necessary to control hemoglobin in the target range. Beginning at week 8, the dose of vadadustat could be increased or decreased to maintain hemoglobin levels as needed. Intravenous iron use was allowed.

The underlying demographics and profiles of these CKD subjects were well-balanced across the three cohorts, and reflective of the United States DD-CKD population as reported in the literature. Average age was 58 years, with an average time on dialysis of 4.6 years. The most common cause of end-stage renal disease was diabetes mellitus and/or hypertension. Baseline hemoglobin levels were similar at 10.4-10.6 g/dL in all three cohorts and the serum ferritin levels indicated that the subjects were iron replete at study entry and throughout the study.

For subjects in all three dosing cohorts (converted from ESA) who completed the study, the primary endpoint of maintaining stable mean hemoglobin levels over 16 weeks was achieved. In the sensitivity analysis using last observation carried forward to account for early discontinuations, mean Hb levels remained stable in the 300 mg daily dose cohort and modest declines were observed in the 450 mg daily and 450 mg three-times weekly dose cohorts. Post-hoc analyses indicated that baseline pre-conversion ESA dose was inversely associated with mean change in hemoglobin. Consistent with previous studies, all three starting dose regimens suggested an improvement in iron mobilization, as reflected by increases in total iron binding capacity and serum iron, and decreases in serum ferritin and hepcidin levels. Only one subject in the 300 mg once daily cohort had a single hemoglobin excursion to 13.1 g/dL.

These data support further development of vadadustat daily dosing to assess its long-term safety and efficacy in subjects on hemodialysis. These data also support further investigation of three times weekly dosing of vadadustat.

Adverse events were balanced across the three cohorts with 83% of subjects with at least one AE. There were no discernible trends in the frequency of AEs or SAEs by dose cohort. The most frequently reported AEs were nausea and diarrhea, 11.7% and 10.6%, respectively, with no apparent dose relationship. The majority of AEs were mild or moderate in severity. SAEs were reported in 13 subjects, or 13.8%, including two subjects with acute myocardial infarction considered not related to vadadustat by the investigator. No SAEs were reported as related to vadadustat and no deaths occurred during the study. Haase et al published the results of this study in *Nephrology Dialysis Transplantation* 2018.

Vadadustat Clinical Program

The following chart summarizes the current clinical program for our product candidate, vadadustat, which is in Phase 3 development.

Phase 1 and Phase 2 data led us to the design of our Phase 3 clinical program for vadadustat. The vadadustat Phase 3 program in DD-CKD patients with anemia due to CKD, called INNO₂VATE, and in NDD-CKD patients with anemia due to CKD, called PRO₂TECT, is designed to enroll up to approximately 7,600 patients evaluating once daily oral dosing of vadadustat against an injectable ESA active comparator, darbepoetin alfa. The enrollment numbers and the completion of INNO₂VATE and PRO₂TECT will be driven by the accrual of major adverse cardiovascular events, or MACE.

In August 2016, the first patient was dosed in INNO₂VATE. We completed enrollment in the larger of the two INNO₂VATE studies, which enrolled 3,554 subjects, in February 2019, and we expect to complete enrollment in the smaller INNO₂VATE study, enrolling approximately 350 subjects, by April 2019. We anticipate completing the larger of the two INNO₂VATE studies in the first quarter of 2020, with completion of the smaller INNO₂VATE study and availability of top-line data expected in the second quarter of 2020, subject to the accrual of MACE.

The first patient was dosed in PRO₂TECT in December 2015. We expect full enrollment of PRO₂TECT in 2019. We anticipate reporting top-line data for the PRO₂TECT studies in mid-2020, subject to the accrual of MACE. As of December 31, 2018, we expect the remaining external aggregate contract research organization, or CRO, costs of INNO₂VATE and PRO₂TECT to be in the range of \$190.0 million to \$220.0 million.

In both the PRO₂TECT and INNO₂VATE Phase 3 programs, the primary efficacy endpoint is the mean change in hemoglobin between baseline and the primary evaluation period. Non-inferiority, or NI, is achieved if the lower bound of the 95% confidence interval for the between-group difference of the mean hemoglobin change does not fall below the pre-specified NI margin. Both the PRO₂TECT and INNO₂VATE programs will include the primary safety endpoint of the assessment of MACE, with a comparison of vadadustat to darbepoetin alfa. MACE is defined as the composite endpoint of all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke. To assess MACE, a pooled analysis of time to first MACE event from the two Phase 3 studies in each program (PRO₂TECT and INNO₂VATE) will be performed. NI is achieved if the upper bound of the 95% confidence interval for the hazard ratio of vadadustat to darbepoetin alfa does not exceed the pre-specified NI margin. We obtained feedback from the United States and European regulatory authorities regarding the design of these programs.

In addition, we have initiated a Phase 2 clinical study of vadadustat, FO₂RWARD-2, which will evaluate a modified approach to once-daily and three-times weekly dosing, including assessment of a vadadustat starting dose based on pre-conversion ESA dose and higher titration doses of vadadustat (750 mg and 900 mg). We expect to initiate two additional Phase 3 clinical studies of vadadustat, EXPLOR₂E and TRILO₂GY-2, which will evaluate modified once daily and three times weekly dosing of vadadustat, respectively. We believe data from these studies could support registration of the modified approach to once daily dosing and supplemental registration of three times weekly dosing, and further characterize vadadustat and further strengthen our potential commercial position if vadadustat is approved for marketing.

We completed a series of clinical drug-drug interaction studies largely focusing on transporter pathways evaluating vadadustat as a victim (using probe inhibitors) or perpetrator (using probe substrates) of drug interactions. No meaningful drug interactions were observed with atorvastatin (P-gp/OATP1B1 substrate), pravastatin (OATP1B1/1B3 substrate), digoxin (P-gp substrate), furosemide (OAT1/OAT3 substrate), adefovir (OAT1 substrate), cyclosporine (P-gp/BCRP/OATP inhibitor), probenecid (OAT3 and UGT inhibitor), or rabeprazole (gastric acid-reducing agent). With concomitant administration of vadadustat, a mild-to-moderate interaction was observed with simvastatin (OATP1B1/1B3 substrate), and moderate drug interactions were observed with rosuvastatin (BCRP/OATP1B1/1B3 substrate), ferrous sulfate, and sulfasalazine (BCRP substrate). In addition, in vitro drug-drug interaction studies demonstrated a very low risk of vadadustat for drug interactions due to alteration of metabolic enzyme activities, i.e. cytochrome P450 or UDP-glucuronosyltransferase isoforms. No clinical drug-interaction was observed with celecoxib (CYP2C9).

MTPC's Phase 3 Clinical Program of Vadadustat in Japanese Patients

On March 12, 2019, we announced positive top-line results from two Phase 3 active-controlled pivotal studies evaluating vadadustat in Japanese subjects with anemia due to CKD (J01 and J03 Studies). These studies were conducted by our development and commercialization collaboration partner in Japan, MTPC. Each study, one in non-dialysis dependent subjects and one in hemodialysis-dependent subjects, met its primary endpoint. In addition, results from two Phase 3 single-arm studies conducted by MTPC in peritoneal dialysis subjects and hemodialysis subjects (J02 and J04 Studies) further support vadadustat's potential in these indications. MTPC expects to submit a Japanese New Drug Application in 2019 for vadadustat for the treatment of anemia due to CKD.

The Phase 3 randomized, open-label, active-controlled correction and conversion study (J01 Study) assessed the efficacy and safety of vadadustat compared to darbepoetin alfa, an ESA, in 304 Japanese non-dialysis dependent subjects with anemia due to CKD, with a treatment duration of 52 weeks. Data from the planned analysis at 24 weeks are provided. The study met its primary endpoint, with the mean hemoglobin, or Hb, level at week 20 and week 24 at 11.66 g/dL (95% CI 11.49, 11.84 g/dL) for vadadustat-treated subjects compared to 11.93 g/dL (95% CI 11.76, 12.10 g/dL) for darbepoetin alfa-treated subjects. The difference in mean Hb was -0.26 g/dL (95% CI -0.50, -0.02 g/dL), achieving the pre-specified non-inferiority criterion of -0.75 g/dL. The incidence of adverse events, or AEs, was 72.2% in the vadadustat-treated group compared to 73.2% in the darbepoetin alfa-treated group. The most common AEs reported in vadadustat-treated subjects were nasopharyngitis (14.6%), diarrhea (10.6%), constipation (5.3%), and contusion (5.3%). The incidence of SAEs was 13.9% in the vadadustat-treated group compared to 14.4% in the darbepoetin alfa-treated group; no SAE was considered related to study drug. No deaths were reported in the vadadustat-treated group, and one fatal myocardial infarction was reported in the darbepoetin alfa-treated group, which was assessed as not related to study drug.

The Phase 3 randomized, double-blind, active-controlled conversion study (J03 Study) assessed the efficacy and safety of vadadustat compared to darbepoetin alfa in 323 Japanese hemodialysis subjects with anemia due to CKD who had been receiving ESA therapy prior to study screening, with a treatment duration of 52 weeks. Group level data at 24 weeks from this ongoing double-blind study are provided. The study met its primary endpoint, with the mean Hb level at week 20 and week 24 at 10.61 g/dL (95% CI 10.45, 10.76 g/dL) for vadadustat-treated subjects compared to

10.65 g/dL (95% CI 10.50, 10.80 g/dL) for darbepoetin alfa-treated subjects. The difference in mean Hb was -0.05 g/dL (95% CI -0.26, 0.17 g/dL), achieving the pre-specified non-inferiority criterion of -0.75 g/dL. The incidence of AEs was 89.5% in the vadadustat-treated group compared to 88.2% in the darbepoetin alfa-treated group. The most common AEs reported in vadadustat-treated subjects were nasopharyngitis (19.8%), diarrhea (10.5%), and shunt stenosis (8.0%). The incidence of SAEs was 13.0% in the vadadustat-treated group compared to 10.6% in the darbepoetin alfa-treated group; no SAE was considered related to study drug.

The Phase 3 open-label, single-arm study (J02 Study) assessed the efficacy and safety of vadadustat in 42 Japanese peritoneal dialysis subjects with anemia due to CKD, with a treatment duration of 24 weeks. The mean Hb level at week 20 and week 24 was 11.35 g/dL (95% CI 10.99, 11.70 g/dL) for vadadustat-treated subjects. Thirty-eight subjects (90.5%) experienced an AE and twelve (28.6%) experienced an SAE. One SAE of fatal myocardial ischemia was assessed as possibly related to vadadustat by the investigator.

The Phase 3 open-label, single-arm correction study (J04 Study) evaluated the safety and efficacy of vadadustat, with a treatment duration of 24 weeks, in 24 Japanese hemodialysis subjects with anemia due to CKD who had not been receiving ESA therapy prior to study screening or who underwent ESA washout during screening. The mean Hb level at week 20 and week 24 was 10.75 g/dL (95% CI 10.35, 11.14 g/dL) for vadadustat-treated subjects. Twenty-three subjects (95.8%) experienced an AE, and seven (29.2%) experienced an SAE. No SAE was assessed as related to study drug, and no deaths were reported.

Commercialization

We plan to commercialize vadadustat, subject to FDA approval, in the United States with our well-established, nephrology-focused commercial organization, while leveraging our collaboration with Otsuka and its U.S. commercial organization. We also granted Otsuka exclusive rights to commercialize vadadustat in Europe, China and certain other markets, subject to marketing approvals. In Japan and certain other countries in Asia, we granted MTPC exclusive rights to commercialize vadadustat, subject to marketing approvals. In addition, we granted Vifor Pharma an exclusive license to sell vadadustat solely to FKC, which manages approximately 40% of the dialysis patients in the United States, at its U.S. dialysis clinics, subject to FDA approval of vadadustat, vadadustat's reimbursement under a bundled reimbursement model, and a milestone payment by Vifor Pharma. During the term of the license agreement, Vifor Pharma may not sell to FKC or its affiliates any HIF product that competes with vadadustat in the United States. For more information about our license, collaboration and strategic agreements relating to vadadustat, see Part I, Item 1. Business – License, Collaboration and Other Strategic Agreements – Vadadustat.

Development Candidates

In addition to vadadustat, we are developing a HIF-based portfolio of other product candidates that target serious diseases of high unmet need. Our portfolio includes product candidates developed internally as well as in-licensed product candidates. In February 2017, we signed an exclusive agreement with Janssen Pharmaceutica NV, or Janssen, a subsidiary of Johnson & Johnson, or the Janssen Agreement, for access to an extensive library of well-characterized HIF pathway compounds with potential applications across multiple therapeutic areas. Our strategic focus will be to identify and develop candidates for kidney disease indications.

Manufacturing and Supply

Overview

We neither own nor operate, and currently have no plans to own or operate, any manufacturing or distribution facilities. We currently rely on third-party contract manufacturing organizations, or CMOs, to produce all of our preclinical and clinical material and commercial supply and third-party distributors to distribute Auryxia. We expect to continue to rely on either existing or alternative distributors and CMOs to distribute our products and supply our ongoing and planned preclinical and clinical studies and for commercial production.

We have established relationships with several CMOs under which the CMOs manufacture preclinical and clinical supplies of vadadustat drug substance and drug product and clinical and commercial supply of Auryxia drug substance and drug product. All clinical and commercial supplies are manufactured under current Good Manufacturing Practices, or cGMPs, which is a regulatory standard for the production of pharmaceuticals that will be used in humans.

Auryxia

We have established CMO relationships for the supply of Auryxia to help ensure that we will have sufficient material for clinical trials and ongoing commercial sales. The drug substance for Auryxia is supplied by Siegfried Evionnaz SA (two sites) and BioVectra Inc. (one site), pursuant to supply agreements with pricing structured on a per-kilogram basis. Auryxia drug product is supplied by Patheon Manufacturing Services LLC (Thermo Fisher) (three sites) pursuant to a Master Manufacturing Service Agreement with per-bottle pricing structured on a tiered basis, with the price reduced as the product volume increases. These agreements require that we satisfy certain minimum purchase requirements, but we are not obligated to use them as our sole suppliers. In addition, we are continuing to establish the basis for long-term commercial production capabilities to supply the potential expanded demand for Auryxia in future years. For more information about our manufacturing agreements for Auryxia, see Part II, Item 7. Management's

Discussion and Analysis and Note 16 to our consolidated financial statements in Part II, Item 8. Financial Statements and Supplementary Data.

As we continue to build inventory for the expanded commercialization of Auryxia, we intend to expand capacity to produce Auryxia under cGMP requirements. Our third party manufacturers have other clients and may have other priorities that could affect their ability to perform the work satisfactorily and/or on a timely basis. Both of these occurrences would be beyond our control.

Auryxia is a small molecule. The synthesis of Auryxia is reliable and reproducible from starting materials available from multiple sources at commercially relevant scale. Auryxia can be readily formulated into compressed tablets with standard ingredients using common manufacturing processes. As with any supply program, obtaining raw materials and finished drug product of the required quality and quantity cannot be guaranteed, and we cannot ensure that we will be successful in this endeavor.

We utilize third parties for the commercial distribution of Auryxia, including wholesale distributors and certain specialty pharmacy providers. We have also engaged Cardinal Health as the exclusive third-party logistics distribution agent for commercial sales of Auryxia.

Vadadustat

We currently have redundant supply arrangements in place for the preclinical and clinical supply of vadadustat. We intend to put supply agreements in place for commercial manufacturing of vadadustat in the near future. We plan to mitigate potential commercial supply risks for vadadustat, if any, through inventory management and redundant manufacturing arrangements for both drug substance and drug product; however, the timing of such arrangements is uncertain and may occur following the launch of vadadustat, if approved.

Vadadustat is a small molecule. The synthesis of vadadustat is reliable and reproducible from starting materials available from multiple sources at commercially relevant scale using no unusual manufacturing equipment. Vadadustat can be readily formulated into compressed tablets with standard ingredients using common manufacturing processes. As with any supply program, obtaining raw materials and finished drug product of the required quality and quantity cannot be guaranteed and we cannot ensure that we will be successful in this endeavor.

License, Collaboration and Other Strategic Agreements

Auryxia

License Agreement with Panion & BF Biotech, Inc.

In November 2005, Keryx entered into a license agreement with Panion. Under the license agreement, we acquired the exclusive worldwide rights, excluding certain Asian-Pacific countries, for the development, marketing and commercialization of ferric citrate. Under the agreement, Panion is eligible to receive from us milestone payments and royalty payments based on a mid-single digit percentage of net sales of ferric citrate in the licensed territory.

The license agreement terminates upon the expiration of our obligations to pay royalties thereunder. In addition, we may terminate the license agreement (i) in its entirety or (ii) with respect to one or more countries of the territory covered by the agreement, in either case upon 90 days' notice. We and Panion also have the right to terminate the license agreement upon the occurrence of a breach of a material provision of the license agreement, subject to certain cure provisions, or certain insolvency events.

On October 24, 2018, prior to the consummation of the Merger, we and Keryx entered into a letter agreement with Panion, the Panion Letter Agreement, pursuant to which Panion agreed to rescind any and all prior termination threats or notices relating to the license agreement and waived its rights to terminate the license agreement based on any breach by Keryx of our obligation to use commercially reasonable efforts to commercialize Auryxia outside the United States until the parties execute an amendment to the license agreement in accordance with the terms of the Panion Letter Agreement following consummation of the Merger. These terms include establishing a joint steering committee consisting of Panion and Akebia representatives to oversee the development and commercialization of Fexeric in Europe and providing Panion with an exclusive license under Keryx-owned patents covering the rights to make, use, sell, offer for sale and import ferric citrate in certain countries in the Asia-Pacific region. The parties intend to work together to agree on a commercialization plan for Fexeric in Europe following execution of the amendment. The amendment is expected to include alternatives in the event a commercialization plan is not agreed upon, such as payment of an annual license maintenance fee to Panion or the return of European intellectual property rights to Panion. Under the terms of the Panion Letter Agreement, Panion also agreed that we will have the right, but not the obligation, to conduct any litigation against any infringer of patent rights under the license agreement on the terms

agreed upon in the Panion Letter Agreement. In addition, Keryx made a \$500,000 payment to Panion promptly after execution of the Panion Letter Agreement.

During the period from December 12, 2018 to December 31, 2018, Panion earned \$0.4 million in royalty payments relating to the sales of Auryxia in the U.S. and JT and Torii net sales of Riona in Japan, as we are required to pay a low double-digit percent of sublicense income to Panion under the terms of the license agreement, excluding any income under the JT and Torii sublicense.

Sublicense Agreement with Japan Tobacco Inc. and Torii Pharmaceutical Co., Ltd.

In September 2007, Keryx entered into a Sublicense Agreement with JT and Torii, under which JT and Torii obtained the exclusive sublicense rights for the development and commercialization of ferric citrate in Japan. Effective June 8, 2009, Keryx entered into an Amended and Restated Sublicense Agreement, which was amended in June 2013, or the Revised Agreement, with JT and Torii, which, among other things, provided for the elimination of all significant on-going obligations under the Sublicense Agreement.

In January 2014, JT and Torii received manufacturing and marketing approval of ferric citrate from the Japanese Ministry of Health, Labour and Welfare. Ferric citrate, launched in May 2014 and being marketed in Japan by Torii under the brand name Riona, is indicated as an oral treatment for the improvement of hyperphosphatemia in patients with CKD, including NDD-CKD and DD-CKD. Under the terms of the license agreement with JT and Torii, we are eligible to receive royalty payments based on a tiered double-digit percentage of net sales of Riona in Japan escalating up to the mid-teens, subject to certain reductions upon expiration or termination of the Panion license agreement, and may also receive up to an additional \$55.0 million upon the achievement of certain annual net sales milestones. In accordance with our revenue recognition policy, royalty revenues are recognized in the quarter that JT and Torii provide their written report and related information to us regarding sales of Riona, which generally will be one quarter following the quarter in which the underlying sales by JT and Torii occurred. We recorded \$0.1 million in license revenue related to royalties earned on net sales of Riona in Japan during the period from December 12, 2018 to December 31, 2018. We record the associated mid-single digit percentage of net sales royalty expense due to Panion, the licensor of ferric citrate, in the same period as the royalty revenue from JT and Torii is recorded.

The sublicense terminates upon the expiration of all underlying patent rights. Also, JT and Torii may terminate the sublicense agreement with or without cause upon at least six months prior written notice to us. Additionally, either party may terminate the sublicense agreement for cause upon 60 days' prior written notice after the breach of any uncured material provision of the sublicense agreement, or after certain insolvency events.

Vadadustat

U.S. Collaboration with Otsuka Pharmaceutical Co. Ltd.

On December 18, 2016, we entered into a collaboration and license agreement with Otsuka, or the Otsuka U.S. Agreement, pursuant to which we agreed to co-exclusively collaborate with Otsuka with respect to the development and commercialization of vadadustat in the United States, subject to the approval of vadadustat by the FDA. We continue to lead the ongoing global Phase 3 development program for vadadustat. Under the Otsuka U.S. Agreement, subject to the terms of the Otsuka Funding Option, as described below, we control and retain final decision making authority with respect to, among other things, the development of vadadustat. Our obligations related to the conduct of the current global development plan include the associated manufacturing and supply services for vadadustat.

Under the terms of the Otsuka U.S. Agreement, Otsuka paid us an upfront payment of \$125.0 million and we expect Otsuka to provide additional funding of \$201.3 million or more, depending on the actual costs incurred, toward the vadadustat global Phase 3 development program. In addition, if the development costs exceed a certain threshold, or the Cost Threshold, then we may elect to require Otsuka to increase the aggregate percentage of the current global development costs it funds under the Otsuka U.S. Agreement and the Otsuka International Agreement, as defined below, from 52.5% to 80%, or the Otsuka Funding Option. In such event, the excess of the payments made under such election and Otsuka's allocated share of the current global development costs is fully creditable against future payments due to us under the arrangement, provided that future payments due to us may not be reduced by more than 50% in any calendar year and any remaining creditable amount above 50% in any calendar year will be applied to subsequent future payments until fully credited. In addition, decisions regarding certain development matters will be made jointly by us and Otsuka in accordance with the procedures set forth in the Otsuka U.S. Agreement. In September 2018, we exercised the Otsuka Funding Option, which will be effective when the Cost Threshold is exceeded. We estimate that the Cost Threshold will be exceeded in the second quarter of 2019. We are eligible to receive from Otsuka up to \$190.0 million in development and regulatory milestones and up to \$575.0 million in specified commercial milestones.

