Akebia Therapeutics, Inc.
Form 10-K
March 12, 2018

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2017

OR

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

AKEBIA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

| | |
|---|---|
| Delaware<br>(State or other jurisdiction of incorporation or organization) | 20-8756903<br>(I.R.S. Employer Identification No.) |
| 245 First Street, Suite 1100, Cambridge, MA<br>(Address of principal executive offices) | 02142<br>(Zip Code) |

Registrant’s telephone number, including area code: (617) 871-2098

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.00001 per share, traded on The NASDAQ Global Market

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

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

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the 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 |
| Non-accelerated filer | (Do not check if a smaller reporting company) | Smaller reporting company<br>Emerging growth company |

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the 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, 2017, was $576,393,274.

The number of shares of registrant's common stock outstanding as of March 1, 2018 was 48,346,171.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Proxy Statement for the registrant's 2018 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," "contemplate," "continue," "could," "designed," "estimate," "expect," "forecast," "future," "goal," "intend," "likely," "possible," "potential," "predict," "project," "strategy," "seek," "should," "target," "will," "would," and other words and terms of similar meaning. These forward-looking statements include, but are not limited to, statements about:

- the potential therapeutic applications of the HIF pathway;
- the potential of our pipeline 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 candidates;
- 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, revenues, capital requirements, need for additional capital, 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, disclosure controls and procedures;
- the timing of the availability and presentation 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;
- the timing of or likelihood of regulatory filings and approvals, including labeling or other restrictions;
- 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 our collaborators and licensees, and the anticipated arrangements and benefits under our collaboration and license agreements;
- 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;
- the impact of accounting standards and estimates;
- our facilities, lease commitments, and future availability of facilities;
- our employees, employee compensation, and employee relations; and
- the implementation of our business model and strategic plans for our business, product candidates and technology.

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, 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.

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.

PART I

Item 1. Business

Overview

We are a biopharmaceutical company focused on developing and commercializing novel therapeutics for patients based on hypoxia-inducible factor, or HIF, biology, and building our pipeline while leveraging our development and commercial expertise in renal disease. HIF is the primary regulator of the production of red blood cells, or RBCs, in the body, as well as other important metabolic functions. Pharmacologic modulation of the HIF pathway may have broad therapeutic applications. Our lead product candidate, vadadustat, is an oral therapy in Phase 3 development and has the potential to set a new standard of care in the treatment of anemia due to chronic kidney disease, or CKD. Our management team has extensive experience in developing and commercializing drugs for the treatment of renal and metabolic disorders, as well as a deep understanding of HIF biology. This unique combination of HIF and renal expertise is enabling us to advance a pipeline of HIF-based therapies to potentially address serious diseases.

HIF, a pathway involving hundreds of genes, is the same pathway used by the body to adapt to lower oxygen availability, or hypoxia, such as that experienced with a moderate increase in altitude. At higher altitudes, the body responds to lower oxygen levels by increasing the availability of HIF, which coordinates the interdependent processes of iron utilization and erythropoietin, or 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. HIF protein is constantly being produced under normal oxygen conditions, but is quickly degraded by prolyl hydroxylases, or PH. Under hypoxic conditions, HIF-PHs are inhibited, allowing HIF to stimulate erythropoiesis. These findings have opened up new possibilities for developing therapeutics, such as HIF-PH inhibitors, which have the potential to treat many diseases.

Our lead product candidate, vadadustat, is a HIF-PH inhibitor, or HIF-PHI, in Phase 3 development for the treatment of anemia due to CKD. Anemia is common in patients with CKD, and its prevalence increases as CKD progresses. 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. In patients with CKD, anemia results from inadequate EPO levels, which negatively affect RBC production. In addition, iron, which is essential to RBC production, may be deficient in patients with CKD. Left untreated, anemia significantly 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 from CKD is currently treated by injectable recombinant human erythropoiesis-stimulating agents, or injectable ESAs, such as EPOGEN® (epoetin alfa) and Aranesp® (darbepoetin alfa), or with iron supplementation or RBC 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 $7.0 billion in 2016. The vast majority of these sales were for the treatment of anemia due to CKD.

When administered to a patient, injectable ESAs provide supra-physiological levels of exogenous erythropoietin 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. Today, anemia is either not treated or inadequately treated in the majority of non-dialysis dependent, or NDD, CKD patients. There is

an unmet need for treatment options that offer an improved safety profile and such agents would have significant market potential.