The Otsuka U.S. Agreement establishes a profit share for the commercialization of vadadustat in the United States. The parties will equally share all net sales of vadadustat in the United States, if approved, and each party will bear half

of all costs in the United States, including medical affairs, commercialization and manufacturing costs.

Under the Otsuka U.S. Agreement, we and Otsuka will jointly conduct, and will have equal responsibility for, all medical affairs and commercialization activities pursuant to plans agreed by the parties. We will remain responsible for manufacturing vadadustat. Additionally, the parties agreed not to promote, market or sell any competing product in the territory covered by the agreement.

International Collaboration with Otsuka Pharmaceutical Co. Ltd.

On April 25, 2017, we entered into a collaboration and license agreement with Otsuka, or the Otsuka International Agreement, pursuant to which we granted Otsuka an exclusive license for the development and commercialization of vadadustat in certain territory outside the United States. The territory covered by the Otsuka International Agreement includes the European Union, Russia, China, Australia, Canada, the Middle East and certain other countries, or the Otsuka International Territory, but excludes Latin America and previously licensed jurisdictions. Under the Otsuka International Agreement, Otsuka is responsible for certain development activities and commercializing vadadustat in the Otsuka International Territory, while we lead the ongoing global Phase 3 development program. Otsuka will fund a significant percentage of the costs of such global development program regardless of the total actual costs ultimately incurred. Subject to the terms of the Otsuka Funding Option, we retain final decision-making authority with respect to, among other things, the manufacture and supply of vadadustat in the Otsuka International Territory, the global Phase 3 development program, and the global brand strategy for vadadustat. Otsuka will have final decision-making authority with respect to certain development activities and commercialization matters in the Otsuka International Territory. Additionally, the parties agreed not to promote, market or sell any competing product in the territory covered by the agreement.

Under the terms of the Otsuka International Agreement, we expect Otsuka to pay us at least \$249.3 million, comprised of \$73.0 million that was paid upon execution of the Otsuka International Agreement and \$176.3 million or more, depending on actual costs incurred, of development funding. In addition, we are eligible to receive from Otsuka up to \$132.0 million in development and regulatory milestones and up to \$525.0 million in commercial milestones, subject to reduction as described above. Otsuka also agreed to make tiered, escalating royalty payments ranging from low double digits up to thirty percent of net sales of vadadustat within the Otsuka International Territory. In limited circumstances, upper tier royalties may be subject to reduction if the supply price charged by us to Otsuka for vadadustat exceeds certain agreed upon thresholds, and royalty payments may also be reduced if a generic product is launched, on a country-by-country basis. Otsuka may elect to conduct additional studies of vadadustat in the European Union, subject to our right to delay such studies based on our objectives outside the Otsuka International Territory. Otsuka will pay a percentage of the costs of any such studies, and we will pay its portion of the costs in the form of a credit against future amounts due to us under the Otsuka International Agreement.

Collaboration with Mitsubishi Tanabe Pharma Corporation

On December 11, 2015, we entered into a collaboration agreement with MTPC, or the MTPC Agreement, providing MTPC with exclusive development and commercialization rights to vadadustat in Japan and certain other Asian countries, or the MTPC Territory. In addition, we will supply vadadustat for both clinical and commercial use in the MTPC Territory, subject to MTPC's option to manufacture commercial drug product in the MTPC Territory.

We and MTPC agreed that, instead of including Japanese patients in our global Phase 3 program for vadadustat, MTPC would be the sponsor of a Phase 3 program for vadadustat in Japan. Following consultation with the Japanese Pharmaceuticals and Medical Devices Agency, or the PMDA, MTPC initiated its Phase 3 development program for vadadustat in Japan in the fourth quarter of 2017.

Under the terms of the MTPC Agreement, MTPC will make payments to us of up to \$245.0 million in the aggregate based on the achievement of certain development, regulatory and sales milestones, as well as tiered double-digit royalty payments of up to 20% on sales of vadadustat in the MTPC Territory, subject to reduction upon launch of a generic product on a country-by-country basis. MTPC is responsible for the costs of the Phase 3 program for vadadustat in Japan and will make no additional funding payments for our global Phase 3 program for vadadustat. Additionally, the development costs of approximately \$20.5 million for our Phase 2 studies in Japan were reimbursed to us by MTPC, of which the last remaining \$0.5 million was collected in the fourth quarter of 2018. We and MTPC

recently announced topline data from two pivotal Phase 3 clinical studies for vadadustat in Japan.

In addition, in September 2017 we agreed to provide MTPC with an option to access data from our global Phase 3 vadadustat program for payments to us of up to \$25.0 million.

Vifor Pharma License Agreement

On May 12, 2017, we entered into a License Agreement with Vifor Pharma, or the Vifor Agreement, pursuant to which we granted Vifor Pharma an exclusive license to sell vadadustat solely to FKC, an affiliate of Fresenius Medical Care North America, in the United States, subject to the approval of vadadustat for DD-CKD patients by the FDA, inclusion of vadadustat in a bundled reimbursement model, and payment by Vifor Pharma of a \$20 million milestone upon the occurrence of these two events. The Vifor Agreement is structured as a profit share arrangement between us and Vifor Pharma in which we will receive a majority of the profit from Vifor Pharma's sales of vadadustat to FKC in the United States. We will share the milestone payment and the revenue from the profit share with Otsuka pursuant to the Otsuka U.S. Agreement. We retain all rights to commercialize vadadustat for use in the NDD-CKD market and in other dialysis organizations in the United States, which will be done in collaboration with Otsuka if approved by the FDA.

Prior and subject to FDA approval of vadadustat, we and Vifor Pharma plan to enter into a commercial supply agreement for vadadustat pursuant to which we would supply all of Vifor Pharma's commercial requirements for vadadustat in the United States. In addition, pursuant to the Vifor Agreement, Vifor Pharma entered into supply agreements that govern the terms pursuant to which Vifor Pharma would supply vadadustat to FKC for use in patients at its dialysis centers, subject to FDA approval; however, FKC is not obligated to utilize vadadustat in its clinics. During the term of the Vifor Agreement, Vifor Pharma will not sell to FKC or its affiliates any HIF product that competes with vadadustat in the United States.

Janssen Pharmaceutica NV Research and License Agreement

On February 9, 2017, we entered into a Research and License Agreement, the Janssen Agreement, pursuant to which Janssen granted us an exclusive license under certain intellectual property rights to develop and commercialize worldwide certain HIF-PH-targeted compounds.

Under the terms of the Janssen Agreement, Janssen granted us a license for a three-year research term to conduct research on Janssen's HIF compound portfolio, unless we elect to extend such research term for up to two additional one-year periods upon payment of an extension fee. During the research term, we may designate one or more compounds as candidates for development and commercialization. Once a compound is designated for development and commercialization, we will be solely responsible for the development and commercialization of the compound worldwide at our own cost and expense.

Under the terms of the Janssen Agreement, we paid an upfront payment of \$1.0 million in cash to Janssen and issued a warrant to purchase 509,611 shares of our common stock, the fair value of which was approximately \$3.4 million. In addition, Janssen could be eligible to receive up to an aggregate of \$16.5 million from us in specified development milestone payments on a product-by-product basis. Janssen will also be eligible to receive up to \$215.0 million from us in specified commercial milestones as well as tiered, escalating royalties ranging from a low to mid-single digit percentage of net sales, on a product-by-product basis and subject to reduction upon expiration of patent rights or the launch of a generic product in the territory.

Janssen also has a right of first offer to engage in exclusive negotiations with us to develop and commercialize certain products developed by us containing compounds for the treatment of inflammatory bowel disease.

Intellectual Property

The proprietary nature of, and protection for, our products, product candidates and our discovery programs, processes and know-how are important to our business. Our policy is to seek to protect our proprietary position by, among other methods, filing 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 know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position. Additionally, we may benefit from a variety of statutory frameworks in the United States, Europe and other countries that provide periods of non-patent-based exclusivity for qualifying molecules. See “—Regulatory Matters.”

Our commercial success will depend in part on obtaining and maintaining patent protection of our current products as well as current and future product candidates, methods of their use and the methods used to develop and manufacture them, as well as successfully defending these patents against third-party challenges. Our ability to stop third parties from making, using, selling, offering to sell or importing our products depends on the extent to which we have rights under valid and enforceable patents that cover these activities. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be

commercially useful in protecting our product candidates, discovery programs and processes. Even once patents successfully issue, third parties may challenge the validity, enforceability, inventorship, or scope thereof, which may result in such patents being narrowed, invalidated or held not infringed or unenforceable. For this and more comprehensive risks related to our intellectual property, please see “Risk Factors—Risks Related to Our Intellectual Property.”

Individual patents extend for varying periods of time depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued from applications filed in the United States are effective for 20 years from the earliest filing date of a United States non-provisional application or an international application filed under the Patent Cooperation Treaty. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of the FDA regulatory review period, however, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest international filing date. Patent term recapture for loss of term as a result of the regulatory review period is available in some foreign jurisdictions. In the United States, a patent’s term may also be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent.

Changes in either the patent laws or interpretations of patent laws in the United States and other countries can diminish our ability to protect our inventions and enforce our intellectual property rights. Accordingly, we cannot predict the breadth or enforceability of claims that may be granted in our patents or in third-party patents. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Our ability to maintain and solidify our proprietary position for our drugs and technology will depend on our success in obtaining effective claims and enforcing those claims once granted. We do not know whether any of the patent applications that we may file or license from third parties will result in the issuance of any patents. The issued patents that we own or license or may receive or acquire in the future may be challenged, invalidated or circumvented, and the rights granted under any issued patents may not provide us with sufficient protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may be able to independently develop and commercialize similar drugs or duplicate our technology, business model or strategy without infringing our patents. Because of the extensive time required for clinical development and regulatory review of a drug we may develop, it is possible that, before any of our drugs can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent. The patent positions for Auryxia and vadadustat are summarized below.

Auryxia Patent Portfolio

Pursuant to our license with Panion & BF Biotech, Inc., or Panion, we have the exclusive rights under a series of patents and patent applications to commercialize Auryxia worldwide, excluding certain Asian-Pacific countries. These patents and patent applications include claims directed to compositions of matter, pharmaceutical compositions, methods of treatment, as well as methods for the manufacture of Auryxia.

Our patent rights include fourteen issued U.S. patents listed in the Orange Book covering the composition of matter, method of treating hyperphosphatemia, and pharmaceutical compositions of Auryxia. The expected expiration dates for these patents are between 2020 and 2030 plus any additional patent term extensions that may be available. These patents are currently being asserted against several generic companies for patent infringement. See Part I, Item 3. Legal Proceedings.

Pursuant to our sublicense with our Japanese partner, Japan Tobacco Inc., or JT, and its subsidiary, Torii Pharmaceutical Co. Ltd., or Torii, we have exclusively sublicensed certain Japanese patent rights to JT and Torii. These sublicensed rights include several Japanese patents and pending patent applications with composition of matter claims and methods of use claims covering Riona, the trade name under which JT and Torii market ferric citrate in Japan. The expected expiration dates for these patents are between 2022 and 2026. To date, to our knowledge, no contested proceedings or third-party claims have been lodged against any of these Japanese patents.

On November 25, 2015, a third party filed an opposition to our issued European Patent No. 1 931 689, or the '689 EP Patent, in the European Patent Office ("EPO"). During the oral proceedings, which took place on June 27, 2017, the Opposition Division of the EPO revoked the '689 EP Patent. On December 6, 2017, we filed an Appeal of the decision of the Opposition Division, which is presently pending. According to European practice, the revocation of the patent is stayed until an appeal is finally resolved. We anticipate the appeal will take a few years to resolve, during which time the patent will remain in force.

On December 23, 2016, a third party filed an opposition to our issued European Patent No. 1 978 807, or the '807 EP Patent, in the EPO. During the oral proceedings, which took place on June 8, 2018, the Opposition Division of the EPO maintained the '807 EP Patent as granted. This decision resulted in the maintenance of all the claims of the patent, including claims directed to the use of ferric citrate for preventing, reversing, maintaining or delaying progression of chronic kidney disease. On November 16, 2018, the third party filed an appeal of the decision of the Opposition Division, which is presently pending. We anticipate the appeal will take a few years to resolve.

Vadadustat Patent Portfolio

We hold eight issued patents covering the composition of matter, polymorph, method of treating anemia, and pharmaceutical compositions of vadadustat in the United States and additional patents issued or pending in many other major jurisdictions worldwide, including Europe, Japan, China, South Korea, Brazil, Mexico, Russia, Israel and India. The expected expiration dates for these patents are between 2027 and 2034 plus any extensions or adjustments of term available under national law.

In July 2011, a third party filed an opposition to our issued European Patent No. 2044005, or the '005 EP Patent. During the oral proceedings, which took place on April 10, 2013, the Opposition Division of the European Patent Office maintained the '005 EP Patent based on the third auxiliary request filed during the oral proceedings. This decision resulted in the maintenance of a claim directed to a compound chosen from a group of eight compounds, including vadadustat, as well as claims to compositions and methods for treating various diseases, including, but not limited to, anemia. Both parties appealed the decision of the Opposition Division. On February 27, 2018, we withdrew the '005 EP Patent from appeal and filed a divisional patent application to pursue a focused claims set that includes claims for vadadustat, as well as pharmaceutical compositions and methods of treating anemia. We cannot be assured that such claims in the divisional patent application will be granted by the European Patent Office. If such claims are not granted, or the scope of the claims is significantly narrowed, we may not be able to adequately protect our rights, provide sufficient exclusivity, or preserve our competitive advantage.

In September 2018, Dr. Reddy's Laboratories Limited filed an opposition to our issued Indian Patent No. 287720, or the '720 IN Patent, in the Indian Patent Office.

We also hold patents and patent applications directed to processes for manufacturing vadadustat, dosing regimens, formulations, and various other aspects relating to the treatment of anemia using vadadustat that are expected to expire between 2032 and 2036 exclusive of possible patent term extensions or adjustments.

Other Intellectual Property Rights

We depend upon trademarks, trade secrets, know-how and continuing technological advances to develop and maintain our competitive position. To maintain the confidentiality of trade secrets and proprietary information, we require our employees, scientific advisors, consultants and collaborators, upon commencement of a relationship with us, to execute confidentiality agreements and, in the case of parties other than our research and development collaborators, to agree to assign their inventions to us. These agreements are designed to protect our proprietary information and to grant us ownership of technologies that are developed in connection with their relationship with us. These agreements may not, however, provide protection for our trade secrets in the event of unauthorized disclosure of such information.

In addition to patent protection, we may utilize orphan drug regulations, pediatric exclusivity or other provisions of the Food, Drug and Cosmetic Act of 1938, as amended, or FDCA, such as new chemical entity exclusivity or new formulation exclusivity, to provide market exclusivity for a drug candidate. In the United States, the FDA has the authority to grant additional data protection for approved drugs where the sponsor conducts specified testing in pediatric or adolescent populations. If granted, this pediatric exclusivity may provide an additional six months which are added to the term of data protection as well as to the term of a relevant patent, to the extent these protections have not already expired. We may also seek to utilize market exclusivities in other territories, such as in the EU. We cannot assure that our drug products or any drug candidates we may acquire or in-license, will obtain such orphan drug designation, pediatric exclusivity, new chemical entity exclusivity or any other market exclusivity in the United States, EU or any other territory, or that we will be the first to receive the respective regulatory approval for such drugs so as to be eligible for any market exclusivity protection.

Know-How

In addition to patents, we rely upon unpatented know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, employees and consultants and invention assignment provisions in the confidentiality agreements with our employees. These agreements are designed to protect our proprietary information and, in the case of the invention assignment provisions, to grant us ownership of technologies that are developed by our employees. These agreements may be breached, and we may not have adequate remedies for any breach.

To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

The Hatch-Waxman Act

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant's product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are usually not required to conduct, or submit results of, nonclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to make certain certifications to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed (ii) the listed patent has expired (iii) the listed patent has not expired but will expire on a particular date and approval is sought after patent expiration or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA applicant may also elect to submit a Section viii statement, certifying that its proposed ANDA label does not contain or carve out any language regarding the patented method-of-use, rather than certify to a listed method-of-use patent.

If the applicant does not challenge the listed patents, the ANDA will not be approved until all the listed patents claiming the referenced product have expired. A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months from receiving the Paragraph IV certification, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA applicant. Also, the ANDA will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Exclusivity

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains an active moiety that has not been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which time the FDA cannot accept any ANDA seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which the FDA cannot approve an ANDA for a generic drug that includes such changes.

An ANDA may be submitted one year before NCE exclusivity expires if a Paragraph IV certification is filed. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA may be filed before the expiration of the exclusivity period.

On August 23, 2018, Keryx submitted a Citizen Petition requesting, inter alia, that FDA recognize that Auryxia is eligible for five years of NCE exclusivity based on its novel active ingredient and for three years exclusivity for the IDA Indication. On January 19, 2019, FDA responded that Auryxia is eligible for a three-year exclusivity period for the IDA Indication, which expires on November 6, 2020. FDA, however, denied the NCE exclusivity based on its determination that Auryxia contains a previously-approved active moiety (ferric cation). FDA's decision on the Citizen Petition is subject to further review both within FDA and in the courts. On February 21, 2019, Akebia filed a Petition for Reconsideration of FDA's decision on the NCE determination for Auryxia.

Patent Term Extension

After NDA approval, owners of relevant drug patents or their agents may apply for up to a five-year patent extension for delays caused by FDA regulatory review. The allowable patent term extension is calculated as half of the drug's testing phase which is the time between IND submission and NDA submission, and all of the review phase, which is the time between NDA submission and approval, up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

We have filed applications under the patent term extension provisions of 35 U.S.C. § 156 for U.S. Patent Nos. 8,299,298, 8,093,423, 7,767,851, 5,753,706, and 8,338,642 each of which covers Auryxia for delays caused by FDA regulatory review. If granted, we can utilize the patent term extension on one of these patents, however, we cannot assure you that we can obtain any extension of the term of these patents. Upon expiration of these patents, competitors who obtain the requisite regulatory approval may potentially offer products with the same composition and/or method of use as our product, so long as the competitors do not infringe any other patents that we may own or license.

For patents that might expire before a determination regarding patent term extension, the patent owner or its agent may request an interim patent term extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. We have filed for and received interim patent term extension in accordance with 35 U.S.C. § 156(e)(2) for U.S. Patent No. 5,753,706, which currently has an expiration date of February 3, 2020.

In addition, certain jurisdictions outside of the U.S., including Japan, have provisions that provide for patent term extension. In October 2014, following the regulatory approval of Riona in Japan, the Japan Patent office granted the patent term extensions filed by our sublicensee, JT, for Japanese Patents Nos. 4964585 and 4173553. As a result of the extension of patent term, Japanese Patents Nos. 4964585 and 4173553 will expire in November 2025 and November 2022, respectively.

Third-Party Filings

We are aware of certain United States patents issued to FibroGen, Inc., or FibroGen, directed to, among other things, purportedly new methods of using previously known heterocyclic carboxamide compounds for purposes of treating or affecting specified conditions. We do not believe these currently issued FibroGen United States patents will prevent us from commercializing vadadustat in the United States for the treatment of anemia due to CKD; nor do we make any admission that any of such patents are valid or enforceable. Under United States law, a person may be able to patent a discovery of a new way to use a previously known compound, even if such compound itself is patented, provided the newly discovered use is novel and non-obvious. Such a method-of-use patent, however, if valid, only protects the use of a claimed compound for the specified methods claimed in the patent. This type of patent does not prevent persons from using the compound for any previously known use of the compound. Further, this type of patent does not prevent persons from making and marketing the compound for an indication that is outside the scope of the patented method. We are not aware of any valid United States patents issued to FibroGen that claim methods of using any of our product candidates for purposes of inhibiting HIF-PHs for the treatment of anemia secondary to CKD.

We filed an opposition in Europe against FibroGen's European Patent No. 1463823, or the '823 EP Patent, and an oral proceeding took place March 8 and 9, 2016. Following the oral proceeding, the Opposition Division of the EPO ruled that the patent as granted did not meet the requirements for patentability under the European Patent Convention and, therefore, revoked the patent in its entirety. FibroGen has appealed that decision and the appeal process is expected to take several years. Likewise, with regard to the invalidity proceeding that we filed in Japan against certain claims of FibroGen's Japanese Patent No. 4804131, or the '131 JP Patent, which is the Japanese counterpart to the '823 EP Patent, the Japan Patent Office, or JPO, issued a preliminary decision finding all of the challenged claims to be invalid. FibroGen subsequently amended the claims and the JPO accepted the amendments. The resulting '131 JP Patent does not cover vadadustat or any pyridine carboxamide compounds. To date, FibroGen has been unsuccessful in its attempts to obtain a patent in the United States covering the same claim scope as it obtained initially in Europe and Japan in the '823 EP Patent and '131 JP Patents. In the event FibroGen were to obtain such a patent in the United States, we may decide to challenge the patent as we have done in Europe and Japan.

On May 13, 2015, May 20, 2015 and July 6, 2015, we filed oppositions to FibroGen's European Patent Nos. 2322155, or the '155 EP Patent, 1633333, or the '333 EP Patent, and 2322153, or the '153 EP Patent requesting the patents be revoked in their entirety. These related patents claim, among other things, various compounds that either stabilize HIF or inhibit a HIF hydroxylase or a HIF prolyl hydroxylase for treating or preventing various conditions, including, inter alia, iron deficiency, microcytosis associated with iron deficiency, anemia of chronic disease, anemia wherein the subject has a transferrin saturation of less than 20%, anemia refractory to treatment with exogenously administered erythropoietin, or EPO, and microcytosis in microcytic anemia. Such method of use patents do not prevent persons from using the compound for other uses, including any previously known use of the compound. In particular, these patents do not claim methods of using any of our product candidates for purposes of inhibiting hypoxia-inducible factor prolyl hydroxylases, or HIF-PHs, for the treatment of anemia secondary to CKD. While we do not believe these patents will prevent us from commercializing vadadustat for the treatment of anemia secondary to CKD, we filed these oppositions to provide us and our collaborators with maximum flexibility for developing vadadustat and our pipeline of HIF-PH compounds.