Vadadustat is designed to stimulate erythropoiesis and effectively treat renal anemia while avoiding the supra-physiologic EPO levels previously observed with injectable ESAs. In addition, vadadustat, if approved, would provide patients with an oral treatment option, rather than an injection. For these reasons, we believe that vadadustat has the potential to set a new standard of care for the treatment of anemia due to CKD.

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 NDD-CKD patients with anemia, called $PRO_2TECT$, and in dialysis dependent, or DD, CKD patients with anemia, called $INNO_2VATE$, is designed to enroll up to approximately 6,900 patients evaluating once daily oral dosing of vadadustat against an injectable ESA active comparator, darbepoetin alfa. The enrollment numbers and the completion of $PRO_2TECT$ and $INNO_2VATE$ will be driven by the accrual of major adverse cardiovascular events, or MACE. In December 2015, the first patient was dosed in $PRO_2TECT$, and the first patient was dosed in $INNO_2VATE$ in August 2016. As of December 31, 2017, we expect the remaining external aggregate contract research organization, or CRO, costs of $PRO_2TECT$ and $INNO_2VATE$ to be in the range of $420.0 million to $450.0 million. We anticipate reporting top-line clinical data for the $PRO_2TECT$ and $INNO_2VATE$ studies in 2019, subject to the accrual of MACE events. Subject to marketing approvals, we plan to launch vadadustat for the treatment of anemia due to CKD in 2020.

We revised the study designs of $FO_2$RWARD and TRI$LO_2$GY, which we believe will provide additional characterization and differentiation of vadadustat and further strengthen our commercial position if our product candidate is approved. The revised $FO_2$RWARD study will include once-daily and three-times weekly dosing, data to inform ESA-switching protocols, a larger sample size, and a broader dialysis population that is inclusive of hyporesponders, or patients with anemia due to CKD who are on dialysis and do not adequately respond to injectable ESA. Hyporesponders represent approximately 10-15% of subjects with anemia due to DD-CKD, yet they account for 30-40% of total injectable ESA use. These patients have demonstrated a persistently higher risk of mortality than non-hyporesponders, and represent a high unmet need. Given its differentiated mechanism of action, we believe that vadadustat may provide a treatment option for these patients. The revised TRI$LO_2$GY study will include once-daily and three-times weekly dosing and an ESA control, a larger sample size, and a design that can generate data to inform switching from Epogen®, Aranesp® and Mircera®.

If vadadustat is approved by the United States Food and Drug Administration, or FDA, we plan to establish our own commercial organization in the United States while leveraging our collaboration with Otsuka Pharmaceutical Co. Ltd., or Otsuka, and its well-established commercial organization in the United States. 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 May 2017, we entered into an exclusive license agreement with Vifor (International) Ltd., or Vifor Pharma, to sell vadadustat solely to Fresenius Kidney Care Group LLC, or FKC, dialysis clinics in the United States subject to approval by the FDA and inclusion of vadadustat in a bundled reimbursement model. 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.

In addition to vadadustat, we are developing a HIF-based portfolio of product candidates that target serious diseases of high unmet need. Our portfolio includes product candidates developed internally as well as in-licensed product candidates, such as AKB-5169. In February 2017, we signed an exclusive agreement with Janssen Pharmaceutica NV, or Janssen, a subsidiary of Johnson & Johnson, for access to an extensive library of well-characterized HIF pathway compounds with potential applications across multiple therapeutic areas. The lead compound, AKB-5169, is a differentiated preclinical compound in development as an oral treatment for inflammatory bowel disease, or IBD. We intend to complete further preclinical development of this compound, and we are targeting submitting an Investigational New Drug application, or IND, to the FDA in 2018.

Upcoming Milestones

Anemia Overview

Anemia is a term used to describe a decrease in RBCs. RBCs contain a protein called hemoglobin that is responsible for moving oxygen throughout the body. As a result, anemia is measured by the level of hemoglobin in the blood. Patients with CKD often have anemia because the kidneys do not make enough EPO, which stimulates the body to make RBCs. Less EPO causes the body to make fewer RBCs and hemoglobin, decreasing the supply of oxygen throughout the body. Anemia is a serious medical condition that exists when hemoglobin drops below 13 g/dL in men and 12 g/dL in women and, if left untreated, is associated with chronic fatigue, increased risk of progression of multiple diseases, and death. Successful treatment of anemia significantly improves patients' quality of life and is associated with decreased cardiovascular morbidity, less frequent hospitalizations and lower mortality risk.

Chronic Kidney Disease

CKD, a common cause of anemia, 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.

As detailed in the table below, based on prevalence, CKD is estimated to affect approximately 37 million people in the United States. Additionally, the prevalence of anemia increases with the severity of CKD from an estimated 20% in Stage 3 non-dialysis to an estimated 95% in Stage 5 dialysis.

Stages and Prevalence of Chronic Kidney Disease in the United States

| Stage | Description | GFR (mL/min/1.73m$^2$)[a] | U.S. Prevalence Rates[b, c] | Estimated Number of U.S. Patients (millions)[d, e] |
|---|---|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥90 | 4.6% | 11.2 |
| 2 | Kidney damage with mildly 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 |
| 5 | Kidney failure (includes non-dialysis, dialysis and transplant) | <15 (or dialysis) | 0.3% (calculated) | 0.7 |

Sources:

[a] GFR categories defined in the August 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Anemia in Chronic Kidney Disease, p. vii.

[b] U.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.

[c] U.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.

[d]

Estimated 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 the Company to U.S. population data for people 20 years and older from www.census.gov.

[e] Estimated 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 numbers of elderly people are increasing. This effect will be enhanced 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.

Current Treatments Leave a Substantial Unmet Need

Injectable ESAs are currently the standard of care for treating anemia in patients with CKD and must be administered intravenously or subcutaneously along with iron supplements. In 2006, data was published on the risks of injectable ESA use by these patients, forcing physicians to balance serious safety concerns against the efficacy of injectable ESAs. The well-documented safety concerns associated with the use of injectable ESAs include increased cardiovascular risk and the potential for increased rate of tumor progression in patients with cancer[1].

As a result of the safety concerns related to injectable ESA use, patients live with lower hemoglobin levels, higher rates of RBC transfusions, and receive more intravenous iron, or IV iron, to treat anemia due to CKD. IV iron and RBC transfusions also subject patients to safety risks. The risks of RBC transfusions include the development of antibodies to foreign antigens, which may negatively impact candidacy for kidney transplantation, the potential transmission of blood-borne pathogens and iron overload with chronic transfusions. The risks of IV iron use include hypersensitivity reactions, including fatal anaphylactic-type reactions.

The graph below, based on a post hoc analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency, or CHOIR, study suggests that patients achieving higher hemoglobin levels with lower injectable ESA doses had better outcomes than patients receiving higher injectable ESA doses despite lower achieved hemoglobin levels. Therefore, higher injectable ESA doses, not the achieved hemoglobin level, appeared to be most strongly correlated with adverse outcomes.

[1] Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339(9):584-590.
Pfeffer MA, Burdmann EA, Chen CY, Coopper ME, de Zeeuw D, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361(21):2019-2032.

Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355(20):2085-2098.
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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 under the "Vadadustat Clinical Development Overview" section 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.
- 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.

- Vadadustat was dosed orally once daily and three-times weekly. Phase 2 studies have shown that vadadustat can be orally dosed once daily in NDD-CKD subjects over 20 weeks of dosing. In addition, a Phase 2 clinical study in DD-CKD subjects demonstrated that in subjects who remained on therapy, once daily or three-times weekly oral dosing of vadadustat maintained stable hemoglobin levels in subjects converting from injectable ESA therapy over 16 weeks.
- 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.

For the above reasons, we believe that vadadustat has the potential to stimulate erythropoiesis while demonstrating a reduced risk of cardiovascular and thrombotic events compared to injectable ESAs. These cardiovascular and thrombotic risks have been associated with supra-physiologic increases in EPO levels and excessive hemoglobin fluctuations and/or excursions beyond the target range. The incidence of cardiovascular and thrombotic adverse events associated with vadadustat as compared with darbepoetin alfa, an injectable ESA, is being assessed in the global Phase 3 program for vadadustat.

Market Potential

We believe there is significant market opportunity for an oral HIF-based product, such as vadadustat, to potentially treat dialysis and non-dialysis patients with anemia due to CKD, some of whom are receiving injectable ESA therapy and many of whom are not due to the safety concerns and other barriers to treatment associated with injectable ESAs.