Oppositions to the '155 EP Patent and the '153 EP Patent were also filed by Glaxo Group Limited, or Glaxo, and by Bayer Intellectual Property GmbH, Bayer Pharma Aktiengesellschaft, and Bayer Animal Health GmbH, or, collectively, Bayer.

With regards to the opposition that we filed in Europe against the '333 EP Patent, an oral proceeding took place on December 8 and 9, 2016. Following the oral proceeding, the Opposition Division of the EPO ruled that the patent as granted did not meet the requirements for patentability under the European Patent Convention and, therefore, revoked the patent in its entirety. On December 9, 2016, FibroGen filed a notice to appeal the decision to revoke the '333 EP Patent.

In oral proceedings held on May 29, 2017, regarding the '155 EP Patent, the Opposition Division of the EPO ruled that the '155 EP Patent as granted did not meet the requirements for patentability under the European Patent Convention and, therefore, revoked the patent in its entirety. FibroGen filed a notice to appeal the decision to revoke the '155 EP Patent on May 29, 2017.

Subsequently, in related oral proceedings held on May 31, 2017 and June 1, 2017 for the '153 EP Patent, the Opposition Division of the EPO maintained the patent after FibroGen significantly narrowed the claims to an indication for which vadadustat is not intended to be developed. We and Glaxo separately filed notices to appeal the decision to maintain the '153 EP Patent on November 9, 2017. Bayer filed a notice to appeal the decision on November 14, 2017.

Competition

The pharmaceutical and biotechnology industries are highly competitive. Our competitors include pharmaceutical companies and biotechnology companies, as well as universities and public and private research institutions. In addition, companies that are active in different but related fields represent substantial competition for us. Many of our competitors have significantly greater capital resources, larger research and development staffs and facilities and greater experience in drug development, regulation, manufacturing and marketing than we do. These organizations also compete with us to recruit qualified personnel, attract partners for joint ventures or other collaborations, and license technologies that are competitive with ours. To compete successfully in this industry, we must identify novel and unique drugs or methods of treatment and then complete the development of those drugs as treatments in advance of our competitors.

Auryxia

Hyperphosphatemia Competition

Auryxia is competing in the Hyperphosphatemia Indication in the United States with other FDA-approved phosphate binders such as Renagel® (sevelamer hydrochloride) and Renvela® (sevelamer carbonate), both marketed by Genzyme Corporation (a wholly-owned subsidiary of Sanofi), PhosLo® and Phoslyra® (calcium acetate), marketed by Fresenius Medical Care North America, Fosrenol® (lanthanum carbonate), marketed by Shire Pharmaceuticals Group plc, and Velporo® (sucroferric oxyhydroxide), marketed by Fresenius Medical Care North America, as well as over-the-counter calcium carbonate products such as TUMS® and metal-based options such as aluminum, lanthanum and magnesium. Many of the phosphate binders listed above are now also available in generic forms. In addition, other phosphate binders are in development, including OPKO Health Inc.'s Alphenra® Tablets (fermagate tablets) and Ardelyx, Inc.'s tenapanor, that may impact the market for Auryxia.

Iron Deficiency Anemia Competition

Auryxia is competing in the IDA Indication in the United States with over-the-counter oral iron, other prescription oral iron formulations, including ferrous gluconate, ferrous fumarate, and polysaccharide iron complex, and IV iron

formulations, including Feraheme[®] (ferumoxytol injection), Venofer[®] (iron sucrose injection), Ferrlicit[®] (sodium ferric gluconate complex in sucrose injection), Injectafer[®] (ferric carboxymaltose injection), and Triferic[®] (ferric pyrophosphate citrate).

In addition, other new therapies are in development for the treatment of IDA that may impact the market for Auryxia, such as Shield Therapeutics' Ferracru[®] (ferric maltol), which is currently approved in Europe for IDA and is seeking FDA approval in the United States.

Vadadustat

If vadadustat is approved and launched commercially, competing branded drugs may include EPOGEN[®] (epoetin alfa) and Aranesp[®] (darbepoetin alfa), both commercialized by Amgen, Procrit[®] (epoetin alfa) and Eprex[®] (epoetin alfa), commercialized by Johnson & Johnson in the United States and Europe, respectively, and Mircera[®] (methoxy PEG-epoetin beta), commercialized by Vifor Pharma in the United States and Roche Holding Ltd. outside the United States. We may also face competition from potential new anemia therapies. There are several other HIF-PHI product candidates in various stages of active development for anemia indications that may be in direct competition with vadadustat if and when they are approved and launched commercially. These candidates are being developed by such companies as FibroGen, Japan Tobacco International, GlaxoSmithKline plc and Bayer HealthCare AG. FibroGen, together with its collaboration partners, Astellas Pharma Inc. and AstraZeneca PLC, is currently in global Phase 3 clinical

development of its product candidate, roxadustat. GlaxoSmithKline plc is currently in global Phase 3 clinical development of its product candidate, daprodustat. Japan Tobacco International and Bayer HealthCare AG are currently in Phase 3 clinical development of their product candidates in Japan. Some of these product candidates may launch in certain Asian markets as early as 2019. In addition, certain companies are developing potential new therapies for renal-related diseases that could potentially reduce injectable ESA utilization and thus limit the market potential for vadadustat if they are approved and launched commercially. Other new therapies are in development for the treatment of conditions inclusive of renal anemia that may impact the market for anemia-targeted treatment.

A biosimilar is a biologic product that is approved based on demonstrating that it is highly similar to an existing, FDA-approved branded biologic product. The patents for the existing, branded biologic product must expire in a given market before biosimilars may enter that market without risk of being sued for patent infringement. In addition, an application for a biosimilar product cannot be approved by the FDA until 12 years after the existing, branded product was approved under a Biologics License Application, or BLA. The patents for epoetin alfa, an injectable ESA, expired in 2004 in the European Union, and the remaining patents expired between 2012 and 2016 in the United States. Because injectable ESAs are biologic products, the introduction of biosimilars into the injectable ESA market in the United States will constitute additional competition for vadadustat if we are able to obtain approval for and commercially launch our product. Several biosimilar versions of injectable ESAs are available for sale in the European Union. In the United States, Pfizer's biosimilar version of injectable ESAs, Retacri® (epoetin alfa-epbx), was approved by the FDA in May 2018 and launched in November 2018 by Vifor Pharma.

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, sales, pricing, reimbursement, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory requirements, require the expenditure of substantial time and financial resources.

Review and Approval of Drug Products in the United States

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations and consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, or ICH, requirements;

- submission to the FDA of an IND, which must be reviewed and active by the FDA before human clinical trials may begin;
- approval by an independent local or central institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed product candidate for each indication;
- preparation and submission to the FDA of a new drug application, or NDA, requesting marketing for one or more proposed indications;
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product candidate, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product candidate's identity, strength, quality and purity;

satisfactory completion of FDA audits of clinical trial sites and records to assure compliance with GCPs and good practices, or GxPs, the integrity of the clinical data and that adequate controls and oversight are in place regarding manufacturing, clinical trials, pharmacovigilance, safety, data management, vendor oversight, collection and reporting of serious adverse events and other activities;

payment of user fees and securing FDA approval of an NDA; and

compliance with any post-approval requirements and/or commitments, including the potential requirement to implement a risk evaluation and mitigation strategy, or REMS, and potentially post-market requirement, or PMR, and commitment, or PMC, studies.

Preclinical Studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as in vitro and animal studies to assess the safety and activity of the product candidate for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, will likely continue after the IND is submitted through the time of the NDA submission.

The IND and IRB Processes

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their voluntary informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped through interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be obtained prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. As a required component of the IND application, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the submission of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold or require that the sponsor amend the clinical protocol to include additional safety measurements. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin (or resume if the clinical trial had been ongoing at the time a clinical hold was imposed).

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the

clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls, or CMC.

A sponsor may choose, but is not required, to conduct a foreign clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain FDA regulatory requirements in order to use the trial as support for an IND or application for marketing approval. These requirements to protect the rights, welfare, and safety of patients are also stipulated in applicable ICH guidance.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct a continuing review and reapprove the trial at least annually. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data monitoring committee, or DMC. DMCs may be charged with monitoring efficacy, safety, and/or study conduct. A DMC provides a recommendation for whether or not a clinical trial should move forward at designated check points based on available data from the trial. A recommendation by a DMC to suspend or terminate development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its website, <https://clinicaltrials.gov/>.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with initiation, conduct, or completion of clinical investigations that could support marketing approval of the product candidate or otherwise compromise the potential development of the product candidate.

On December 13, 2016, the 21st Century Cures Act, or Cures Act, established (and the 2017 Food and Drug Administration Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly

available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its product candidates available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in four sequential phases, which may overlap or be combined:

Phase 1. The product candidate is initially introduced into a small number of healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition (e.g., cancer) and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

Phase 2. The product candidate is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product candidate for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3. These clinical trials are commonly referred to as “pivotal” studies, which denote a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a product candidate. The product candidate is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product candidate for approval, identify adverse effects, establish the overall risk-benefit profile of the product candidate and to provide adequate information for the labeling of the product candidate.

Phase 4. Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials conducted under the IND must be submitted at least annually to the FDA and, more frequently, if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

The FDA or the sponsor or the data monitoring committee 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.

Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB’s requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Under the Pediatric Research Equity Act of 2003, or PREA, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The legislation requires the FDA to meet with drug sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after the FDA’s receipt of the study plan. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements.

Submission of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things are submitted to the FDA as part of an NDA requesting approval to market the product candidate for one or more indications. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is \$2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2019 is \$309,915. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for product candidates with orphan designation and a waiver for certain small businesses.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. This is known as the filing decision. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to certain performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. A product that has been designated as a breakthrough therapy may also be eligible for review within six months if supported by clinical data at the time of submission of the NDA. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing such as active pharmaceutical ingredients, finished drug product manufacturing, control testing laboratories, as well as packaging and labeling facilities. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. The applicant of the NDA may also have their records, processes, procedures, training, and other aspects reviewed during an inspection. The FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain drug applications, including applications for drugs in a shortage or drugs for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks.

Finally, the FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy, Priority Review

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track

application does not begin until the last section of the NDA is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, in 2012, Congress enacted the Food and Drug Administration Safety and Improvement Act. This law established a new regulatory scheme allowing for expedited review of products designated as “breakthrough therapies.” A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed drug represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's review clock goal for taking action on a marketing application from ten months to six months. For new chemical entities, or NCEs, the review clock starts after the NDA is filed with a total clock of twelve and eight months, respectively.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, analyses, or information in order for the FDA to reconsider the application. This may include the requirement to conduct another clinical study or studies. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements and Commitments

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. In addition, conditions of NDA approval may include sponsor agreement to PMR or PMC studies, which are designed to further assess drug safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. These may include additional studies, registries, data collection, analyses, and/or information.

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the

establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, or complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
 - product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a product candidate's safety or effectiveness are prohibited before the product candidate is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA or in a manner that is inconsistent with the product's prescribing information. In the United States, healthcare professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific conditions, for a manufacturer to engage in nonpromotional, truthful and non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. In addition, companies may also promote information that is consistent with the prescribing information and have the ability to proactively speak to formulary committee members of payors regarding data for an unapproved drug or unapproved uses of an approved drug under some relatively recent guidance from the FDA. However, if a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products and drug samples are subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are “abbreviated” because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is “bioequivalent” to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if “the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug.” Upon approval of an ANDA, the FDA indicates whether the generic product is “therapeutically equivalent” to the RLD in its publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” also referred to as the “Orange Book.” Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA’s designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight months for a drug that has three or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA’s drug shortage list. The new legislation also authorizes FDA to expedite review of “competitor generic therapies” or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant’s product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same

extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Pediatric Studies and Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product is effective in the pediatric population studied, rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which an ANDA or 505(b)(2) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by the proposed product.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Drug Products Outside the United States

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Clinical Trial Approval in the European Union

Requirements for the conduct of clinical trials in the European Union including GCP are set forth in the Clinical Trials Directive 2001/20/EC, or the Clinical Trials Directive, and the GCP Directive 2005/28/EC, or the GCP Directive. Pursuant to the Clinical Trials Directive and the GCP Directive 2005/28/EC, as amended, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the EU member states. Under this system, approval must be obtained from the competent national authority of each EU member state in which a study is planned to be conducted. To this end, a clinical trial application, or CTA, is submitted to the local competent authority in each country (or member state) where the clinical trial is being conducted, which must be supported by an investigational medicinal product dossier, or IMPD, and further supporting information prescribed by Clinical Trials Directive and the GCP Directive and other applicable guidance documents. These documents may be amended and/or updated by the EC at any time. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application in that country.

In April 2014, the EU passed the new Clinical Trials Regulation (EU) No 536/2014, or the new Clinical Trials Regulation, which is set to replace the current Clinical Trials Directive. To ensure that the rules for clinical trials are identical throughout the European Union, the new EU clinical trials legislation was passed as a regulation that is directly applicable in all EU member states. All clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive until the new Clinical Trials Regulation becomes applicable. According to the current plans of the European Medicines Agency, or EMA, the new Clinical Trials Regulation is expected to become applicable in 2019. The Clinical Trials Directive will, however, still apply three years from the date of entry into application of the new Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for old system.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trial in the European Union. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the EU portal; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states; a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts (Part I is assessed jointly by all member states concerned, and Part II is assessed separately by each member state concerned); strictly defined deadlines for the assessment of clinical trial applications; and the involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Clinical Trials Regulation.

As in the United States, there are similar requirements in the European Union for posting clinical trial information online at the website, <https://eudract.ema.europa.eu/>, and in other countries as well.

PRIME Designation in the European Union

In March 2016, the EMA launched an initiative, the PRIority MEDicines, or PRIME, scheme, to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIME scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated agency contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies, or CAT, are appointed early in the PRIME scheme, facilitating increased understanding of the product at the EMA's committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain marketing approval of a product under EU regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a

centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various EU member states where such product has not received marketing approval in any EU member state before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Within this framework, manufacturers may seek approval of hybrid medicinal products under Article 10(3) of Directive 2001/83/EC. Hybrid applications rely, in part, on information and data from a reference product and new data from appropriate pre-clinical tests and clinical trials. Such applications are necessary when the proposed product does not meet the strict definition of a generic medicinal product, or bioavailability studies cannot be used to demonstrate bioequivalence, or there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product. In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC, as amended by Directive 2003/63/EC.

Hybrid medicinal product applications have automatic access to the centralized procedure when the reference product was authorized for marketing via that procedure. Where the reference product was authorized via the decentralized procedure, a hybrid application may be accepted for consideration under the centralized procedure if the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a community authorization for the medicinal product is in the interest of patients at the community level.

A marketing authorization may be granted only to an applicant established in the European Union. Regulation (EC) No. 1901/2006, or Pediatric Regulation, provides that prior to obtaining a marketing authorization in the European Union, an applicant must demonstrate compliance with all measures included in a Pediatric Investigation Plan, or PIP, approved by the Pediatric Committee of the EMA, or PDCO, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP. The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which marketing authorization is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the marketing authorization is obtained in all member states of the European Union and study results are included in the product information, even when negative, the product is eligible for six months' supplementary protection certificate extension. For orphan-designated medicinal products, the 10-year period of market exclusivity is extended to 12 years.

Periods of Authorization and Renewals in the European Union

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the relevant EU member state. To that end, the marketing authorization holder must provide the EMA or the relevant competent authority of the EU member state with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the relevant competent authority of the EU member state decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any marketing authorization that is not followed by the marketing of the medicinal product on the EU market (in the case of the centralized procedure) or on the market of the EU member state which delivered the marketing authorization within three years after authorization ceases to be valid.

Regulatory Data Exclusivity in the European Union

In the European Union, innovative medicinal products authorized in the European Union on the basis of a full marketing authorization application (as opposed to an application for marketing authorization that relies on data available in the marketing authorization dossier for another, previously approved, medicinal product) are entitled to eight years of data exclusivity. During this period, applicants for authorization of generics of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product. Innovative medicinal products are also entitled to ten years' market

exclusivity. During this ten-year period no generic of this medicinal product can be placed on the EU market. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Pediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the European Union, applicants must demonstrate compliance with all measures included in an EMA approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are set forth in the Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP. If an applicant obtains a marketing authorization in all EU member states, or a marketing authorization granted in the Centralized Procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom (U.K.) voted in favor of leaving the European Union (commonly referred to as “Brexit”). Thereafter, on March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The United Kingdom has a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the European Union. If no formal withdrawal agreement is reached between the United Kingdom and the European Union, then it is expected the United Kingdom's membership of the European Union will automatically terminate two years after the submission of the notification of the United Kingdom's intention to withdraw from the European Union. Discussions between the United Kingdom and the European Union focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date in these negotiations and ongoing uncertainty within the UK Government and Parliament sustains the possibility of the United Kingdom leaving the European Union on March 29, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

Since the regulatory framework for pharmaceutical products in the U.K. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the U.K. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the U.K.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Pharmaceutical Coverage, Pricing and Reimbursement

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product candidate could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

For example, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration, or Administration, have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' advertisements to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D

plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. It is expected that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Outside the United States, ensuring adequate coverage and payment for a product also involves challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require a clinical trial that compares the cost effectiveness of a product to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians, teaching hospitals and other healthcare providers, patient privacy laws and regulations, and other healthcare laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to be made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government.
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

• the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

• the U.S. Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;

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- the federal transparency requirements, known as the federal Physician Payments Sunshine Act (renamed the Open Payments Act), under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;
- the PDMA and its implementation regulations, as well as the DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by third-party payors, including private insurers, and state gift ban and disclosure law requirements that differ from the federal Physician Payments Sunshine Act in terms of the nature and type of transfers of value that are reportable and the types of covered recipients.
- Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines, such as the Pharmaceutical Research and Manufacturers of America Code on Interactions with Health Care Professionals, known as the PhRMA Code. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare.

In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has not been clearly defined. The Affordable Care Act provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, is no longer effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer

Americans to be insured by 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole”. Congress will likely consider other legislation to replace elements of the ACA during the next Congressional session.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Laws Relating to Foreign Trade

We are subject to various federal and foreign laws that govern our international business practices. These laws include the FCPA which prohibits U.S. companies and their representatives from paying, offering to pay, promising, or authorizing the payment of anything of value to any foreign government official, government staff member, political party, or political candidate for the purposes of obtaining or retaining business, or to otherwise obtain favorable treatment or influence a person working in an official capacity. In many countries, the health care professionals we regularly interact with may meet the FCPA's definition of a foreign government official. Additionally, interactions with or on the part of our partners, collaborators, contract research organizations, vendors or other agents may also implicate the FCPA. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect their transactions and to devise and maintain an adequate system of internal accounting controls. Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents unique challenges in the pharmaceutical industry because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments made by pharmaceutical companies to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Our international operations could also be subject to compliance with national laws of other countries, such as the United Kingdom Bribery Act of 2010, or U.K. Bribery Act. The U.K. Bribery Act applies to any company "carrying on business" in the United Kingdom, irrespective of where the offending conduct occurs. The U.K. Bribery Act applies to bribery activities both in the public and private sector and prohibits the provision of an "advantage" intended to induce or reward "improper performance" of the recipient's function. The failure by a company to prevent third parties from providing a bribe on its behalf could also constitute an offense. Penalties under the U.K. Bribery Act include potentially unlimited fines for companies and criminal sanctions for corporate officers under certain circumstances.

There are local antibribery and anticorruption laws in countries where we are conducting clinical trials, such as Brazil and Russia, and many of these also carry the risk of significant financial or criminal penalties. Our clinical trial operations could also result in enforcement actions by U.S., U.K., or other governmental authorities. There are also trade laws within the United States and in other regions that regulate the sale, purchase, import, export, reexport, transfer and shipment of goods, currency, products, materials, services and technology. Violations of these laws can lead to serious consequences, including substantial fines.

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, 2018, we had 325 employees, 324 of whom were full-time. None of our employees is represented by any collective bargaining unit. We believe that we maintain good relations with our employees.

Available Information

Our principal executive offices are located at 245 First Street, Cambridge, Massachusetts 02142. Our telephone number is (617) 871-2098. Our website address is www.akebia.com. The information on our website or that may be accessed by links on our website is not incorporated by reference into this Form 10-K. We make available, free of charge and through our website, our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and any amendments to any such reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after they are electronically filed with or furnished to the U.S. Securities and Exchange Commission.

Item 1A. Risk Factors

We face a variety of risks and uncertainties in our business. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also become important factors that affect our business. If any of the following risks occurs, our business, financial statements and future growth prospects could be materially and adversely affected.

Risks Related to our Merger with Keryx

We may fail to realize the anticipated benefits of our merger with Keryx, those benefits may take longer to realize than expected, and we may encounter significant integration difficulties and liabilities, which may have a material adverse effect on our business and financial position.

On December 12, 2018, we completed a merger, or the Merger, whereby Keryx Biopharmaceuticals, Inc., or Keryx, became a wholly owned subsidiary of ours. There can be no assurance that we will realize the full benefit of the anticipated synergies and cost savings relating to the Merger or that these benefits will be realized within the expected time frames or at all. Our ability to realize the anticipated benefits of the Merger will depend, to a large extent, on our ability to continue to integrate our business and Keryx's business and realize anticipated growth opportunities and synergies. If we are unable to successfully integrate the businesses, or integrate them in a timely fashion, we may face material adverse effects including, but not limited to (i) diversion of the attention of management and key personnel and potential disruption of our ongoing business, (ii) the loss of employees, (iii) challenges of managing a larger company, including challenges of conforming standards, controls, procedures and accounting and other policies and compensation structures, (iv) difficulties in achieving anticipated cost savings, (v) declines in our results of operations, financial condition or cash flows, (vi) a decline in the market price of our common stock, and (vii) potential liabilities, adverse consequences, increased expenses or other problems associated with our company following completion of the Merger. Many of these factors are outside of our control, and any one of them could result in increased costs, decreased expected revenues and further diversion of management time and energy, which could materially impact our business, financial statements and prospects.

In addition, following the Merger, we have become responsible for Keryx's liabilities and obligations, including with respect to legal, financial, regulatory and compliance matters, including certain post-approval regulatory requirements with respect to Auryxia and Fexeric, and obligations under collaboration, license, supply and manufacturing agreements. These obligations will result in additional cost and investment by us and, if we have underestimated the amount of these costs and investments or if we fail to satisfy any such obligations, we may not realize the anticipated benefits of the transaction. Also, due to the Merger and ongoing integration, we may forego or delay pursuit of other opportunities that may have proven to have greater commercial potential.