We estimate that approximately 400,000-450,000 U.S. dialysis patients are currently receiving some injectable ESA treatment for anemia due to CKD. According to the 2017 U.S. Renal Data System, or USRDS, Annual Data Report, there are approximately 438,000 US patients on hemodialysis and 49,000 patients on peritoneal dialysis, with approximately 90% of patients and 75% of patients receiving ESA therapy, respectively.

Data from the 2015 USRDS Annual Data Report indicate that the collective injectable ESA treatment rate in NDD-CKD patients decreased by approximately half from 2009 to 2013, following the emergence of cardiovascular safety concerns associated with injectable ESAs and kidney disease guideline updates. This change in injectable ESA treatment rate suggests there is potential to treat a large patient population with HIF-based products who are not receiving injectable ESAs today. Moreover, many patients are not treated with an injectable ESA even though their hemoglobin concentration is below the ESA treatment initiation threshold suggested by the Kidney Disease Improving Global Outcomes, or KDIGO.

HIF-PH Inhibition: A Mechanism of Action That Is Designed to Mimic the Body's Physiologic Response to Hypoxia

Vadadustat is designed to work by a mechanism of action that differs from injectable ESAs. This mechanism of action is referred to as HIF-PH inhibition. HIF is the primary regulator of the production of RBCs and is responsible for orchestrating the body's physiologic response to lower levels of oxygen, or hypoxia. In response to hypoxia, a coordinated adaptive response occurs resulting in both an increase in RBC production, a normal biological process known as erythropoiesis, and enhancement of the delivery of iron to the bone marrow, ensuring the incorporation of iron into hemoglobin to support erythropoiesis. HIFa is constitutively expressed in the cytoplasm but broken down immediately under normal oxygen conditions by the HIF-PHa enzymes. Inhibition of these enzymes allows HIFa concentrations to build and translocate to the nucleus to initiate hypoxic gene transcription, where it binds to the HIFß protein. When bound together, HIFa and HIFß stimulate erythropoiesis and iron transfer proteins. With continued stabilization of the HIFa protein either by staying at higher altitude or by the administration of a HIF-PHI, the level of hemoglobin and RBCs will rise in order to increase the amount of oxygen circulating in the blood.

Vadadustat Clinical Development Overview

The following 17 studies of vadadustat have evaluated the safety, tolerability, pharmacokinetic and pharmacodynamic properties of vadadustat and supported further clinical development:

- nine completed Phase 1 studies in normal healthy volunteers (CI 0001, CI 0002, CI 0006, CI 0008, CI 0010, CI 0012, CI 0013, CI-0019, and CI-0020);
- one completed Phase 1 study in DD-CKD subjects with anemia (CI 0009);
- five completed Phase 2 studies in NDD-CKD subjects with anemia (CI 0003, CI 0004, CI 0005, CI 0007, CI-0021); and
- two completed Phase 2 studies in DD-CKD subjects with anemia (CI 0011, CI-0022).

The results from three of these studies are summarized below.

Vadadustat Clinical Development Summary

Findings from two clinical studies demonstrated that vadadustat stimulated endogenous EPO production while avoiding excessive increases, achieved the desired outcomes of raising and maintaining hemoglobin, and increased iron mobilization to support erythropoiesis. Vadadustat's safety profile has generally been consistent across Phase 1 and 2 studies completed to date. The common adverse events, or AEs, and serious adverse events, or SAEs, for the respective studies are discussed 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 39%, 69%, and 86% over baseline, at 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 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 at 16.7%, with evidence of a dose-related effect. No 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 1 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 rate 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 variations of hemoglobin from baseline, known as hemoglobin excursions, of ≥13 g/dL.

The average age of subjects was 66 years; approximately 75% of subjects had diabetes mellitus; and the mean estimated GFR was 25 mL/min/1.73m$^2$. 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 2 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 were considered drug-related by the investigator. The percentage of subjects who had an SAE resulting in dialysis initiation, an 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. There were three deaths in vadadustat-treated subjects of which two were considered to be unrelated to vadadustat and one was considered by the investigator to be possibly related because no autopsy was performed to assess relatedness. 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. The study supports both daily and three-times weekly vadadustat dosing regimens as viable options. 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.