Further, it is possible that there may be unknown, contingent or other liabilities or problems that may arise in the future, the existence and/or magnitude of which we were previously unaware. Any such liabilities or problems could have an adverse effect on our business, financial condition or results of operations.

Lawsuits have been filed challenging the Merger and additional lawsuits may be filed in the future. Any rescission, monetary damages, or other adverse judgment could have a material adverse effect on us.

In October and November 2018, four purported shareholders of Keryx filed four separate putative class actions against Keryx and the former members of Keryx's Board of Directors and, with respect to one action, Alpha Therapeutics Merger Sub, Inc. and Akebia, challenging the disclosures made in connection with the Merger. Among other things, the complaints seek rescission of the Merger or rescissory damages; a declaration that that the defendants violated Sections 14(a) and 20(a) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and Rule 14a-9 thereunder; and an award of plaintiffs' costs, including reasonable allowance for attorneys' fees and experts' fees. In

addition, in December 2018, a purported stockholder of Keryx filed a complaint against Keryx pursuant to Section 220 of the Delaware General Corporation Law, which seeks inspection of various Keryx books and records, purportedly to investigate “possible wrongdoing,” in connection with Keryx’s negotiation and approval of the Merger, as well as the independence of former members of Keryx’s Board of Directors (some of whom are current members of our Board of Directors). In addition to the production of books and records, the Section 220 action seeks costs and expenses incurred in the action, including reasonable attorneys’ fees. See Part I, Item 3. Legal Proceedings for further information relating to the lawsuits. Additional lawsuits arising out of the Merger may be filed in the future. We could be forced to expend significant resources in the defense of these lawsuits, including but not limited to, costs associated with the indemnification of Keryx and Akebia directors and officers, and the lawsuits, regardless of outcome, could have a negative effect on our reputation, stock price and results of operations. In addition, rescission of the Merger, monetary damages or other adverse judgment would have a material adverse effect on our business and financial position.

Our financial statements include goodwill and other intangible assets as a result of the Merger. These assets could become impaired in the future under certain conditions.

Accounting standards in the United States require that one party to the Merger be identified as the acquirer. In accordance with these standards, the Merger was accounted for as an acquisition of all outstanding shares of Keryx common stock by us, as the acquirer, and followed the acquisition method of accounting for business combinations. Our assets and liabilities were consolidated with those of Keryx on our financial statements. We measured Keryx's assets acquired and liabilities assumed by us at their fair values, including net tangible and identifiable intangible assets acquired and liabilities assumed, as of the consummation of the Merger. The excess of the purchase price over the fair value of Keryx's assets and liabilities was recorded as goodwill. The Merger added approximately \$384.7 million of goodwill and definite lived intangible assets to our financial statements. In accordance with generally accepted accounting principles, or GAAP, we will be required at least annually to review the carrying value of our goodwill, and for definite lived intangible assets when indicators of impairment are present, to determine if any adverse conditions exist or a change in circumstances has occurred that would indicate impairment of the value of these assets. Conditions that could indicate impairment and necessitate an evaluation of these assets include, but are not limited to, a significant adverse change in the business climate or the legal or regulatory environment within which we operate. In addition, the deterioration of a company's market capitalization significantly below its net book value is an indicator of impairment. To the extent goodwill or other intangible assets become impaired, we may be required to incur material charges relating to such impairment. Such a potential impairment charge could have a material impact on our future operating results and financial position.

Risks Related to our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception, and anticipate that we will continue to incur significant losses and cannot guarantee when, if ever, we will become profitable or attain positive cash flows.

Investment in pharmaceutical product development and commercialization is highly speculative because it entails upfront capital expenditures and significant risk that a product candidate will fail to gain marketing approval or that an approved product will not be commercially viable. Since our inception, we have devoted most of our resources to research and development, including our preclinical and clinical development activities and, following the Merger, commercialization. We have financed our operations primarily through sales of equity securities, our strategic collaborations and, following the Merger, product revenues. Prior to the Merger, we had no products approved for commercial sale and had not generated any revenue from the sale of products. We are not currently profitable and have incurred net losses each year since our inception, including net losses of \$143.6 million for the year ended December 31, 2018. As of December 31, 2018, we had an accumulated deficit of \$514.4 million. We cannot guarantee when, if ever, we will become profitable. Our ability to generate product revenue and achieve profitability depends significantly on our success in many areas, including the following:

- developing, commercializing and marketing Auryxia, vadadustat, if approved, or any other product or product candidate, including those that may be in-licensed or acquired;
- completing preclinical and clinical development of our product candidates;
- seeking and obtaining marketing approvals for our product candidates after completion of clinical studies and the timing of such approvals;
- developing sustainable and scalable manufacturing processes for Auryxia, vadadustat and any other product or product candidate, including those that may be in-licensed or acquired;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate products that are compliant with good manufacturing practices, or GMPs, and services to support the clinical development and the market demand for our products and product candidates, including those that may be in-licensed or acquired;

- launching and commercializing our product candidates, either directly or with a collaborator or distributor;
- obtaining sufficient pricing and reimbursement for Auryxia, vadadustat and any other product or product candidate, including those that may be in-licensed or acquired from private and governmental payors;
- obtaining market acceptance of Auryxia, vadadustat and any other product candidate, including those that may be in-licensed or acquired as viable treatment options;
- the size of any market in which Auryxia, vadadustat and any other product or product candidate, including those that may be in-licensed or acquired, receive approval and obtaining adequate market share in those markets;

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- addressing any competing products;
- identifying, assessing, acquiring and/or developing new product candidates;
- negotiating favorable terms in any transaction into which we may enter, including collaboration, merger, acquisition and licensing arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. The amount of our future net losses will depend, in part, on the rate of our future expenditures, and our financial position will depend, in part, on our product revenues and our ability to obtain funding through equity or debt financings or strategic collaborations. We expect to continue to incur significant expenses if and as we:

- conduct our development program of vadadustat for the treatment of anemia due to chronic kidney disease, or CKD, including PRO₂TECT, INNO₂VATE, FO₂RWARD-2, TRILO₂GY-2 and EXPLO₂RE, and develop plans for and conduct the preclinical and clinical development of any other potential product candidates;
- continue our commercialization activities for Auryxia and plan for the commercialization of vadadustat, if approved, and any other product candidate;
 - continue our Merger-related integration activities;
- seek marketing approvals for our product candidates that successfully complete clinical studies, and maintain marketing approvals for Auryxia and any product candidate for which we obtain marketing approval, including complying with any post-marketing regulatory requirements;
- have our product candidates manufactured for clinical trials and for commercial sale;
- initiate additional preclinical, clinical or other studies for vadadustat and any other product candidates, or any post-marketing approval studies, Phase 4 studies or any other clinical trials for Auryxia and Fexeric;
- seek to discover and develop additional product candidates;
- engage in transactions, including strategic, merger, collaboration, acquisition and licensing transactions, pursuant to which we would market and develop commercial products, or develop other product candidates and technologies;
- make royalty, milestone or other payments under our license agreements and any future in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel;
- continue to create additional infrastructure and expend additional resources to support our operations as a public company, including any additional infrastructure and resources necessary to support a transition from our status as an emerging growth company; and
- experience any delays or encounter issues with any of the above.

We also could be forced to expend significant resources in the defense of the pending securities class action and shareholder derivative lawsuits brought against us, Keryx and certain of Keryx's former directors and officers, some of whom are current directors and officers of ours, and other legal proceedings, as described under Part I, Item 3. Legal Proceedings, or any other such lawsuits brought against us in the future.

Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to accurately predict the timing or amount of increased expenses. 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. In any particular quarter, the progress of our clinical development and our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

Even if we succeed in receiving marketing approval for and are able to commercialize vadadustat, we will continue to incur substantial research and development and other expenditures to develop and market, if approved, any other product candidates as well as any costs relating to post-marketing requirements for Auryxia, vadadustat and any other product candidates that may receive marketing approval. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital.

Our expenses could increase beyond expectations if we are required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities, or if we otherwise believe it is necessary, to change our manufacturing processes or assays, to amend or replace our study protocols, to repeat any of our clinical trials, to perform studies in addition to, different from or larger than those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates. Even if our product candidates are approved for commercial sale, we anticipate incurring significant costs associated with commercializing Auryxia, vadadustat, if approved, and any other approved product candidate. In addition, our ability to generate revenue would be negatively affected if the size of our addressable patient population is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the patient population for treatment is narrowed by competition, physician choice, coverage or reimbursement, or payor or treatment guidelines. Even though we generate revenue from Auryxia and may generate revenues from the sale of any product candidates that may be approved in the future, we may never generate revenue that is significant enough to become and remain profitable, and we may need to obtain additional funding to continue operations.

We will require substantial additional financing to achieve our goals. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.

As of December 31, 2018, our cash and cash equivalents and available for sale securities were \$321.6 million. We expect to continue to expend substantial amounts for the foreseeable future continuing to commercialize Auryxia and developing and commercializing vadadustat, if approved, and any other product candidates. These expenditures will include costs associated with research and development, potentially obtaining marketing approvals and having our products manufactured, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise, including as a result of our decision to include certain elements in our development programs. Because the outcome of our current and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amount of funding necessary to successfully complete the development and commercialization of our product candidates. Our future capital requirements depend on many factors, including:

- significant costs associated with our global Phase 3 development program for vadadustat for the treatment of anemia due to CKD. As of December 31, 2018, we expect the remaining external aggregate contract research organization, or CRO, costs of PRO₂TECT and INNO₂VATE, which are designed to enroll up to approximately 7,600 subjects, to be in the range of \$190.0 million to \$220.0 million; the estimated costs for PRO₂TECT and INNO₂VATE could increase significantly due to a number of factors, including changes in target enrollment and enrollment rates, accrual of major adverse cardiovascular events, or MACE, detection of unexpected safety signals, the addition of new investigative sites, modification of clinical trial protocols, performing other studies in support of the Phase 3 program, choosing to add third-party vendors to support the program, and any other factor that could delay completion of PRO₂TECT and INNO₂VATE;
- the cost and timing of commercialization activities for Auryxia and our product candidates, if approved for marketing, including product manufacturing, marketing, sales and distribution costs;
- the results of our meetings with the FDA, the EMA and other regulatory authorities and any consequential effects on study design, study size and resulting operating costs;
- difficulties or delays in enrolling patients in our clinical trials;
- the timing of, and the costs involved in, obtaining marketing approvals for vadadustat and any other product candidates that we may develop or acquire, including to fund the preparation and filing of regulatory submissions

with the FDA, the EMA and other regulatory authorities, if clinical studies are successful;

- the cost of conducting the FO₂RWARD-2, TRILO₂GY-2 and EXPLO₂RE clinical studies or any post-marketing approval studies, Phase 4 studies or any other clinical trials for Auryxia and Fexeric;
- the cost, timing and outcome of our efforts to obtain marketing approval for vadadustat in the United States, Europe and in other jurisdictions;
- the scope, progress, results and costs of additional preclinical, clinical, or other studies for vadadustat and Auryxia, as well as any studies of any other product candidates;

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- the cost of securing and validating commercial manufacturing of vadaustat and maintaining our manufacturing arrangements for Auryxia, or securing and validating additional arrangements;
- the costs involved in preparing, filing and prosecuting patent applications and maintaining, defending and enforcing our intellectual property rights, including litigation costs, and the outcome of such litigation;
- the costs involved in any legal proceedings to which we are a party;
- Merger-related integration costs;
- our ability to attract, hire and retain qualified personnel; and
- the extent to which we engage in transactions, including collaboration, merger, acquisition and licensing transactions pursuant to which we would develop and market commercial products, or develop other product candidates and technologies.

Furthermore, we expect to continue to incur additional costs associated with operating as a public company, including any additional infrastructure and resources necessary to support a transition from our status as an emerging growth company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We expect our cash resources, including the timing of committed research and development funding from our collaborators, to fund our current operating plan into the third quarter of 2020. We have based these estimates on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Furthermore, our development milestones may not be achieved, we may not receive the anticipated funding from our collaboration partners, and we may not secure other sources of financing. If and until we can generate a sufficient amount of product revenues, we expect to finance future cash needs through public or private equity or debt offerings, payments from our collaborators, strategic transactions, or a combination of these approaches. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic objectives.

We also have a \$40.0 million revolving loan facility, or the Revolving Loan Facility, with Silicon Valley Bank, or SVB. The borrowing base under the Revolving Loan Facility, or any other asset-based credit facility into which we may enter in the future, may be significantly lower than the total commitment under any such facility and therefore may limit the total amount we may be able to borrow. As of December 31, 2018, we had approximately \$16.0 million in available borrowing base under the Revolving Loan Facility, of which \$15.0 million had been drawn down. In addition, the Revolving Loan Facility includes certain restrictive covenants, including the requirement to maintain compliance with a liquidity ratio. Upon an event of default under the Revolving Loan Facility, SVB is entitled to accelerate and demand payment of all amounts outstanding under Revolving Loan Facility, stop advancing money or extending credit to Keryx, demand that Keryx deposit at least 105% of the face amount of any letters of credit remaining undrawn to secure all obligations thereunder, and exercise other remedies available to SVB under the Revolving Loan Facility and at law or in equity. We have determined that events of default have already occurred, and we have not obtained a formal waiver from SVB with respect to these events of default. As a result, we have classified the outstanding principal of \$15.0 million as a current liability in our consolidated balance sheet as of December 31, 2018. So long as these events of default are not waived or otherwise resolved, SVB has the right to take any of the foregoing remedies. If SVB were to accelerate all of the obligations outstanding under the Revolving Loan Facility, we would be required to pay the outstanding principal and other fees to SVB, and we would no longer have access to the Revolving Loan Facility. We expect our cash resources to fund our current operating plan into the third quarter of 2020, which assumes the payment of all amounts due to SVB and no future borrowings under the Revolving Loan Facility. We cannot assure that we will be able to obtain alternative sources of financing on favorable terms or at all.

Any additional fundraising efforts may divert our management's attention away from their day-to-day activities, which may adversely affect our ability to develop and commercialize Auryxia, vadaustat and any other product candidates. Also, additional funds may not be available to us in sufficient amounts or on acceptable terms or at all. If we are

unable to raise additional capital in sufficient amounts when needed or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of Auryxia, vadadustat and any other product candidates. Any of these events could significantly harm our business, financial condition and prospects.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our product and product candidates on unfavorable terms to us.

We expect to finance our cash needs through product revenues, public or private equity or debt offerings, payments from our collaborators, strategic transactions, or a combination of these approaches. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our common stockholders will be diluted, our fixed payment obligations may increase, any such securities may have rights senior to those of our common stock, and the terms may include liquidation or other preferences and anti-dilution protections that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, make capital expenditures, declare dividends, acquire, sell or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic transactions with third parties, we may have to do so at an earlier stage than otherwise would be desirable. In connection with any such strategic transactions, we may be required to relinquish valuable rights to our product and product candidates, future revenue streams or research programs or grant licenses on terms that are not favorable to us. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts for Aurixia, vadadustat, or any other product candidates that we develop or acquire, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

We may engage in strategic transactions to acquire assets, businesses, or rights to products, product candidates or technologies or form collaborations or make investments in other companies or technologies that could harm our operating results, dilute our stockholders' ownership, increase our debt, or cause us to incur significant expense.

As part of our business strategy, we may engage in additional strategic transactions to expand and diversify our portfolio, including through the acquisition of assets, businesses, or rights to products, product candidates or technologies or through strategic alliances or collaborations, similar to the Merger and our collaboration and license arrangements. We may not identify suitable strategic transactions, or complete such transactions in a timely manner, on a cost-effective basis, or at all. Moreover, we may devote resources to potential opportunities that are never completed or we may incorrectly judge the value or worth of such opportunities. Even if we successfully execute a strategic transaction, we may not be able to realize the anticipated benefits of such transaction, may incur additional debt or assume unknown or contingent liabilities in connection therewith, and may experience losses related to our investments in such transactions. Integration of an acquired company or assets into our existing business may not be successful and may disrupt ongoing operations, require the hiring of additional personnel and the implementation of additional internal systems and infrastructure, and require management resources that would otherwise focus on developing our existing business. Even if we are able to achieve the long-term benefits of a strategic transaction, our expenses and short-term costs may increase materially and adversely affect our liquidity. Any of the foregoing could have a detrimental effect on our business, results of operations and financial condition.

In addition, future transactions may entail numerous operational, financial and legal risks, including:

- incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions;
- exposure to known and unknown liabilities, including possible intellectual property infringement claims, violations of laws, tax liabilities and commercial disputes;
- higher than expected acquisition and integration costs;
- difficulty in integrating operations and personnel of any acquired business;
- increased amortization expenses or, in the event that we write-down the value of acquired assets, impairment losses;
- impairment of relationships with key suppliers or customers of any acquired business due to changes in management and ownership;

inability to retain personnel, customers, distributors, vendors and other business partners integral to an in-licensed or acquired product, product candidate or technology;

potential failure of the due diligence processes to identify significant problems, liabilities or other shortcomings or challenges;

entry into indications or markets in which we have no or limited direct prior development or commercial experience and where competitors in such markets have stronger market positions; and

other challenges associated with managing an increasingly diversified business.

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If we are unable to successfully manage any transaction in which we may engage, our ability to develop new products and continue to expand and diversify our portfolio may be limited.

Risks Related to Commercialization

Our ability to successfully commercialize our product, Auryxia, our late-stage product candidate, vadadustat, if approved, and any other product or product candidate, including our ability to achieve their widespread market acceptance, is critical to the success of our business.

Our ability to generate significant product revenue will depend almost entirely on our ability to execute on our commercialization plans and the level of market adoption for, and the continued use of, our product, Auryxia, and, if approved, our late-stage product candidate, vadadustat, by physicians, hospitals, patients, and/or healthcare payors, including government payors, consumers, managed care organizations and specialty pharmacies. If we are not successful in commercializing Auryxia and vadadustat, if approved, including achieving and maintaining an adequate level of market adoption, our profitability and our future business prospects will be adversely impacted. Market acceptance of Auryxia and any other product candidate that may be approved, including vadadustat depends on a number of other factors, including:

- the availability of adequate coverage and reimbursement by third-party payors and governmental authorities;
- the safety and efficacy of the product, as demonstrated in clinical trials and in the post-marketing setting;
- the prevalence of the disease treated by our product;
- the clinical indications for which the product is approved and the product label approved by regulatory authorities, including any warnings or limitations that may be required on the label as a consequence of potential safety risks associated with the product;
- the countries in which marketing approvals are obtained;
- the claims we and our collaborators are able to make regarding the safety and efficacy of our products;
- the success of our physician and patient communications and education programs;
- acceptance by physicians and patients of the product as a safe and effective treatment and the willingness of the target patient population to try new therapies and of physicians to prescribe new therapies;
- the cost, safety and efficacy of the product in relation to alternative treatments;
- the timing of receipt of marketing approvals and product launch relative to competing products and potential generic entrants;
- relative convenience and ease of administration;
- the prevalence and severity of adverse side effects;
- adverse publicity about our products or favorable or adverse publicity about competing products;
- the effectiveness of our and our collaborators' sales, marketing and distribution efforts; and
- the restrictions on the use of our products together with other medications, if any.

Market acceptance is critical to our ability to generate significant product revenue. In addition, any product or product candidate, if approved and commercialized, may achieve only limited market acceptance or none at all. If any of our approved products is not accepted by the market to the extent that we expect, we may not be able to generate product revenue and our business would suffer.

Generic competitors are seeking approval of generic versions of Auryxia and the market entry of one or more generic competitors would limit Auryxia sales and have an adverse impact on our business and results of operation.

Although composition and use of Auryxia are currently claimed by 14 issued patents that are listed in the FDA's Orange Book, we cannot assure you that we will be successful in defending against third parties attempting to invalidate or design around our patents or assert that our patents are invalid or otherwise unenforceable or not infringed, or in competing against third parties introducing generic equivalents of Auryxia or any of our future

products.

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The Hatch-Waxman Act allows applicants seeking to market a generic equivalent of a drug product that relies, in whole or in part, on the FDA's prior approval of a patented brand name drug, to provide notice to the holder of the New Drug Application for the brand name drug of its application, called a Paragraph IV certification notice, if the applicant is seeking to market its product prior to the expiration of the patents with claims directed to the brand name drug. After the introduction of a generic competitor, a significant percentage of the prescriptions written for a product may be filled with the generic version, resulting in a loss in sales of the branded product. To date, we have received four Paragraph IV certification notice letters regarding Abbreviated New Drug Applications, or ANDAs, submitted to the FDA requesting approval for generic versions of Auryxia tablets (210 mg iron per tablet). For more information on these Paragraph IV certification notice letters and any related litigation, see Part I, Item 3. Legal Proceedings. Generic competition for Auryxia or any of our future products could have a material adverse effect on our sales, results of operations and financial condition.

In addition, litigation to enforce or defend intellectual property rights is complex, costly and involves significant management time. If our Orange Book listed patents are successfully challenged by a third party and a generic version of Auryxia is approved and launched, revenue from Auryxia could decline significantly which would have a material adverse effect on our sales, results of operations and financial condition.

If we are unable to maintain sales, marketing and distribution capabilities or to enter into additional agreements with third parties, we may not be successful in commercializing Auryxia or any of our product candidates if they are approved.

In order to market Auryxia, we intend to continue to invest in sales and marketing, which will require substantial effort and significant management and financial resources. We will need to devote significant effort, in particular, to recruiting individuals with experience in the sales and marketing of pharmaceutical products. Competition for personnel with these skills is significant.

There are risks involved with maintaining our own sales, marketing and distribution capabilities, including the following:

- potential inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- potential inability of sales personnel to obtain access to physicians;
- potential lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- costs and expenses associated with maintaining our own sales and marketing organization.

If we are unable to maintain our own sales, marketing and distribution capabilities and our arrangements with third parties with respect to sales, marketing and distribution, or we are unsuccessful in entering into additional arrangements with third parties to sell, market and distribute our product candidates or are unable to do so on terms that are favorable to us, we will not be successful in commercializing our product candidates.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product and product candidates, if approved, which could make it difficult for us to sell any approved products profitably.