Adverse events were balanced across the three cohorts. There were no discernible trends in the frequency of AEs or SAEs by dose cohort. The most frequently reported AEs were nausea and diarrhea with no apparent dose relationship. The majority of AEs were mild or moderate in severity. SAEs were reported in 13 subjects, or 13.8%; no SAEs were reported as related to vadadustat and no deaths occurred during the study. Reported events appear to be consistent in frequency and severity with previous clinical experience and co-morbidities described in medical literature in subjects with CKD. The results of this study were reported at the American Society of Nephrology meeting in November 2015 and the National Kidney Foundation Spring Clinical Meeting in April 2016.

Phase 3 Global Program

We are conducting two global Phase 3 studies to support an indication for the treatment of anemia in NDD-CKD patients and two global Phase 3 studies to support an indication for the treatment of anemia in DD-CKD patients, the

details of which are below. In addition, we plan to initiate another Phase 3 DD-CKD study, known as TRILO$_2$GY, in late 2018 or early 2019.

- CI-0014: “Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD CKD) (PRO$_2$TECT - CORRECTION)”
- CI-0015: “Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD CKD) (PRO$_2$TECT CONVERSION)”

- CI-0016: "Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction or Maintenance Treatment of Anemia in Subjects with Dialysis-Dependent Chronic Kidney Disease (DD CKD) (INNO$_2$VATE – CORRECTION/ CONVERSION)"
- CI-0017: "Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Dialysis-Dependent Chronic Kidney Disease (DD-CKD) (INNO$_2$VATE CONVERSION)"

In both the PRO$_2$TECT and INNO$_2$VATE Phase 3 programs, the primary efficacy endpoint is the mean change in hemoglobin between baseline, which is the mean pretreatment hemoglobin, and the primary evaluation period, concluding non-inferiority, or NI, when the upper 95% confidence interval of the hazard ratio of vadadustat to darbepoetin alfa does not exceed the NI margin. Both the PRO$_2$TECT and INNO$_2$VATE 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 will be performed, concluding NI when the upper 95% confidence interval of the hazard ratio of vadadustat to darbepoetin alfa does not exceed the NI margin. We obtained feedback from the United States and European regulatory authorities regarding the design of these programs.

Overall, the PRO$_2$TECT and INNO$_2$VATE Phase 3 programs are designed to enroll up to approximately 6,900 CKD subjects. We have engaged IQVIA, formerly known as Quintiles IMS, as our primary clinical CRO for the PRO$_2$TECT and INNO$_2$VATE programs. As of December 31, 2017, we expect the remaining external aggregate CRO costs of the PRO$_2$TECT and INNO$_2$VATE programs to be in the range of $420.0 million to $450.0 million. Such estimated costs could increase significantly if PRO$_2$TECT and INNO$_2$VATE takes longer to complete or if we choose to add additional investigative sites, add additional patients, modify the clinical trial protocol, or perform other studies in support of PRO$_2$TECT and INNO$_2$VATE.

We plan to initiate a Phase 3 study, TRILO$_2$GY, based on the results of our Phase 2 study (CI-0011) which demonstrated that vadadustat, administered once-daily or three-times weekly, maintained hemoglobin levels in hemodialysis subjects who were converted from existing injectable ESA therapy and remained on therapy. We had planned to initiate TRILO$_2$GY in early 2018 but have since revised the study design, and now expect initiation in late 2018 or early 2019, with top-line data expected in early 2020. The revised study design will include once-daily and three-times weekly dosing and an ESA control, a larger sample size, and a design that can generate data to inform switching from Epogen®, Aranesp® and Mircera®. We believe this new study design will provide additional characterization and differentiation of vadadustat and further strengthen our commercial position if the drug is approved.

Additional Studies

We have completed a thorough QT, or TQT, study in accordance with FDA guidance. The study showed that vadadustat does not alter cardiac repolarization intervals in normal healthy volunteers following a single dose of up to 1,200 mg. In addition, a drug-drug interaction, or DDI, study was conducted to evaluate the effect of vadadustat on celecoxib, a substrate for the hepatic cytochrome P450 enzyme CYP2C9. Based on this study it was concluded that vadadustat does not inhibit CYP2C9 to any appreciable extent. Therefore, no clinically significant effect of vadadustat on drugs that are CYP2C9 substrates, for example statins such as losartan or rosuvastatin, would be expected through this specific mechanism. Additional DDI studies are planned.