Market acceptance and sales of any approved products will depend significantly on the availability of adequate coverage and reimbursement from third-party payors and may be affected by existing and future healthcare reform measures. Government authorities and third-party payors decide which drugs they will cover, as well as establish formularies or implement other mechanisms to manage utilization of products and determine reimbursement levels. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

a covered benefit under its health plan;
safe, effective and medically necessary;
appropriate for the specific patient; and
cost effective.

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Obtaining coverage and reimbursement approval for a product from a government or other third-party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor. In the United States, there are multiple government and private third-party payors with varying coverage and reimbursement levels for pharmaceutical products. Within Medicare, for oral drugs dispensed by pharmacies and also administered in facilities, coverage and reimbursement may vary depending on the setting. The Centers for Medicare & Medicaid Services, or CMS, local Medicare administrative contractors and/or Medicare Part D plans may have some responsibility for determining the medical necessity of such drugs, and therefore coverage, for different patients. Different reimbursement methodologies may apply, and CMS may have some discretion in interpreting their application in certain settings. As an oral drug, Auryxia is covered by Medicare only under Part D. In September 2018, CMS communicated to Medicare Part D sponsors that CMS does not consider Auryxia to be covered under Part D when it is used solely for the treatment of iron deficiency anemia in patients with CKD not on dialysis, or the IDA Indication. CMS does, however, consider Auryxia to be a covered Part D drug when it is used for its other FDA-approved indication: the control of serum phosphorus levels in CKD patients on dialysis, or the Hyperphosphatemia Indication. As a result, Part D sponsors now utilize a prior authorization edit or other process for all Auryxia prescriptions for Medicare beneficiaries to ensure that Auryxia is being used for the Part D covered indication. We are engaging in discussions with CMS and Part D sponsors on this matter as we believe that Auryxia should qualify for coverage under Part D of the CMS regulations when it is used for the IDA Indication. If we are unsuccessful in our efforts to obtain Part D coverage for the IDA Indication, our ability to commercialize Auryxia for this indication will be adversely impacted. While we believe that the vast majority of the Part D prescriptions written for Auryxia today are for the Hyperphosphatemia Indication and therefore will continue to be covered by Part D plans with prior authorization, the prior authorization requirement may have an adverse impact on market acceptance of Auryxia and may influence physicians' prescribing decisions. We cannot predict the impact of the CMS determination or prior authorization changes on our operations and they could have a material adverse effect on our revenue and results of operations going forward.

Medicaid reimbursement of drugs will also vary by state. Private third-party payor reimbursement policies may also vary and may or may not be consistent with Medicare reimbursement methodologies. Manufacturers of outpatient prescription drugs may be required to provide discounts or rebates under government healthcare programs or to certain third-party payors in order to obtain coverage of such products.

Additionally, we may be required to enter into contracts with third-party payors offering rebates or discounts on our products in order to obtain favorable formulary status. We may not be able to agree upon commercially reasonable terms with such third-party payors or provide data sufficient to obtain favorable coverage and reimbursement for many reasons, including that we may be at a competitive disadvantage relative to companies with more extensive product lines. We cannot be sure that coverage or adequate reimbursement will be available for any of our product candidates. Even if we obtain coverage for any approved product, third-party payors may not establish adequate reimbursement amounts which may reduce the demand for our product and prompt us to have to reduce pricing for the products. If reimbursement is not available or is limited, we may not be able to commercialize certain of our products. In addition, in the United States third-party payors are increasingly attempting to contain healthcare costs by limiting both coverage and reimbursement levels for new drugs. As a result, significant uncertainty exists as to whether and how much reimbursement third-party payors will provide for newly approved drugs which, in turn, will put downward pressure on the pricing of drugs.

If vadadustat is approved and included in the fixed reimbursement model for a bundle of dialysis services, or the bundle, we would be required to enter into contracts to supply vadadustat to specific dialysis clinics, instead of through third-party payors, which we believe could be challenging. In May 2017, we entered into a license agreement pursuant to which we will grant Vifor (International) Ltd., or Vifor Pharma, an exclusive license to sell vadadustat solely to Fresenius Kidney Care Group LLC, or FKC, in the United States, subject to FDA approval and inclusion in the bundle. Under this license agreement with Vifor Pharma, or the Vifor Agreement, FKC is not obligated to utilize

vadadustat in its clinics. In addition, even if FKC chooses to utilize vadadustat in its clinics in the United States, it is not restricted from utilizing other therapies for anemia due to CKD. The Vifor Agreement does not restrict us from entering into supply agreements with other dialysis clinics, such as DaVita, one of the largest operators of dialysis clinical in the United States, however, the dialysis clinics may choose not to contract with us for vadadustat or they may choose to contract with us for a limited supply of vadadustat. Although we currently believe it is likely that vadadustat will be included in the bundle, if vadadustat is not included in the bundle, then the Vifor Agreement will not become effective, and patients would access vadadustat through contracts we negotiate with third-party payors for reimbursement of vadadustat, which would be subject to the risks and uncertainties described above. Additionally, if there are updates to the recently published Transitional Drug Add-On Payment Adjustment, or TDAPA, rule that decreases the basis for reimbursement during the transition period or if TDAPA is eliminated, then our profitability may be adversely affected. We may be unable to sell vadadustat, if approved, to dialysis providers on a profitable basis if CMS significantly reduces the level of reimbursement for dialysis services and providers choose to use alternative therapies or look to negotiate their contracts with us. Our profitability may also be affected if our costs of production increase faster than increases in reimbursement levels. Adequate coverage and reimbursement of our products by government and private insurance plans is central to patient and provider acceptance of any products for which we receive marketing approval.

Price controls may be imposed, which may adversely affect our future profitability.

In some countries, including member states of the European Union, or EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take a significant amount of time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices, and in certain instances render commercialization in certain markets infeasible or disadvantageous from a financial perspective. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available products in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or government authorities may lead to further pressure on the prices or reimbursement levels. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, the commercial launch of our product candidate could be delayed, possibly for lengthy periods of time, we or our collaborators may not launch at all in a particular country, we may not be able to recoup our investment in one or more product candidates, and there could be a material adverse effect on our business.

Recently, there has been considerable public and government scrutiny in the United States of pharmaceutical pricing and proposals to address the perceived high cost of pharmaceuticals. There have also been several recent state legislative efforts to address drug costs, which generally have focused on increasing transparency around drug costs or limiting drug prices or price increases. Adoption of new legislation at the federal or state level could affect demand for, or pricing of, our product candidates, if approved, and could diminish our ability to establish what we believe is a fair price for our products, ultimately diminishing our revenue for our products if they are approved.

Approval of Fexeric in the EU does not ensure successful commercialization and reimbursement.

On September 23, 2015, the European Commission, or EC, approved Fexeric for the control of elevated serum phosphorus levels, or hyperphosphatemia, in adult patients with CKD, including pre-dialysis and dialysis patients. The EC also considered ferric citrate coordination complex as a New Active Substance, or NAS, which provides 10 years of data and marketing exclusivity in the EU.

Fexeric has never been marketed in the EU, and we do not intend to commercialize Fexeric in the EU on our own. We have not been successful in finding a suitable commercialization partner for Fexeric in the EU to date. We cannot assure you that we will be able to find a suitable commercialization partner in the EU or otherwise create value from our European rights. The EC's approval of Fexeric in the EU was contingent on, among other things, our commencing marketing of Fexeric by September 23, 2018, however, we received an extension to March 25, 2019, and a subsequent extension to December 23, 2019. If we are unable to commence marketing Fexeric in the EU by December 23, 2019, the Fexeric approval in the EU will cease to be valid. We are working with Panion & BF Biotech, Inc., or Panion, the licensor of our rights to ferric citrate to formulate a commercial plan for Fexeric in Europe. See below for additional information about our arrangements with Panion. There can be no assurances that we will successfully work with Panion with respect to the European commercialization of Fexeric in a timely manner or at all, or that the EC will not

revoke its approval of Fexeric if we fail to market Fexeric by the deadline or for any other reason.

The commercial success of Fexeric is subject to the same types of risks we face with commercializing Auryxia in the United States. In addition, in European countries, pricing and payment of prescription pharmaceuticals is subject to more extensive governmental control than in the United States. Pricing negotiations with European governmental authorities can take six to twelve months or longer after the receipt of regulatory approval and product launch. If reimbursement for Fexeric is unavailable in any country in which reimbursement is sought, limited in scope or amount, or if pricing is set at or reduced to unsatisfactory levels, our ability or any potential partner's ability to successfully commercialize Fexeric in such a country would be impacted negatively. Furthermore, if these measures prevent us or any potential partner from selling Fexeric on a profitable basis in a particular country, they could prevent the commercial launch or continued sale of Fexeric in that country. We may never commercialize Fexeric in the EU or reach or maintain profitability with respect to Fexeric in the EU.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully than, we do.

The development and commercialization of new drugs is highly competitive and subject to rapid and significant technological change. Our future success depends on our ability to demonstrate and maintain a competitive advantage with respect to the development and commercialization of our product and product candidates. Our objective is to continue to commercialize Auryxia and develop and commercialize new products with superior efficacy, convenience, tolerability and/or safety. In many cases, any approved products that we commercialize will compete with existing, market-leading products.

Auryxia is competing in the hyperphosphatemia market in the United States with other FDA-approved phosphate binders such as Renagel[®] (sevelamer hydrochloride) and Renvela[®] (sevelamer carbonate), both marketed by Genzyme Corporation (a wholly-owned subsidiary of Sanofi), PhosLo[®] and Phoslyra[®] (calcium acetate), marketed by Fresenius Medical Care North America, Fosrenol[®] (lanthanum carbonate), marketed by Shire Pharmaceuticals Group plc, and Velporo[®] (sucroferric oxyhydroxide), marketed by Fresenius Medical Care North America, as well as over-the-counter calcium carbonate products such as TUMS[®] and metal-based options such as aluminum, lanthanum and magnesium. Many of the phosphate binders listed above are now also available in generic forms. In addition, other phosphate binders are in development, including OPKO Health Inc.'s Alpharett[®] Tablets (fermagate tablets) and Ardelyx, Inc.'s tenapanor, that may impact the market for Auryxia.

Auryxia is competing in the IDA market in the United States with over-the-counter oral iron, ferrous sulfate, other prescription oral iron formulations, including ferrous gluconate, ferrous fumarate, and polysaccharide iron complex, and IV iron formulations, including Feraheme[®] (ferumoxytol injection), Venofer[®] (iron sucrose injection), Ferrlicit[®] (sodium ferric gluconate complex in sucrose injection), Injectafer[®] (ferric carboxymaltose injection), and Triferic[®] (ferric pyrophosphate citrate).

In addition, other new therapies are in development for the treatment of IDA that may impact the market for Auryxia, such as Shield Therapeutics' Ferracrit[®] (ferric maltol), which is currently approved in Europe for IDA and is seeking FDA approval in the United States.

Furthermore, Auryxia's commercial opportunities may be reduced or eliminated if our competitors develop and market products that are less expensive, more effective or safer than Auryxia. Other companies have product candidates in various stages of pre-clinical or clinical development to treat diseases for which we are marketing Auryxia.

If vadadustat is approved and launched commercially, competing drugs may include EPOGEN[®] (epoetin alfa) and Aranesp[®] (darbepoetin alfa), both commercialized by Amgen, Procrit[®] (epoetin alfa) and Eprex[®] (epoetin alfa), commercialized by Johnson & Johnson in the United States and Europe, respectively, and Mircera[®] (methoxy PEG-epoetin beta), commercialized by Vifor Pharma in the United States and Roche Holding Ltd. outside the United States. We may also face competition from potential new anemia therapies. There are several other HIF-PHI product candidates in various stages of development for anemia indications that may be in direct competition with vadadustat if and when they are approved and launched commercially. These candidates are being developed by such companies as FibroGen, Japan Tobacco International, GlaxoSmithKline plc and Bayer HealthCare AG. FibroGen, together with its collaboration partners, Astellas Pharma Inc. and AstraZeneca PLC, is currently in global Phase 3 clinical development of its product candidate, roxadustat. GlaxoSmithKline plc is currently in global Phase 3 clinical development of its product candidate, daprodustat. Japan Tobacco International and Bayer HealthCare AG are currently in Phase 3 clinical development of their product candidates in Japan. Some of these product candidates may launch in certain Asian markets as early as 2019. In addition, certain companies are developing potential new therapies for renal-related diseases that could potentially reduce injectable ESA utilization and thus limit the market potential for vadadustat if they are approved and launched commercially. Other new therapies are in development for

the treatment of conditions inclusive of renal anemia that may impact the market for anemia-targeted treatment.

A biosimilar is a biologic product that is approved based on demonstrating that it is highly similar to an existing, FDA-approved branded biologic product. The patents for the existing, branded biologic product must expire in a given market before biosimilars may enter that market without risk of being sued for patent infringement. In addition, an application for a biosimilar product cannot be approved by the FDA until 12 years after the existing, branded product was approved under a Biologics License Application, or BLA. The patents for epoetin alfa, an injectable ESA, expired in 2004 in the EU, and the remaining patents expired between 2012 and 2016 in the United States. Because injectable ESAs are biologic products, the introduction of biosimilars into the injectable ESA market in the United States will constitute additional competition for vadadustat if we are able to obtain approval for and commercially launch our product. Several biosimilar versions of injectable ESAs are available for sale in the EU. In the United States, Pfizer's biosimilar version of injectable ESAs, Retacrit® (epoetin alfa-epbx), was approved by the FDA in May 2018 and launched in November 2018.

Many of our potential competitors have significantly greater financial, manufacturing, marketing, drug development, technical and human resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining marketing approvals, recruiting patients and manufacturing pharmaceutical products. Large and established companies such as Amgen and Roche, among others, compete in the market for drug products to treat kidney disease. In particular, these companies have greater experience and expertise in conducting preclinical testing and clinical trials, obtaining marketing approvals, manufacturing such products on a broad scale and marketing approved products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in late stages of development, and have collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we are developing obsolete. Smaller and other early stage companies may also prove to be significant competitors. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or marketing approval, or discovering, developing and commercializing competitive products, before, or more effectively than, we do. If we are not able to compete effectively against potential competitors, our business will not grow and our financial condition and operations will suffer.

The commercialization of Riona in Japan, our efforts with respect to the potential commercialization of Fexeric in the EU and our current and future efforts with respect to the development and commercialization of our products and product candidates outside of the United States subject us to a variety of risks associated with international operations, which could materially adversely affect our business.

Our Japanese sublicensee, JT, and its subsidiary, Torii, commercialize Riona as an oral treatment for the improvement of hyperphosphatemia in patients with DD-CKD and NDD-CKD in Japan. While Fexeric is not currently marketed in the EU, Fexeric has received conditional marketing approval in the EU as an oral treatment for the control of hyperphosphatemia in adult patients with DD-CKD and NDD-CKD, and we are continuing efforts to find a suitable commercialization partner for Fexeric in the EU. We also granted Otsuka Pharmaceutical Co. Ltd., or Otsuka, exclusive rights to commercialize vadadustat in Europe, China and certain other markets, subject to marketing approvals. In Japan and certain other countries in Asia, we granted Mitsubishi Tanabe Pharma Corporation, or MTPC, exclusive rights to commercialize vadadustat, subject to marketing approvals. We are also conducting our global Phase 3 development with respect to vadadustat for the treatment of anemia due to CKD, and MTPC is carrying out development efforts for vadadustat in Japan. As a result of these and other activities, we are or may become subject to additional risks in developing and commercializing our product and product candidates outside the United States, including:

- political, regulatory, compliance and economic developments that could restrict our ability to manufacture, market and sell our products;
- changes in international medical reimbursement policies and programs;
- changes in health care policies of foreign jurisdictions;
- trade protection measures, including import or export licensing requirements and tariffs;
- our ability to develop relationships with qualified local distributors and trading companies;
- political and economic instability in particular foreign economies and markets;
- diminished protection of intellectual property in some countries outside of the United States;
- differing labor regulations and business practices;
- regulatory and compliance risks that relate to maintaining accurate information and control over sales and distributors' and service providers' activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, or FCPA, the UK Bribery Act or similar local regulation;
- compliance with the EU General Data Protection Regulation, or GDPR;
- 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;

potentially negative consequences from changes in or interpretations of tax laws;
foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;

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- 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; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

Any of these factors may, individually or as a group, have a material adverse effect on our business and results of operations. As and if we continue to expand our commercialization efforts, we may encounter new risks.

Risks Related to the Clinical Development of Vadadustat and our Other Product Candidates

In addition to Auryxia, we will continue to depend heavily on the success of our product candidate, vadadustat, which is currently in Phase 3 development. Clinical drug development involves a lengthy and expensive process with an uncertain outcome. We will incur additional costs in connection with, and may experience delays in completing, or ultimately be unable to complete, the development and commercialization of vadadustat and any other product candidates.

The risk of failure in drug development is high. We currently have only one commercial product, Auryxia, and one product candidate, vadadustat, in clinical development, and we depend heavily on the successful commercialization of Auryxia and the successful clinical development, marketing approval and commercialization of vadadustat, which may never occur. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical trials are expensive, difficult to design and implement, can take several years to complete, and their outcomes are inherently uncertain. Failure can occur at any time during the clinical trial process. Further, the results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their product candidates. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive or maintain marketing approval or commercialize our product candidates. Our clinical trials may take longer to complete than currently anticipated, or may be delayed, suspended, required to be repeated, prematurely terminated or may not successfully demonstrate safety and/or efficacy for a variety of other reasons, such as:

- the costs are greater than we anticipate;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate;
- enrollment in our clinical trials and accrual of MACE events may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, such as our CRO's, may fail to comply with regulatory requirements, perform effectively, or meet their contractual obligations to us in a timely manner, or at all, or we may fail to communicate effectively or provide the appropriate level of oversight of such third-party contractors;
- the supply or quality of our starting materials, drug substance and drug product necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- regulators, international data monitoring committees, or IDMCs, institutional review boards, or IRBs, safety committees, or ethics committees, may require that we suspend or terminate our clinical trials for various reasons, including noncompliance with regulatory requirements, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using our product candidate, or a finding that the participants are being exposed to

unacceptable health risks;

clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials, repeat a clinical trial or abandon product development programs;

lack of adequate funding to continue a clinical trial, including unforeseen costs due to enrollment delays, requirements to conduct additional clinical trials or repeat a clinical trial and increased expenses associated with the services of our CROs and other third parties;

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failure to initiate, delay of or failure to complete a clinical trial as a result of an Investigational New Drug application, or IND, being placed on clinical hold by the FDA, the EMA, the Japanese Pharmaceuticals and Medical Devices Agency, or PMDA, or other regulatory authorities, or for other reasons;

- we may determine to change or expand a clinical trial, including after it has begun;
- clinical trial sites and investigators deviating from the clinical protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial, or failure by us or our CROs to communicate effectively or provide the appropriate level of oversight of such clinical sites and investigators;
- delay or failure in having subjects complete a clinical trial or return for post-treatment follow-up;
- delay or failure in recruiting and enrolling suitable subjects to participate in a clinical trial;
- inability, delay, or failure in identifying and maintaining a sufficient number of clinical trial sites, many of which may already be engaged in other clinical programs;
- delay or failure in reaching agreement with the FDA, the EMA, PMDA or other regulatory authorities on a clinical trial design upon which we are able to execute;
- delay or failure in obtaining authorization to commence a clinical trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical trial;
- delays in reaching, or failure to reach, agreement on acceptable terms with prospective clinical trial sites and prospective CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- the FDA, the EMA, PMDA or other regulatory authorities may require us to submit additional data or impose further requirements before permitting us to initiate a clinical trial or during an ongoing clinical trial;
- the FDA, the EMA, PMDA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;
- the design of our clinical trials;
- failure to comply with good practice quality guidelines and regulations, or GXP, including good laboratory practice, or GLP, good clinical practice, or GCP, and current good manufacturing practice, or cGMP; or
- changes in governmental regulations or administrative actions.

If we are unable to successfully complete clinical trials of our product candidates or other studies, if the results of those trials and studies are not positive or are only modestly positive, or if there are concerns with the profile due to efficacy or safety, or if any of the factors listed above occur, the following may occur:

- regulators may require that we conduct additional clinical trials, repeat clinical trials or conduct other studies of our product candidates beyond those that we currently contemplate;
- we may be delayed in obtaining marketing approval for our product candidates;
- we may not obtain marketing approval for our product candidates at all;
- we may obtain approval for indications or patient populations that are not as broad as intended or desired;
- we may obtain approval with labeling that includes significant use or distribution restrictions or safety warnings that would reduce the potential market for our products or inhibit our ability to successfully commercialize our products;
- we may be subject to additional post-marketing restrictions and/or requirements; or
- the product may be removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in preclinical and clinical development or receiving the requisite marketing approvals. Our preclinical studies or clinical trials may need to be restructured or may not be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do. This could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Even if we obtain favorable clinical results in our Phase 3 studies, we may not be able to obtain marketing approval for, or successfully commercialize, vadadustat, or we may experience significant delays in doing so, any of which would materially harm our business.

The clinical trials of our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous governmental authorities in the United States, and in other countries where we and our collaborators intend to test and, if approved, market any product candidates. Before obtaining marketing approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication. This process can take many years and marketing approval may never be achieved. Of the large number of drugs in development in the United States and in other jurisdictions, only a small percentage successfully complete the FDA's and other jurisdictions' marketing approval processes and are commercialized. Accordingly, even if we are able to obtain the requisite capital to continue to fund our development programs, we may be unable to successfully develop or commercialize vadadustat or any other product candidates.

We and Otsuka, our collaboration partner, are not permitted to market vadadustat in the United States until we receive approval from the FDA, in the EU until we receive approval from the EMA, or in any other jurisdiction until the requisite approval from regulatory authorities in such jurisdiction is received. MTPC, our collaboration partner in Asia, will not be permitted to market vadadustat in Japan without approval from the PMDA or in any other jurisdiction until the requisite approval from regulatory authorities in such jurisdiction is received. As a condition to receiving marketing approval for vadadustat, we must complete Phase 3 studies and any additional preclinical or clinical studies required by the FDA, the EMA, PMDA or other regulatory authorities. Vadadustat may not be successful in clinical trials or receive marketing approval. Further, vadadustat may not receive marketing approval even if it is successful in clinical trials.

Obtaining marketing approval in the United States and other jurisdictions is a complex, lengthy, expensive and uncertain process that typically takes many years and depends upon numerous factors, including the substantial discretion of the regulatory authorities. Even if our product candidates demonstrate safety and efficacy in clinical studies, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain marketing approval. In addition, the safety concerns associated with injectable ESAs may affect the FDA's, EMA's, PMDA's or other regulatory authorities' review of the safety results of compounds in development for treatment of the same indications as injectable ESAs, including vadadustat. Further, the policies or 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. It is possible that vadadustat and any other product candidates will never obtain marketing approval. The FDA may delay, limit or deny approval of vadadustat or any other product candidates for many reasons including, among others:

- we may not be able to demonstrate that vadadustat is safe and effective in treating anemia due to CKD or that any other product candidate is safe and effective for its proposed indication(s) to the satisfaction of the FDA;
- the results of our clinical trials may only be modestly positive, or there may be concerns with the profile due to efficacy or safety;
- the FDA may require us to complete both the INNO₂VATE clinical program and the PRO₂TECT clinical program for vadadustat prior to filing our NDA even if one of these programs finishes in advance of the other;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA for marketing approval;
- the FDA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the FDA may not approve the formulation, labeling or specifications we request for vadadustat or any other product candidate;

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the FDA may approve vadadustat or any other product candidate for use only in a small patient population or for fewer or more limited indications than we request;

• the FDA may require that we conduct additional clinical trials or repeat one or more clinical trials;

• the FDA may grant approval contingent on the performance of costly post-marketing clinical trials;

• we, or our CROs or vendors, may fail to comply with GXP;

• the CROs that we retain to conduct our clinical trials may not perform effectively or take actions that adversely impact our clinical trials, or we may fail to communicate effectively or provide the appropriate level of oversight of our CROs;

• we or our third party manufacturers may fail to perform in accordance with the FDA's cGMP requirements;

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- the FDA may disagree with inclusion of data obtained from certain regions outside the United States to support the NDA for potential reasons such as differences in clinical practice from United States standards;
- the FDA may disagree with our interpretation of data from our preclinical studies and clinical trials;
- the FDA could deem that our financial relationships with certain principal investigators constitute a conflict of interest, such that the data from those principal investigators may not be used to support our applications;
- an FDA Advisory Committee or other regulatory advisory group or authority could recommend non-approval or restrictions on approval;
- the FDA's decision-making regarding vadadustat and any other product candidates may be impacted by the results of competitors' clinical trials and safety concerns of marketed products used to treat the same indications as the indications for which vadadustat and any other product candidates are being developed;
- the FDA may not approve the manufacturing processes or facilities of third party manufacturers with whom we contract; or
- the policies or regulations of the FDA may significantly change in a manner that renders our clinical data insufficient for approval, or requires us to amend or submit new clinical protocols.

In addition, similar reasons may cause the EMA or PMDA or other regulatory authorities to delay, limit or deny approval of vadadustat or any other product candidate outside the United States.

If we experience delays in obtaining approval, or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired, which could have a material adverse effect on our business.

We may find it difficult to enroll patients in our clinical studies, which could delay or prevent clinical studies of our product candidates.

Identifying and qualifying patients to participate in clinical studies of our product candidates is critical to our success. The timing of our clinical studies depends, in part, on the speed at which we can recruit patients to participate in testing our product candidates. Patients may be unwilling to participate in our clinical studies of vadadustat or other product candidates because of concerns about adverse events observed with injectable ESAs, other investigational agents and commercial products in CKD or for other reasons, including competitive clinical studies for similar patient populations. In addition, patients currently receiving treatment with injectable ESAs may be reluctant to participate in a clinical trial with an investigational drug. Finally, competition for clinical trial sites may limit our access to subjects appropriate for studies of vadadustat and any other product candidates. As a result, the timeline for recruiting patients, conducting studies and obtaining marketing approval of vadadustat and any other product candidates may be delayed. These delays could result in increased costs, delays in advancing our development of vadadustat and any other product candidates, or termination of the clinical studies altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical studies in a timely manner. Patient enrollment is affected by many factors, including:

- severity of the disease under investigation;
- design of the study protocol;
- size and nature of the patient population;
- eligibility criteria for, and design of, the study in question;
- perceived risks and benefits of the product candidate under study, including as a result of adverse effects observed in similar or competing therapies;
- proximity and availability of clinical study sites for prospective patients;
- availability of competing therapies and clinical studies and clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to available therapies or other product candidates in

development;

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- efforts to facilitate timely enrollment in clinical studies;
- clinical trial sites and investigators failing to perform effectively;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

We may not be able to initiate or continue clinical studies if we cannot enroll a sufficient number of eligible patients to participate in the clinical studies required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical studies as planned, we may need to delay, limit or terminate ongoing or planned clinical studies, any of which could have a material adverse effect on our business.

We may not be able to conduct clinical trials in some jurisdictions outside of the United States.

We and our collaboration partners currently expect to seek marketing approval of vadadustat for the treatment of anemia due to CKD in markets outside the United States, including the EU and Japan. Our ability to successfully initiate, enroll and complete a clinical study in any country outside of the United States is subject to numerous additional risks unique to conducting business in jurisdictions outside the United States, including:

- difficulty in establishing or managing relationships with qualified CROs, physicians and clinical trial sites;
- different local standards for the conduct of clinical studies;
- difficulty in complying with various and complex import laws and regulations when shipping drug to certain countries; and
- the potential burden of complying with a variety of laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatments.

Data obtained from studies conducted in the United States may not be accepted by the EMA, PMDA and other regulatory authorities outside of the United States. Also, certain jurisdictions require data from studies conducted in their country in order to obtain approval in that country. For example, in Japan, MTPC is conducting a Phase 3 program of vadadustat, which is separate from our global Phase 3 program of vadadustat.

If we or our collaboration partners have difficulty conducting our clinical studies in jurisdictions outside the United States as planned, we may need to delay, limit or terminate ongoing or planned clinical studies, any of which could have a material adverse effect on our business.

Positive results from preclinical and clinical studies are not necessarily predictive of the results of any future clinical studies.

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. Success in preclinical studies may not be predictive of similar results in humans during clinical trials, successful results from early or small clinical trials may not be replicated in later and larger clinical trials, and successful interim results from ongoing clinical studies may not be indicative of results obtained when those studies are completed. For example, our encouraging preclinical and clinical results for vadadustat thus far do not ensure that the results of any future clinical trials will demonstrate similar results. Our global Phase 3 development program for vadadustat is enrolling a larger number of subjects and will treat subjects for longer periods than our prior trials, which will result in a greater likelihood that adverse events may be observed. Due to these and other differences between our global Phase 3 development program for vadadustat and our prior trials, our positive results from preclinical and clinical studies may not be replicated in our global Phase 3 development program for vadadustat. Many companies in the biopharmaceutical industry have suffered significant setbacks in late-stage clinical trials after achieving positive results in early stage development, and we may face similar setbacks. If the results of our ongoing or future clinical trials for vadadustat or any other product candidates are inconclusive with respect to efficacy, if we do not meet our clinical endpoints with statistical significance, or if there are safety concerns or adverse events, we may be prevented from or delayed in obtaining marketing approval for vadadustat or

any other product candidates.

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We may not be successful in our efforts to identify, acquire, discover, develop and commercialize additional products or product candidates, which could impair our ability to grow.

Although we continue to focus a substantial amount of our efforts on the commercialization of Auryxia and the development and potential commercialization of vadadustat, a key element of our long-term growth strategy is to acquire, develop and/or market additional products and product candidates. Research programs to identify product candidates require substantial technical, financial and human resources, regardless of whether product candidates are ultimately identified. Our research and development programs may initially show promise, yet fail to yield product candidates for clinical development or commercialization for many reasons, including the following:

- the research methodology used may not be successful in identifying potential indications and/or product candidates;
- we may not be able or willing to assemble sufficient resources to acquire or discover additional product candidates;
- a product candidate may be shown to have harmful side effects, a lack of efficacy or otherwise does not meet applicable regulatory criteria;
- product candidates we develop may nevertheless be covered by third-party 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 not be capable of being produced in commercial quantities at an acceptable cost, or at all; or
- a product candidate may not be accepted as safe and effective by patients, the medical community, or third-party payors, if applicable.

If any of these events occurs, we may be forced to abandon our development efforts for one or more of our programs, or we may not be able to identify, discover, develop or commercialize additional product candidates, which would have a material adverse effect on our business.

Because we have limited financial and managerial resources, we focus on research programs and product candidates for specific indications. 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 or a greater likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Because our internal research capabilities are limited, we may be dependent upon other pharmaceutical and biotechnology companies, academic scientists, and other researchers to sell or license products or technology to us. The success of this strategy depends partly upon our ability to identify, select, and acquire promising product candidates and products. The process of proposing, negotiating and implementing a license or acquisition of a product candidate or an approved product is lengthy and complex. Other companies, including some with substantially greater financial, marketing and sales resources, may compete with us for the license or acquisition of a product candidate or an approved product. We have limited resources to identify and execute the acquisition or in-licensing of third-party products, businesses, and technologies and integrate them into our current infrastructure.

Moreover, we may devote resources to potential acquisitions or in-licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts, including, for example, with respect to the Merger. Any product candidate that we acquire may require additional development efforts prior to commercial sale, including extensive clinical testing and approval by the FDA, the EMA, PMDA or other regulatory authorities, or post-approval testing or other requirements if approved. All product candidates are prone to risks of failure typical of pharmaceutical product development, including the possibility that a product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot provide assurance that any products that we develop or approved products that we acquire will be manufactured profitably, achieve market acceptance or not require substantial post-marketing clinical trials.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our product candidates or to acquire or develop suitable potential product candidates or approved products, which could materially adversely affect our future growth and prospects. We may focus our efforts and resources on potential product candidates or other programs that ultimately prove to be unsuccessful.

Auryxia, vadadustat or other products and product candidates may cause undesirable side effects or have other properties that delay or limit their commercial potential, or in the case of our product candidates, prevent their marketing approval.

Undesirable side effects caused by our product or product candidates or competing products in development that utilize a common mechanism of action could cause us or regulatory authorities to interrupt, delay or halt clinical trials, could result in a more restrictive label or the delay, denial or withdrawal of marketing approval by the FDA or other regulatory authorities, and could lead to potential product liability claims. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics.

If we or others identify undesirable side effects caused by Auryxia, vadadustat, or other products or product candidates, either before or after receipt of marketing approval, a number of potentially significant negative consequences could result, including:

- our clinical trials may be put on hold;
- patient recruitment could be slowed, and enrolled patients may not want to complete the clinical trial;
- we may be unable to obtain marketing approval for our product candidates or regulatory authorities may withdraw approvals of products;
- regulatory authorities may require warnings on the label such as the warning on Auryxia's label regarding iron overload;
- Risk Evaluation and Mitigation Strategies, or REMS, or FDA-imposed risk management plans that use risk minimization strategies to ensure that the benefits of certain prescription drugs outweigh their risks, may be required;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining marketing approval and, ultimately, market acceptance of Auryxia, vadadustat or other products or product candidates, could substantially increase our costs, and could significantly impact our ability to successfully commercialize Auryxia, vadadustat, or other products and product candidates and generate revenues.

The patient populations treated with Auryxia and the subjects in our clinical studies for vadadustat, have CKD, a serious disease that increases the risk of cardiovascular disease including heart attacks and stroke and, ultimately, may cause kidney failure. Many patients with CKD are elderly with comorbidities making them susceptible to significant health risks. Therefore, the likelihood of these subjects having adverse events, including serious adverse events, while participating in our studies is high. In our Phase 1 and Phase 2 studies of vadadustat, adverse events were reported. For example, in our Phase 2b study of vadadustat in non-dialysis subjects with anemia due to CKD, one subject with multiple co-morbidities and concomitant medications, including chlorthalidone, had a serious adverse event of liver function test abnormal, considered a case of drug induced liver injury meeting the biochemical criteria of Hy's Law, which was assessed as probably related to vadadustat. Serious adverse events considered related to vadadustat and any other product candidates could have a material adverse effect on the development of such product candidates and our business as a whole. Our understanding of adverse events in prior clinical trials of our product candidates may change as we gather more information, and additional unexpected adverse events may be observed in future clinical trials.

The most commonly reported adverse reactions in the clinical trials that supported the approval of Auryxia for the Hyperphosphatemia Indication in the United States included diarrhea (21%), discolored feces (19%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%). Gastrointestinal adverse reactions were the most common reason for discontinuing Auryxia (14%) in clinical trials for the Hyperphosphatemia Indication. The most commonly reported adverse reactions in the clinical trials that supported the approval of Auryxia in the United States for the IDA Indication included discolored feces (22%), diarrhea (21%), constipation (18%), nausea (10%), abdominal pain (5%) and hyperkalemia (5%). Diarrhea was the most common reason for discontinuing Auryxia (2.6%) in clinical trials for

the IDA Indication.

Furthermore, any post-marketing clinical trials conducted, if successful, may expand the patient populations treated with Auryxia, or any other products we acquire or for which we receive marketing approval, within or outside of their current indications or patient populations, which could result in the identification of previously unknown side effects, increased frequency or severity of known side effects, or detection of unexpected safety signals. In addition, as Auryxia and any other products are commercialized, they will be used in larger patient populations and in less rigorously controlled environments than in clinical studies. As a result, regulatory authorities, healthcare practitioners, third-party payors or patients may perceive or conclude that the use of Auryxia or any other products are associated with serious adverse effects, undermining our commercialization efforts.

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Further, if we or others identify previously unknown side effects, if known side effects are more frequent or severe than in the past, if we or others detect unexpected safety signals for our products or product candidates, including Auryxia, vadadustat, or any product or product candidate perceived to be similar to Auryxia, vadadustat, or our other product candidates, or if any of the foregoing are perceived to have occurred, either before or after receipt of marketing approval, a number of potentially significant negative consequences could result, including:

- sales may be impaired;
- regulatory approvals may be restricted or withdrawn;
- we may decide to, or be required to, send drug warnings or safety alerts to physicians, pharmacists and hospitals (or FDA or other regulatory authority may choose to issue such alerts), or we may decide to conduct a product recall or be requested to do so by the FDA or other regulatory authority;
- reformulation of the product, additional nonclinical or clinical studies, changes in labeling or changes to or re-approvals of manufacturing facilities may be required;
- we may be precluded from pursuing additional development opportunities to enhance the clinical profile of a product within its indicated populations, or studying the product or product candidate in additional indications and populations or in new formulations; and
- government investigations or lawsuits, including class action suits, may be brought against us.

Any of the above occurrences could delay or prevent us from achieving or maintaining marketing approval, harm or prevent sales of Auryxia or, if approved, vadadustat or other product candidates, increase our expenses and impair or prevent our ability to successfully commercialize Auryxia, vadadustat or other product candidates

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

We are subject to a complex regulatory scheme that requires significant resources to ensure compliance. Failure to comply with applicable laws could subject us to government scrutiny or government enforcement, potentially resulting in costly investigations and/or fines or sanctions, or impacting our relationships with key regulatory agencies such as the FDA or the EMA.

A variety of laws apply to us or may otherwise restrict our activities, including the following:

- laws and regulations governing the conduct of preclinical and clinical studies in the United States and other countries in which we are conducting such studies;
- laws and regulations in the United States and in countries in which we are interacting with health care providers, patients, patient organizations and other constituencies that prohibit promoting a drug prior to approval and/or reimbursement;
- laws and regulations of countries outside the United States that prohibit pharmaceutical companies from promoting prescription drugs to the general public;
- laws, regulations and industry codes that vary from country to country and govern our relationships with health care providers, patients, patient organizations, and other constituencies, prohibit certain types of gifts and entertainment, establish codes of conduct and, in some instances, require disclosure to, or approval by, regulatory authorities for us to engage in arrangements with such constituencies;
- anti-corruption and anti-bribery laws, including the FCPA, the UK Bribery Act and various other anti-corruption laws in countries outside of the United States;
- data privacy laws existing in the United States, the EU and other countries in which we operate, including the U.S. Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, the GDPR, and state privacy and data protection laws, as well as state consumer protection laws;
- federal securities laws restricting the purchase or sale of any securities while in possession of material, non-public information; and

international trade laws, which are laws that regulate the sale, purchase, import, export, re-export, transfer and shipment of goods, products, materials, services and technology.

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Compliance with these and other applicable laws and regulations requires us to expend significant resources. Failure to comply with these laws and regulations may subject us to government investigations, penalties, damages, fines, the restructuring of our operations, or the imposition of a clinical hold, any of which could materially adversely affect our business and would result in increased costs and diversion of management attention and could delay or prevent the development, regulatory approval and commercialization of our product candidates, any of which could have a material adverse effect on our business.

We may be delayed in obtaining, or be unable to obtain, marketing approval or reimbursement for vadadustat or any other product candidate in certain countries outside of the United States.

Regulatory authorities outside of the United States will require compliance with numerous and varying requirements. The approval procedures vary among jurisdictions and may involve requirements for additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval. In addition, in many countries outside the United States, a drug product must be approved for reimbursement before it can be marketed or sold in that country. In some cases, the prices that we intend to charge for our products are also subject to approval. Approval by the FDA does not ensure approval by regulatory or reimbursement authorities outside the United States, and approval by one regulatory or reimbursement authority outside the United States does not ensure approval by the FDA or any other regulatory or reimbursement authorities. However, the failure to obtain approval or reimbursement in one jurisdiction may negatively impact our ability to obtain approval or reimbursement in another jurisdiction. The marketing approval process in countries outside of the United States may include all of the risks associated with obtaining FDA approval and, in some cases, additional risks. We may not obtain such regulatory or reimbursement approvals on a timely basis, if at all. We may not be able to file for marketing approvals and may not receive the necessary approvals to commercialize our product candidates in any market. Also, favorable pricing in certain countries depends on a number of factors, some of which are outside of our control.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. On March 29, 2017, the United Kingdom formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The United Kingdom has a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the EU. If no formal withdrawal agreement is reached between the United Kingdom and the EU, then it is expected that the United Kingdom's membership of the European Union will automatically terminate two years after the submission of the notification of the United Kingdom's intention to withdraw from the European Union. Discussions between the United Kingdom and the EU focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date in these negotiations and ongoing uncertainty within the UK Government and Parliament sustains the possibility of the United Kingdom leaving the EU on March 29, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

Since a significant proportion of the regulatory framework in the United Kingdom is derived from EU directives and regulations, the withdrawal could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occurs, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or EU for our product candidates, which could significantly and materially harm our business.

Products approved for marketing are subject to extensive post-marketing regulatory requirements and could be subject to post-marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them is approved.

Marketing approvals may be subject to limitations on the approved indicated uses for which the product may be marketed or other conditions of approval, or contain requirements for potentially costly post-marketing studies and surveillance to monitor the safety and efficacy of the product, including REMS, or registries or observational studies. For example, in connection with the FDA approvals of Auryxia, we initially committed to the FDA to conduct certain post-approval pediatric studies of Auryxia under the Pediatric Research Equity Act. With regard to our Hyperphosphatemia Indication, we committed to completing the post-approval pediatric study and submitting a final report to the FDA by December 31, 2019, which was recently extended to July 2022 by the FDA in response to our request. With regards to our IDA Indication, we committed to completing the post-approval pediatric study and submitting a final report to the FDA by January 2023. We cannot guarantee that we will be able to complete these studies and submit the final reports in a timely manner. If we are unable to complete these studies successfully, our marketing approval could be suspended or revoked, which would have a material adverse impact on our ability to commercialize Auryxia and our ability to generate revenues from Auryxia. In addition, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for Auryxia, and any other product for which we receive regulatory approval, will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, as well as continued compliance with cGMPs and GCPs for any clinical trials that we conduct post-approval.

Moreover, the FDA and other regulatory authorities closely regulate the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and other regulatory authorities impose stringent restrictions on companies' communications regarding use of their products, and if we promote our products beyond their approved indications or inconsistent with the approved label, we may be subject to enforcement actions or prosecution arising from such activities. Violations of the U.S. Federal Food, Drug, and Cosmetic Act, or the FD&C Act, relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse and other laws, as well as state consumer protection laws, third-party payor actions, shareholder actions and other lawsuits.

Post-approval discovery of previously unknown problems with an approved product, including adverse events of unanticipated severity or frequency or relating to manufacturing operations or processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing, distribution, use or manufacturing of the product;
- withdrawal of the product from the market, or product recalls;
- restrictions on the labeling or marketing of a product;
- fines, restitution or disgorgement of profits or revenues;
- warning or untitled letters or clinical holds;
- refusal by the FDA or other regulatory authorities to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- REMS; and
- injunctions or the imposition of civil or criminal penalties.

Non-compliance with FDA, EMA, PMDA and other regulatory authorities' requirements regarding safety monitoring or pharmacovigilance can also result in significant financial penalties.

The FDA's policies and those of other regulatory authorities may change, and additional government regulations may be enacted. We cannot predict the likelihood, nature or extent of government regulations that may arise from future legislation or administrative action, either in the United States or in other jurisdictions. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially adversely affect our business.

We will incur significant liability if it is determined that we are promoting any "off-label" use of Auryxia or if it is determined that any of our activities violates the federal Anti-Kickback Statute.

Physicians are permitted to prescribe drug products for uses that differ from those approved by the FDA or other applicable regulatory agencies. Although the FDA and other regulatory agencies do not regulate a physician's choice of treatments, the FDA and other regulatory agencies do restrict manufacturer communications regarding unapproved uses of an approved drug. Companies are not permitted to promote drugs for unapproved uses or in a manner that is inconsistent with the FDA-approved labeling. There are also restrictions about making comparative or superiority claims based on safety or efficacy that are not supported by substantial evidence. Accordingly, we may not promote Auryxia in the United States for use in any indications other than the Hyperphosphatemia Indication and the IDA Indication, and all promotional claims must be consistent with the FDA-approved labeling for Auryxia. Promoting a drug off-label is a violation of the FD&C Act and can give rise to liability under the federal False Claims Act, as well as under additional federal and state laws and insurance statutes. The FDA and other regulatory and enforcement authorities enforce laws and regulations prohibiting promotion of off-label uses and the promotion of products for which marketing approval has not been obtained, as well as the false advertising or misleading promotion of drugs. In

addition, laws and regulations govern the distribution and tracing of prescription drugs and prescription drug samples, including the Prescription Drug Marketing Act of 1976 and the Drug Supply Chain Security Act, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the U.S. federal level and set minimum standards for the regulation of drug distributors by the states. A company that is found to have improperly promoted off-label uses or to have otherwise engaged in false or misleading promotion or improper distribution of drugs will be subject to significant liability, potentially including civil and administrative remedies as well as criminal sanctions.

Notwithstanding the regulatory restrictions on off-label promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non-misleading, and non-promotional scientific communications concerning their products in certain circumstances. In addition, under some relatively recent guidances from the FDA, companies may also promote information that is consistent with the prescribing information and proactively speak to formulary committee members of payors regarding data for an unapproved drug or unapproved uses of an approved drug. We intend to engage in these discussions and communicate with healthcare providers, payors and other constituencies in compliance with all applicable laws, regulatory guidance and industry best practices. Although we believe we have put in place a robust compliance program and processes designed to ensure that all such activities are performed in a legal and compliant manner, Auryxia is our first commercial product so our implementation of our compliance program in connection with commercialization activities is still relatively new.

In addition, if a company's activities are determined to have violated the federal Anti-Kickback Statute, this can also give rise to liability under the federal False Claims Act and such violations can result in significant fines, criminal and civil remedies, and exclusion from Medicare and Medicaid. There is increased government focus on relationships between the pharmaceutical industry and physicians, pharmacies (especially specialty pharmacies), and other sources of referrals. Common industry activities, such as speaker programs, insurance assistance and support, relationships with foundations providing copayment assistance, and relationships with patient organizations and patients are receiving increased governmental attention. If any of our relationships or activities is determined to violate applicable federal and state anti-kickback laws, false claims laws, or other laws or regulations, the company and/or company executives and other representatives could be subject to significant fines and criminal sanctions, imprisonment, and potential exclusion from Medicare and Medicaid.

Recent efforts to pursue regulatory reform may limit the FDA's ability to engage in oversight and implementation activities in the normal course, and that could negatively impact our business.

Recently, there have been several executive actions taken, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. On January 30, 2017, an executive order, applicable to all executive agencies including the FDA, was issued that requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation. Interim guidance issued by the Office of Information and Regulatory Affairs within the Office of Management and Budget on February 2, 2017, indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. It is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

We are conducting global clinical trials in countries where corruption is prevalent. In addition, we are subject to a variety of import and export trade laws. Violations of any of these laws by our personnel or by any of our vendors or agents, such as our CROs or CMOs, could have a material adverse impact on our clinical trials and our business and could result in criminal or civil fines and sanctions.

We are subject to complex laws that govern our international business practices. These laws include the FCPA, which prohibits U.S. companies and their intermediaries, such as CROs or CMOs, from making improper payments to

foreign government officials for the purposes of obtaining or keeping business or to obtain any kind of advantage for the company. The FCPA also requires companies to keep accurate books and records and maintain adequate accounting controls. A number of past and recent FCPA investigations by the Department of Justice and the U.S. Securities and Exchange Commission have focused on the life sciences sector.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. Some of the countries in which we are conducting clinical trials have a history of corruption, which increases our risks of FCPA violations. In addition, the FCPA presents unique challenges in the pharmaceutical industry because in many countries hospitals are operated by the government, and doctors and other hospital employees are considered foreign government officials. Certain payments made by pharmaceutical companies, or on their behalf by CROs, to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Additionally, the UK Bribery Act applies to our global activities and prohibits bribery of private individuals as well as public officials. The UK Bribery Act prohibits both the offering and accepting a bribe and imposes strict liability on companies for failing to prevent bribery, unless the company can show that it had “adequate procedures” in place to prevent bribery. There are also local anti-bribery and anti-corruption laws in countries where we are conducting clinical trials, and many of these also carry the risk of significant financial or criminal penalties.

We are also subject to trade control regulations and trade sanctions laws that restrict the movement of certain goods, currency, products, materials, services and technology to, and certain operations in, various countries or with certain persons. Our ability to transfer people and products among certain countries is subject to maintaining required licenses and complying with these laws and regulations.

The internal controls, policies and procedures, and training and compliance programs we have implemented to deter prohibited practices may not be effective in preventing our employees, contractors, consultants, agents or other representatives from violating or circumventing such internal policies or violating applicable laws and regulations. The failure to comply with laws governing international business practices may impact our clinical trials, result in substantial civil or criminal penalties for us and any such individuals, including imprisonment, suspension or debarment from government contracting, withdrawal of our products, if approved, from the market, or being delisted from The Nasdaq Global Market. In addition, we may incur significant costs in implementing sufficient systems, controls and processes to ensure compliance with the aforementioned laws.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and it also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR provides that EU member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the EU. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations. Similarly, failure to comply with federal and state laws regarding privacy and security of personal information could expose us to fines and penalties under such laws. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Our relationships with healthcare providers, physicians and third-party payors are subject to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security, and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of Auryxia and any other product candidates for which we obtain marketing approval. Our arrangements with healthcare providers, physicians and third-party payors expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute Auryxia and any other product candidates for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by federal and state governments and by governments in foreign jurisdictions in which we conduct our business. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the FD&C Act which among other things, strictly regulates drug product marketing and promotion and prohibits manufacturers from marketing such products for off-label use;
- federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs, and laws requiring notification of price increases;
- the federal anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at \$5,500 to \$11,000 per false claim;
- HIPAA imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the HITECH, and their respective implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals;
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and gift ban and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and which are not preempted by federal laws and often differ from state to state, thus complicating compliance efforts; and
- U.S. state laws restricting interactions with healthcare providers and other members of the healthcare community or requiring pharmaceutical manufacturers to implement certain compliance standards.

Because of the breadth of these U.S. laws, and their non-U.S. equivalents, 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. In addition, recent healthcare reforms have strengthened these laws. For example, the Health Care Reform Act, among other things, amended the intent requirement of the federal anti-kickback law. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate the law. The Health Care Reform Act also amended the False Claims Act, such that violations of the anti-kickback statute are now deemed violations of the False Claims Act.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines, such as the Pharmaceutical Research and Manufacturers of America Code on Interactions with Health Care Professionals, known as the PhRMA Code. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties comply with applicable healthcare laws and regulations involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government funded healthcare programs.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain for any products that are approved in the United States or foreign jurisdictions.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell Auryxia and any product candidates for which we obtain marketing approval. The pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by legislative initiatives. Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any FDA approved product, such as Auryxia.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for Auryxia and any other approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA. Among the provisions of the ACA of potential importance to our business including, without limitation, our ability to commercialize and the prices we obtain for Auryxia and may obtain for any of our product candidates that are approved for sale, are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal anti-kickback statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% starting January 1, 2019) point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

new requirements to report certain financial arrangements with physicians and teaching hospitals;

- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year which will remain in effect through 2027 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for Auryxia or any product candidates for which we may obtain regulatory approval or the frequency with which Auryxia and any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

With the enactment of the Tax Cuts and Jobs Act of 2017, Congress repealed the “individual mandate.” The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause an estimated 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, the President signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole”. Further, each chamber of the U.S. Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA.

The current administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, the President has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor

payments to third-party payors who argued that such payments were owed to them. The effects of this gap in reimbursement on third-party payors, providers, and potentially our business, are not yet known.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States, and members of U.S. Congress and the current administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several recent U.S. congressional inquiries and proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the current administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Including measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Specifically, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the current administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the current administration issued a plan to lower drug prices. Under this blueprint for action, the current administration indicated that the Department of Health and Human Services, or HHS, will take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies, advance biosimilars and generics to boost price competition, evaluate the inclusion of prices in drug makers' ads to enhance price competition, speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers, avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid, work to give Medicare Part D plan sponsors more negotiation power with drug makers, examine which Medicare Part B drug prices could be negotiated by Medicare Part D plans, improve the design of the Medicare Part B Competitive Acquisition Program, update Medicare's drug-pricing dashboard to increase transparency, prohibit Medicare Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance, and require that Medicare Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. More recently, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal anti-kickback statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products or put pressure on our product pricing.

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 expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for Auryxia and any product candidates for which we receive marketing approval or additional pricing pressures. 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 Auryxia and any products candidates for which we receive marketing approval;
- our ability to set a price that we believe is fair for our products;
- our ability to obtain and maintain coverage and reimbursement approval for Auryxia or any other approved product;
- our ability to generate revenues and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the use and disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from the use of hazardous materials by our employees, contractors or consultants, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to our Reliance on Third Parties

If the licensor of certain intellectual property relating to Auryxia terminates, modifies or threatens to terminate existing contracts or relationships with us, our business may be materially harmed.

We do not own the rights to our product, Auryxia. We have licensed and sublicensed the rights, patent or otherwise, to Auryxia from a third-party, Panion, who in turn licenses certain rights to Auryxia from one of the inventors of Auryxia. The license agreement with Panion requires us to meet development milestones and imposes development and commercialization due diligence requirements on us. In addition, under the license agreement, we must pay royalties based on a mid-single digit percentage of net sales of product resulting from the licensed technologies, including Auryxia and pay the patent filing, prosecution and maintenance costs related to the license. If we do not meet our obligations in a timely manner, or if we otherwise breach the terms of our license agreement, Panion could terminate the agreement, and we would lose the rights to Auryxia. For example, following announcement of the Merger, Panion notified Keryx in writing that Panion would terminate the license agreement on November 21, 2018 if Keryx did not cure the breach alleged by Panion, specifically, that Keryx failed to use commercially reasonable best efforts to commercialize Auryxia outside the United States. Keryx disagreed with Panion's claims, and the parties entered discussions to resolve this dispute. On October 24, 2018, prior to the consummation of the Merger, we, Keryx and Panion entered into a letter agreement, or the Panion Letter Agreement, pursuant to which Panion agreed to rescind any and all prior termination threats or notices relating to the license agreement and waived its rights to terminate the license agreement based on any breach by us of our obligation to use commercially reasonable efforts to commercialize Auryxia outside the United States until the parties execute an amendment to the license agreement, in accordance with the terms of the Panion Letter Agreement, following consummation of the Merger. These terms of the amendment to the license agreement include establishing a joint steering committee consisting of Panion and our representatives to oversee the development and commercialization of Fexeric in Europe and providing Panion with an exclusive license under Keryx-owned patents covering the rights to make, use, sell, offer for sale and import ferric citrate in certain countries in the Asia-Pacific region. The parties intend to work together to agree on a commercialization plan for Fexeric in Europe following execution of the amendment to the license agreement. The amendment to the license agreement is expected to include alternatives in the event a commercialization plan is not agreed upon, such as payment of an annual license maintenance fee to Panion or the return of European intellectual property rights to Panion. In addition, under the terms of the Panion Letter Agreement, Panion has agreed that we will have the right, but not the obligation, to conduct any litigation against any infringer of patent rights under the license agreement on the terms agreed upon in the Panion Letter Agreement. Keryx made a \$500,000 payment to Panion in connection with the execution of the Panion Letter Agreement. Even though we entered into the Panion Letter Agreement, there are no assurances that we will successfully negotiate with Panion with respect to the regulatory and commercial plans for Fexeric in Europe, that an amendment to the license agreement will be entered into or that Panion will not allege other breaches of the license agreement or otherwise attempt to terminate the license agreement in the future.

In addition, if Panion breaches its agreement with the inventor from whom it licenses rights to Auryxia, Panion could lose its license, which could impair or delay our ability to develop and commercialize Auryxia.

From time to time, we may have disagreements with Panion, or Panion may have disagreements with the inventor from whom it licenses rights to Auryxia, regarding the terms of the agreements or ownership of proprietary rights, which could impact the commercialization of Auryxia, could require or result in litigation or arbitration, which would be time-consuming and expensive, could lead to the termination of our license agreement with Panion, or force us to negotiate a revised or new license agreement on terms less favorable than the original. In addition, in the event that the owners and/or licensors of the rights we license were to enter into bankruptcy or similar proceedings, we could potentially lose our rights to Auryxia or our rights could otherwise be adversely affected, which could prevent us from continuing to commercialize Auryxia.

We rely on third parties to conduct preclinical and clinical studies for our product candidates. If they do not successfully carry out their contractual duties, comply with regulatory requirements or meet expected deadlines, we may not be able to commercialize Auryxia or obtain marketing approval for or commercialize vadadustat or any other product candidates, and our business could be substantially harmed.

We do not have the ability to independently conduct preclinical and clinical trials. We are currently relying, and expect to continue to rely, on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our current and future preclinical studies and our clinical trials, including our global Phase 3 development program for vadadustat. The third parties on whom we rely may fail to perform effectively, or terminate their engagement with us, for a number of reasons, including the following:

- if the quantity or accuracy of the data obtained by the third parties is compromised due to their failure to adhere to clinical trial protocols or to regulatory requirements, or if the third parties otherwise fail to comply with clinical trial protocols, perform effectively or meet expected deadlines;
- if third parties experience staffing difficulties;
- if we fail to communicate effectively or provide the appropriate level of oversight;
- if third parties undergo changes in priorities or corporate structure or become financially distressed; or
- if they form relationships with other entities, some of which may be our competitors.

Any of these events could cause our preclinical and clinical trials, including post-approval clinical trials, to be extended, delayed, suspended, required to be repeated or terminated, or we may receive untitled warning letters or be the subject of an enforcement action which could result in our failing to obtain marketing approval of vadadustat or any other product candidates on a timely basis, or at all, or fail to maintain marketing approval of Auryxia or any other approved products, any of which would adversely affect our business operations. In addition, if the third parties on whom we rely fail to perform effectively or terminate their engagement with us, we may need to enter into alternative arrangements, which could delay, perhaps significantly, the continued commercialization of Auryxia and the development and commercialization of vadadustat and any other product candidates.

Even though we do not directly control the third parties on whom we rely to conduct our preclinical and clinical trials and therefore cannot guarantee the satisfactory and timely performance of their obligations to us, we are nevertheless responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements, including GXP requirements, and scientific standards, and our reliance on these third parties, including CROs, will not relieve us of our regulatory responsibilities. If we or any of our CROs, their subcontractors, or clinical trial sites fail to comply with applicable GXP requirements, the clinical data generated in our clinical trials may be deemed unreliable or insufficient, our clinical trials could be put on hold, and/or the FDA, the EMA or other regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. In addition, our clinical trials must be conducted with drug product that meets certain specifications and is manufactured under applicable cGMP regulations. These requirements include, among other things, quality control, quality assurance, and the satisfactory maintenance of records and documentation.

We also rely on third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, resulting in additional costs and depriving us of potential product revenue. In addition, we are using an active comparator in our PRO₂TECT and INNO₂VATE clinical programs for vadadustat. If our distributors are unable to obtain sufficient supply of the active comparator for any reason, or supply active comparator to clinical trial sites in a timely manner, our clinical trials may be extended, delayed, suspended or terminated.

We rely on third parties to conduct all aspects of our product manufacturing. If they do not successfully carry out their contractual duties, comply with regulatory requirements or meet expected deadlines, we may not be able to continue commercializing Auryxia or obtain marketing approval for or commercialize vadadustat or any other product candidates, and our business could be substantially harmed.

We do not have any manufacturing facilities and do not expect to independently manufacture any product or product candidates. We currently rely on third party manufacturers to produce all of our commercial, preclinical and clinical material supply. We expect to continue to rely on existing or alternative third party manufacturers to supply our ongoing and planned preclinical and clinical trials and for commercial production. We currently have multiple suppliers of Auryxia's drug substance and one supplier with three approved sites for the supply of Auryxia drug product. If any of our suppliers were to limit or terminate production, or otherwise fail to meet the quality or delivery requirements needed to supply Auryxia at adequate levels, we could experience losses of revenue which could materially and adversely impact our results of operations. We plan to enter into agreements with third party manufacturers to manufacture commercial quantities of drug substance and drug product for vadadustat; however, we may not be able to negotiate these agreements at commercially reasonable terms. For example, a contract manufacturer may require a substantial financial commitment, including but not limited to a commitment to fund the purchase of a new facility or equipment. Our reliance on third party manufacturers increases the risk that we will not have sufficient quantities of our product candidates or the ability to obtain such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

As a result of the large quantity of materials required for Auryxia production and the large quantities of Auryxia tablets that are required for our commercial success, the commercial viability of Auryxia will also depend on adequate supply of starting materials that meet quality, quantity and cost standards and the ability of our contract manufacturers to continually produce drug substance and finished drug product on a commercial scale. Failure to achieve and maintain these levels of supply can jeopardize and prevent the successful commercialization of Auryxia. Moreover, issues that may arise in our scale-up and technology transfer of Auryxia and continued commercial scale manufacture of Auryxia may lead to significant delays in our development and commercial timelines and negatively impact our financial performance. For example, a production-related issue resulted in an interruption in the supply of Auryxia in the third and fourth quarters of 2016. This supply interruption negatively impacted Keryx's revenues in 2016. Although this supply interruption was resolved and actions designed to prevent future interruptions in the supply of Auryxia have been taken, any future supply interruptions for Auryxia or any of our product candidates for which we receive marketing approval would negatively and materially impact our reputation and financial condition.

If any of our third-party manufacturers cannot perform as agreed, including a misappropriation of our proprietary information, or if they terminate their engagements with us, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into agreements with other third party manufacturers, which we may not be able to do on favorable or reasonable terms, if at all. In some cases, there may be a limited number of qualified replacement manufacturers, or the technical skills, or equipment required to manufacture a product or product candidate may be unique or proprietary to the original manufacturer and we may have difficulty transferring such skills or technology to another third party or a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture Auryxia or our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to continue to commercialize or satisfy patient demand for Auryxia or any other product candidate for which we receive marketing approval, or develop and receive marketing approval for our product candidates in a timely manner or within budget.

The facilities and processes used by our third party manufacturers to manufacture Auryxia may be inspected by the FDA and other regulatory authorities at any time, and the facilities and processes used by our third party manufacturers to manufacture our product candidates will be inspected by the FDA, the EMA and other regulatory authorities prior to or after we submit our marketing application. We do not control the manufacturing processes of, and are completely dependent on, our third party manufacturers for compliance with cGMP requirements for manufacture of certain starting materials, drug substance and finished drug product. If our third party manufacturers cannot successfully manufacture material that conforms to our specifications and regulatory requirements, we will not be able to maintain marketing approval for Auryxia or secure and/or maintain marketing approval for our product candidates. In addition, we have no control over the ability of our third party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, the EMA or other regulatory authorities do not approve the facilities being used to manufacture f our product candidates, or if they withdraw any approval of the facilities being used to manufacture Auryxia or any other product candidates for which we receive marketing approval, we may need to find alternative manufacturing facilities, which would significantly impact our ability to continue commercializing Auryxia or develop, obtain marketing approval for or market our product candidates, if approved. Moreover, the failure of our third party manufacturers to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of Auryxia or our product candidates operating restrictions or criminal prosecutions, any of which could significantly and adversely affect the supply of Auryxia or our product candidates. Also, if our starting materials,

drug substance or drug product are damaged or lost while in our third party manufacturers' control, it may impact our ability to supply our products or product candidates and we may incur significant financial harm. In addition, Auryxia and our product candidates may compete with other products and product candidates and products for access to third party manufacturing facilities. A third party manufacturer may also encounter delays brought on by sudden internal resource constraints, labor disputes, or shifting regulatory protocols. Certain of these third party manufacturing facilities may be contractually prohibited from manufacturing our product candidates or products, due to exclusivity provisions in agreements with our competitors. There are a limited number of manufacturers that operate under cGMP regulations and are capable of manufacturing Auryxia and our product candidates for us.

Our current and anticipated future dependence on third parties for the manufacture of Auryxia and our product candidates may adversely affect our ability to continue to commercialize Auryxia or any product candidates that receive marketing approval on a timely and competitive basis and any future profit margins.

Third party manufacturers may be unable to successfully scale-up manufacturing of our product candidates in sufficient quality and quantity, which would delay or prevent us from developing our product candidates and commercializing approved products.

In order to complete our development of and commercialize, if approved, vadadustat and any other product candidates, we will need to work with third party manufacturers to manufacture them in large quantities. Our current and future third party manufacturers may be unable to successfully achieve commercial scale production of vadadustat or increase the manufacturing capacity of any other product candidates for the conduct of clinical trials and commercialization in a timely or cost-effective manner, if at all. In addition, quality issues may arise during scale-up activities. Any changes in our manufacturing processes as a result of scaling up may result in the need to obtain additional marketing approvals. If our third party manufacturers are unable to achieve commercial scale production or there is a need for additional marketing approvals of vadadustat or any other product candidates, or if there are difficulties in increasing the manufacturing capacity for any other product candidates, the development, marketing approval and commercialization of that product candidate may be delayed or infeasible, or ongoing commercialization may be unsuccessful, any of which could significantly harm our business.

The loss of any of our manufacturers could materially harm our business.

We currently have redundant supply arrangements in place for the commercial supply of Auryxia and the preclinical and clinical supply of vadadustat. While we intend to put redundant supply arrangements in place for commercial manufacturing of vadadustat, we may be unsuccessful in doing so due to a number of factors, including that we may not be able to negotiate binding agreements at commercially reasonable terms. Even if we are ultimately successful in entering into redundant supply arrangements for commercial manufacturing of vadadustat, the timing of such arrangements is uncertain.

We do not know whether our third party manufacturers will be able to meet our demand, either because of the nature of our agreements with those third party manufacturers, or, in some cases, our limited experience with those third party manufacturers or our relative importance as a customer to those third party manufacturers. It may be difficult for us to assess their ability to timely meet our demand in the future based on past performance. While our current third party manufacturers have generally met our demand for their products on a timely basis in the past, they may subordinate our needs in the future to their other customers.

If we are unsuccessful in implementing redundant supply arrangements for commercial quantities of vadadustat or if our commercial supply arrangements for Auryxia are terminated, or if any of our third party manufacturers is unable to fulfill the terms of their agreements with us, are subject to regulatory review, or cease their operations for any reason, it could result in delays to our marketing approval and risk that we would not have sufficient quantities of our

product candidates and products for clinical trials and commercialization.

We depend on collaborations with third parties for the development and commercialization of vadadustat and Auryxia. If our collaborations are not successful or if our collaborators terminate their agreements with us, we may not be able to capitalize on the market potential of Auryxia and vadadustat, and our business could be materially harmed.

We sublicensed the rights to commercialize Riona, the trade name for ferric citrate in Japan, to Japan Tobacco, Inc., or JT, and its subsidiary Torii Pharmaceutical Co., Ltd., or Torii, in Japan. We entered into collaboration agreements with Otsuka to develop and commercialize vadadustat in the United States, Europe, China and certain other territories. We also entered into a collaboration agreement with MTPC to develop and commercialize vadadustat in Japan and certain other Asian countries. We may form or seek other strategic alliances, joint ventures, or collaborations, or enter into additional licensing arrangements with third parties that we believe will complement or augment our commercialization efforts with respect to Auryxia and our development and commercialization efforts with respect to vadadustat and any other product candidates. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies.

We may not be able to maintain our collaborations and our collaborations may not be successful due to a number of important factors, including the following:

- collaborators may have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborations may be terminated in accordance with the terms of the collaborations and, if terminated, may make it difficult for us to attract new collaborators or adversely affect how we are perceived in scientific and financial communities, and may result in a need for additional capital and expansion of our internal capabilities to pursue further development or commercialization of the applicable products and product candidates;
- if permitted by the terms of the collaborations, collaborators may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in their strategic focus, availability of funding or other external factors such as a business combination that diverts resources or creates competing priorities;
- if permitted by the terms of the collaborations, collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial, abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- a collaborator with marketing and distribution rights our products may not commit sufficient resources to their marketing and distribution;
- if permitted by the terms of the collaboration, we and our collaborator may have a difference of opinion regarding the development or commercialization strategy for a particular product, and our collaborator may have ultimate decision making authority;
- disputes may arise between a collaborator and us that cause the delay or termination of activities related to research, development or commercialization of Auryxia, vadadustat and any other product candidates, or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may not lead to development or commercialization of products and product candidates in the most efficient manner or at all;
- a significant change in the senior management team, a change in the financial condition or a change in the business operations, including a change in control or internal corporate restructuring, of any of our collaborators, could result in delayed timelines, re-prioritization of our programs, decreasing resources or funding allocated to support our programs, or termination of the collaborations; and
- collaborators may not comply with all applicable regulatory requirements.

If any of these events occurs, the market potential of our products and product candidates could be reduced, and our business could be materially harmed. We also cannot be certain that, following a collaboration, the benefits of the collaboration will outweigh the potential risks.

We may seek to establish additional collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

We will require substantial additional cash to fund the continued commercialization of Auryxia and the development and potential commercialization of vadadustat and any other product candidates. We may decide to enter into additional collaborations for the development and commercialization of vadadustat or Auryxia. Any of these relationships may require us to incur non-recurring and other charges, increase our near and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business.

We may not be successful in entering into additional collaborations as a result of many factors including the following:

- competition in seeking appropriate collaborators;
- a reduced number of potential collaborators due to recent business combinations in the pharmaceutical industry;
- inability to negotiate collaborations on acceptable terms;

- inability to negotiate collaborations on a timely basis;
- a potential collaborator's evaluation of our product or product candidates;
- a potential collaborator's resources and expertise; and
- restrictions due to an existing collaboration agreement.

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If we are unable to enter into additional collaborations, we may have to curtail the commercialization of the product or the development of the product candidate on which we are seeking to collaborate, reduce or delay its development program or other of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further commercialize Auryxia or develop or commercialize our product candidates.

Even if we enter into additional collaboration agreements and strategic partnerships or license our intellectual property, we may not be able to maintain them or they may be unsuccessful, which could delay our timelines or otherwise adversely affect our business.

Risks Related to our Intellectual Property

If we are unable to adequately protect our intellectual property, third parties may be able to use our intellectual property, which could adversely affect our ability to compete in the market.

Our commercial success will depend in part on our ability, and the ability of our licensors, to obtain and maintain patent protection on our drug product and technologies, and to successfully defend these patents against third-party challenges. We seek to protect our proprietary products and technology by filing patent applications in the United States and certain foreign jurisdictions. The process for obtaining patent protection is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications in a cost effective or timely manner. In addition, we may fail to identify patentable subject matter early enough to obtain patent protection. Further, license agreements with third parties may not allow us to control the preparation, filing and prosecution of patent applications, or the maintenance or enforcement of patents. Such third parties may decide not to enforce such patents or enforce such patents without our involvement. Thus, these patent applications and patents may not under these circumstances, be prosecuted or enforced in a manner consistent with the best interests of the company.

Our pending patent applications may not issue as patents and may not issue in all countries in which we develop, manufacture or potentially sell our product(s) or in countries where others develop, manufacture and potentially sell products using our technologies. Moreover, our pending patent applications, if issued as patents, may not provide additional protection for our product.

The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions. No consistent policy regarding the breadth of claims allowed in pharmaceutical and biotechnology patents has emerged to date. Changes in the patent laws or the interpretation of the patent laws in the United States and other jurisdictions may diminish the value of our patents or narrow the scope of our patent protection. Accordingly, the patents we own or license may not be sufficiently broad to prevent others from practicing our technologies or from developing competing products. Furthermore, others may independently develop similar or alternative drug products or technologies or design around our patented drug product and technologies which may have an adverse effect on our business. If our competitors prepare and file patent applications in the United States that claim technology also claimed by us, we may have to participate in interference or derivation proceedings in front of the U.S. Patent and Trademark Office, or USPTO, to determine priority of invention, which could result in substantial cost, even if the eventual outcome is favorable to us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that any related patent may expire prior to, or remain in existence for only a short period following, commercialization, thus reducing any advantage of the patent. The patents we own or license may be challenged or invalidated or may fail to provide us with any competitive advantage. Since we have licensed or sublicensed many patents from third parties, we may not be able to enforce such licensed patents

against third-party infringers without the cooperation of the patent owner and the licensor, which may not be forthcoming. In addition, we may not be successful or timely in obtaining any patents for which we submit applications.

Additionally, the laws of foreign countries may not protect our intellectual property rights to the same extent as do the laws of the United States. For example, claims in a patent application directed to methods of treatment of the human body are not patentable or are restricted in many non-U.S. countries. Further, we may not pursue or obtain patent protection in all major markets. In addition, in jurisdictions outside the United States where we own or license patent rights, we may be unable to prevent unlicensed parties from selling or importing products or technologies derived elsewhere using our proprietary technology.

Generally, the first to file a patent application is entitled to the patent if all other requirements of patentability are met. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Since publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Moreover, the laws enacted by the Leahy-Smith America Invents Act of 2011, or the Act, which reformed certain patent laws in the United States, introduce procedures that permit competitors to challenge our patents in the USPTO after grant, including inter partes review and post grant review. Similar laws exist outside of the United States. The laws of the European Patent Convention, for example, provide for post-grant opposition procedures that permit competitors to challenge, or oppose, our European patents administratively at the European Patent Office.

On November 25, 2015, a third party filed an opposition to our issued European Patent No. 1 931 689, or the '689 EP Patent, which covers Fexeric. During the oral proceedings, which took place on June 27, 2017, the Opposition Division of the European Patent Office, or EPO, revoked the '689 EP Patent. On December 6, 2017, we filed an appeal of the decision of the Opposition Division, which is presently pending. According to European practice, the revocation of the patent is stayed until an appeal is finally resolved. We anticipate the appeal will take a few years to resolve, during which time the patent will remain in force.

On December 23, 2016, a third party filed an opposition to our issued European Patent No. 1 978 807, or the '807 EP Patent, which covers Fexeric. During the oral proceedings, which took place on June 8, 2018, the Opposition Division of the EPO maintained the '807 EP Patent as granted. This decision resulted in the maintenance of all of the claims of the patent, including claims directed to the use of ferric citrate for preventing, reversing, maintaining or delaying progression of chronic kidney disease. On November 16, 2018, the third party filed an appeal of the decision of the Opposition Division, which is presently pending. We anticipate the appeal will take a few years to resolve.

In July 2011, a third party filed an opposition to our issued European patents, European Patent No. 2044005, or the '005 EP Patent, which covers vadadustat. During the oral proceedings, which took place on April 10, 2013, the Opposition Division of the European Patent Office decided to maintain certain claims of the patent directed to a compound chosen from a group of eight compounds, including vadadustat, as well as claims to compositions and methods for treating various diseases including, but not limited to, anemia. Both parties appealed the decision of the Opposition Division. On February 27, 2018, we withdrew the '005 EP Patent from appeal and filed a divisional patent application to pursue a focused claim set that includes claims for vadadustat, as well as pharmaceutical compositions and methods of treating anemia. We cannot be assured that such claims in the divisional application will be granted by the European Patent Office. If such claims are not granted, or the scope of the claims is significantly narrowed, we may not be able to adequately protect our rights, provide sufficient exclusivity, or preserve our competitive advantage.

We may become involved in addressing patentability objections based on third-party submission of references, or we may become involved in defending our patent rights in oppositions, derivation proceedings, reexamination, inter partes review, post grant review, interference proceedings or other patent office proceedings or litigation, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse result in any such proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged on such a basis in the courts or patent offices in the United States and abroad. As a result of such challenges, we may lose exclusivity or freedom-to-operate or patent claims may be narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to prevent third parties from using or commercializing similar or identical products, or limit the duration of the patent protection for our products.

In addition, patents protecting our product candidate might expire before or shortly after such candidate is commercialized. Thus, our patent portfolio may not provide sufficient rights to exclude others from commercializing products similar or identical to ours.

We also rely on trade secrets and know-how to protect our intellectual property where we believe patent protection is not appropriate or obtainable. Trade secrets are difficult to protect. While we require our employees, licensees, collaborators and consultants to enter into confidentiality agreements, this may not be sufficient to adequately protect our trade secrets or other proprietary information. In addition, we share ownership and publication rights to data relating to our drug product and technologies with our research collaborators and scientific advisors. If we cannot maintain the confidentiality of this information, our ability to receive patent protection or protect our trade secrets or other proprietary information will be at risk.

The intellectual property that we own or have licensed relating to our product, Auryxia, is limited, which could adversely affect our ability to compete in the market and adversely affect the value of Auryxia.

The patent rights that we own or have licensed relating to Auryxia are limited in ways that may affect our ability to exclude third parties from competing against us. For example, a third-party may design around our owned or licensed composition of matter patent claims or not market a product for methods of use covered by our owned or licensed patents.

Obtaining proof of direct infringement by a competitor for a method of use patent requires us to demonstrate that the competitors make and market a product for the patented use(s). Alternatively, we can prove that our competitors induce or contribute to others in engaging in direct infringement. Proving that a competitor contributes to, or induces, infringement of a patented method by another has additional proof requirements. For example, proving inducement of infringement requires proof of intent by the competitor. If we are required to defend ourselves against claims or to protect our own proprietary rights against others, it could result in substantial costs to us and the distraction of our management. An adverse ruling in any litigation or administrative proceeding could prevent us from marketing and selling Auryxia, increase the risk that a generic or other similar version of Auryxia could enter the market to compete with Auryxia, limit our development and commercialization of Auryxia, or otherwise harm our competitive position and result in additional significant costs. In addition, any successful claim of infringement asserted against us could subject us to monetary damages or injunction, which could prevent us from making or selling Auryxia. We also may be required to obtain licenses to use the relevant technology. Such licenses may not be available on commercially reasonable terms, if at all.

Moreover, physicians may prescribe a competitive identical product for indications other than the one for which the product has been approved, or “off-label” indications, that are covered by the applicable patents. Although such off-label prescriptions may directly infringe or contribute to or induce infringement of method of use patents, such infringement is difficult to prevent.

In addition, any limitations of our patent protection described above may adversely affect the value of our drug product and may inhibit our ability to obtain a collaboration partner at terms acceptable to us, if at all.

In the United States, the FDA has the authority to grant additional regulatory exclusivity protection for approved drugs where the sponsor conducts specified testing in pediatric or adolescent populations. If granted, this pediatric exclusivity may provide an additional six months which are added to the term of any non-patent exclusivity that has been awarded as well as to the regulatory protection related to the term of a relevant patent, to the extent these protections have not already expired.

In addition to patent protection, we may utilize, if granted by the FDA, pediatric exclusivity or other provisions of the FDCA such as new chemical entity, or NCE, exclusivity, or exclusivity for a new use or new formulation, to provide non-patent market exclusivity for a drug product. The FDCA provides a five-year period of non-patent exclusivity within the United States to the first applicant to gain approval of a new drug application, or NDA, for an NCE. A drug is an NCE if the FDA has not previously approved any other new drug containing the same active moiety, which consists of the molecule(s) or ion(s) responsible for the action of the drug substance (but not including those portions of the molecule that cause it to be a salt or ester or which are not bound to the molecule by covalent or similar bonds). During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an ANDA or 505(b)(2) NDA that references an NDA product with NCE exclusivity may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application (for example, for new indications, dosages, or strengths of an existing drug). This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. The three-year exclusivity period, unlike five-year exclusivity, does not prevent the submission of a competing ANDA or 505(b)(2) NDA. Instead, it only prevents the FDA from granting final approval to such a product until expiration of the exclusivity period. Five-year and three-year exclusivity will not delay the submission (in the case of five-year exclusivity) or the approval (in the case of three-year exclusivity) of a full NDA submitted under section 505(b)(1) of the FDCA; however, an applicant submitting a full NDA would be

required to conduct all of its own studies needed to independently support a finding of safety and effectiveness for the proposed product, or have a full right of reference to all studies not conducted by the applicant.

On August 23, 2018, Keryx submitted a Citizen Petition requesting, inter alia, that FDA recognize that Auryxia is eligible for five years of new chemical entity, or NCE, exclusivity based on its novel active ingredient and for three years exclusivity for the IDA Indication. On January 19, 2019, FDA responded that Auryxia is eligible for a three-year exclusivity period for the IDA Indication, which expires on November 6, 2020. FDA, however, denied the NCE exclusivity based on its determination that Auryxia contains a previously-approved active moiety (ferric cation). FDA's decision on the Citizen Petition is subject to further review both within FDA and in the courts. On February 21, 2019, we filed a Petition for Reconsideration of FDA's decision on the NCE determination for Auryxia.

We cannot assure that Auryxia or any drug candidates we may acquire or in-license will obtain such pediatric exclusivity, NCE exclusivity or any other market exclusivity in the United States, EU or any other territory, or that we will be the first to receive the respective regulatory approval for such drugs so as to be eligible for any market exclusivity protection. We also cannot assure that Auryxia or any drug candidates we may acquire or in-license will obtain patent term extension.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to assist with research, development and manufacture of our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, services agreements, material transfer agreements, consulting agreements, research agreements or other similar agreements with our advisors, employees, third-party contractors, collaborators and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such information becomes known by our competitors, is inadvertently incorporated into the technology of others, or is disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors, and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution with which we may collaborate will usually expect to be granted rights to publish data arising out of such collaboration. We often grant such rights, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration and remove confidential or trade secret information from any such publication. In the future, we may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties or independent development or disclosure or publication of information by any of our employees, advisors, consultants, third-party contractors or collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Litigation or third-party claims of intellectual property infringement may be costly and time consuming and may delay or harm our drug discovery, development and commercialization efforts.

We may be forced to initiate litigation to enforce our contractual and intellectual property rights, or we may be sued by third parties asserting claims based on contract, tort or intellectual property infringement. In addition, third parties may have or may obtain patents in the future and claim that our product or any other technologies infringe their patents. If we are required to defend against suits brought by third parties, or if we sue third parties to protect our rights, we may be required to pay substantial litigation costs, and our management's attention may be diverted from operating our business. In addition, any legal action against our licensor or us that seeks damages or an injunction of our commercial activities relating to our product or other technologies could subject us to monetary liability, a temporary or permanent injunction preventing the development, marketing and sale of our product or such technologies, and/or require our licensor or us to obtain a license to continue to use our product or other technologies. We cannot predict whether our licensor or we would prevail in any of these types of actions or that any required license would be made available on commercially acceptable terms, if at all.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. The pharmaceutical and biotechnology industries are characterized by extensive litigation over patent and other intellectual property rights. We have in the past and may in the future become a party to, or be threatened with, future adversarial litigation or other proceedings regarding intellectual property rights with respect to our drug candidates. As the pharmaceutical and biotechnology industries expand and more patents are issued, the risk increases

that our drug candidates may give rise to claims of infringement of the patent rights of others.

While our product candidates are in preclinical studies and clinical trials, we believe that the use of our product candidates in these preclinical studies and clinical trials in the United States falls within the scope of the exemptions provided by 35 U.S.C. Section 271(e), which provides that it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention solely for uses reasonably related to the development and submission of information to the FDA. As a result of the Merger, our portfolio now includes a commercial product, Auryxia. Consequently, there is an increased possibility of a patent infringement claim against us. We attempt to ensure that our product candidates and the methods we employ to manufacture them, as well as the methods for their use which we intend to promote, do not infringe other parties' patents and other proprietary rights. There can be no assurance they do not, however, and competitors or other parties may assert that we infringe their proprietary rights in any event.

Third parties may hold or obtain patents or other intellectual property rights and allege in the future that the use of our products or product candidates infringes these patents or intellectual property rights, or that we are employing their proprietary technology without authorization. We do not believe that there are any currently issued U.S. patents that will prevent us from commercializing Auryxia or vadadustat; nor do we make any admission that any of such patents are valid, enforceable or infringed. Under U.S. law, a party may be able to patent a discovery of a new way to use a previously known compound, even if such compound itself is patented, provided the newly discovered use is novel and nonobvious. Such a method-of-use patent, however, if valid, only protects the use of a claimed

compound for the specified methods claimed in the patent. This type of patent does not prevent persons from using the compound for any previously known use of the compound. Further, this type of patent does not prevent persons from making and marketing the compound for an indication that is outside the scope of the patented method. We are not aware of any valid U.S. patents issued to FibroGen, or any other person, that claim methods of using any of our product candidates for purposes of inhibiting hypoxia-inducible factor prolyl hydroxylases, or HIF-PHs, for the treatment of anemia due to CKD. For example, we are aware of certain patents that have been acquired by FibroGen directed to certain heterocyclic carboxamide compounds that are described as inhibitors of prolyl-4-hydroxylase. Those patents, however, are believed to have expired as of December 2014.

FibroGen has also filed other patent applications in the U.S. and other countries directed to purportedly new methods of using such previously known heterocyclic carboxamide compounds for purposes of treating or affecting specified conditions, and some of these applications have since issued as patents. To the extent any such patents issue or have been issued, we may initiate opposition or other legal proceedings with respect to such patents. We discuss the status of the opposition and/or invalidation proceedings against certain FibroGen patents in Part I, Item 3. Legal Proceedings of this Annual Report on Form 10-K.

There may be other patents of FibroGen or patents of other third parties of which we are currently unaware with claims to compounds, materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our drug candidates. Also, because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe.

Third parties, including FibroGen, may in the future claim that our product candidates and other technologies infringe upon their patents and may challenge our ability to commercialize vadadustat. Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to continue to commercialize Auryxia or further develop and commercialize vadadustat or any other product candidates. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our products or product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product or product candidate unless we obtained a license under the applicable patents, or until such patents expire or they are finally determined to be held invalid or unenforceable. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or our intended methods of use, including patient selection methods, the holders of any such patent may be able to block or impair our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires or is finally determined to be held invalid or unenforceable. We may also elect to enter into a license in order to settle litigation or in order to resolve disputes prior to litigation. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our products or product candidates. Should a license to a third-party patent become necessary, we cannot predict whether we would be able to obtain a license or, if a license were available, whether it would be available on commercially reasonable terms. If such a license is necessary and a license under the applicable patent is unavailable on commercially reasonable terms, or at all, our ability to commercialize our products or product candidates may be impaired or delayed, which could in turn significantly harm our business.

Further, defense of infringement claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties or redesign our products, which may be impossible or require substantial time and monetary expenditure.

We are currently involved in patent infringement lawsuits and opposition and invalidity proceedings and may in the future be involved in additional lawsuits or administrative proceedings to challenge the patents of our competitors or to protect or enforce our patents, which could be expensive, time consuming, and unsuccessful.

Competitors may infringe our patents or misappropriate our trade secrets or confidential information. To counter infringement or unauthorized use, we may be required to file infringement or misappropriation claims, which can be expensive and time-consuming. We may not be able to prevent infringement of our patents or misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable, or interpreted narrowly and held not infringed and could put our patent applications at risk of not issuing.

In addition, there may be a challenge or dispute regarding inventorship or ownership of patents or applications currently identified as being owned by or licensed to us. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. Interference proceedings provoked by third parties or brought by the US PTO may be necessary to determine the priority of inventions with respect to our patents or patent applications.

Various administrative proceedings are also available for challenging patents, including interference, reexamination, inter partes review, and post-grant review proceedings before the US PTO or oppositions and other comparable proceedings in foreign jurisdictions. An unfavorable outcome in any current or future proceeding in which we are challenging third-party patents could require us to cease using the patented technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms or at all. Even if we are successful, participation in interference or other administrative proceedings before the US PTO or a foreign patent office may result in substantial costs and distract our management and other employees.

For example, we are currently involved in patent infringement lawsuits against several generic companies in the District Courts of Delaware and West Virginia. In addition, we are currently involved in opposition or invalidation proceedings in the European Patent Office, the Japan Patent Office, the Canadian Federal Court and the United Kingdom Patents Court. These proceedings may be ongoing for a number of years and may involve substantial expense and diversion of employee resources from our business. In addition, we may become involved in additional opposition proceedings or other legal or administrative proceedings in the future. For more information, see the other risk factors under “Risks Related to our Intellectual Property” and Part I, Item 3. Legal Proceedings of this Annual Report on Form 10-K.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation and some administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure during discovery. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

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

Periodic maintenance fees on any issued patent are due to be paid to the US PTO and foreign patent agencies in several stages over the lifetime of the patent. The US PTO and governmental patent agencies in other jurisdictions also require compliance with a number of procedural, documentary, fee payment (such as annuities) and other similar provisions during the patent application process. While an inadvertent lapse in many cases can be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees, and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from potential collaborators, prospective licensees and other third parties. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former employers. We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We may be subject to ownership disputes in the future arising, for example, from conflicting obligations of consultants or others who are involved in

developing our product candidates. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

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

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive. Consequentl