Subsequent to our initiation of our Phase 2 study, FO$_2$RWARD, in May 2017, we closed this study and revised its design, which we believe will provide additional characterization and differentiation of vadadustat and further strengthen our commercial position if the drug is approved. The new FO$_2$RWARD study replaces the former one and will include once-daily and three-times weekly dosing, data to inform ESA-switching protocols, a larger sample size,

and a broader dialysis population that is inclusive of hyporesponders, or patients with anemia due to CKD who are on dialysis and do not adequately respond to injectable ESA. Hyporesponders represent approximately 10-15% of subjects with anemia due to DD-CKD, yet they account for 30-40% of total injectable ESA use. These patients have demonstrated a persistently higher risk of mortality than non-hyporesponders, and represent a high unmet need. Given its differentiated mechanism of action, we believe that vadadustat may provide a treatment option for these patients. We expect to initiate the study in the second quarter of 2018, with top-line data expected in late 2018 or early 2019.

Manufacturing and Supply

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

We have established relationships with several CMOs under which the CMOs have manufactured preclinical and clinical supplies of vadadustat drug substance and drug product. All clinical 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. 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 at the appropriate time. 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. The drug substance and drug product for AKB-5169 are supplied to us from single source suppliers with limited capacity.

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.

Strategic Collaborations and Other Significant Agreements

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, and control and retain final decision-making authority with respect to all development of vadadustat, subject to the terms of our other collaboration agreements.

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 $153.6 million or more, depending on the actual costs incurred, toward the vadadustat global development program. In addition, if the development costs exceed a certain threshold, we may require Otsuka to pay a higher percentage of the global development costs. In such event, Otsuka would be reimbursed for such additional funding out of milestone payments and net sales of vadadustat in the United States. In addition, 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, and each party will bear half of all costs in the United States, including medical affairs, commercialization and manufacturing costs. Under the terms of the Otsuka U.S. Agreement, Otsuka had an option to convert the profit share arrangement into a right to receive mid-single digit royalties on net sales of vadadustat; however, on August 4, 2017, Otsuka waived its right to exercise its conversion option in advance of the option’s expiration.

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.

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. 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 will be responsible for certain development activities and commercializing vadadustat in the Otsuka International Territory, while we will continue to 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. We retain final decision-making authority with respect to 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.

Under the terms of the Otsuka International Agreement, we expect Otsuka to pay us at least $236.6 million, comprised of $73.0 million that was paid upon execution of the Otsuka International Agreement and $163.6 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. 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. 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. 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 vadadustat. Additionally, the development costs of approximately $21.4 million for our Phase 2 studies in Japan are reimbursable by MTPC.

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 will grant Vifor Pharma an exclusive license to sell vadadustat solely to FKC, an affiliate of Fresenius Medical Care North America, in the United States.

The parties' rights under the Vifor Agreement are conditioned upon 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 to FDA approval of vadadustat, we and Vifor Pharma will enter into a commercial supply agreement for vadadustat pursuant to which we will supply all of Vifor Pharma's requirements for vadadustat in the United States. In addition, Vifor Pharma will enter into a supply agreement with FKC that will govern the terms pursuant to which Vifor Pharma will supply vadadustat to FKC for use in patients at its dialysis centers. 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 with Janssen, which 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 cost and expense. The Janssen Agreement includes a license to develop and commercialize AKB-5169, a preclinical compound in development as an oral treatment for IBD.

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.

Intellectual Property

The proprietary nature of, and protection for, our 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 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 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 non-provisional filing date. 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. Our issued patents and pending applications with respect to our composition of matter, methods of treatment, and pharmaceutical compositions are expected to expire in 2027 or 2028 (depending on eligibility for patent term adjustment) and our pending applications with respect to processes for manufacturing vadadustat, dosing regimens, formulations, and various other aspects relating to the treatment of anemia using vadadustat are expected to expire between 2032 and 2034, exclusive of possible patent term adjustments or extensions; however, the actual protection afforded by a patent varies on a product by product basis, from country to country and depends upon many factors, including the type of patent, the scope of its coverage, the availability of extensions of patent term, the availability of legal remedies in a particular country and the validity and enforceability of the 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 may receive 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 our most advanced programs are summarized below.

Vadadustat Patent Portfolio

We hold six 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 on the basis of 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.

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.

AKB-5169 Patent Portfolio

There is one issued patent and two pending patent applications covering the AKB-5169 composition of matter, pharmaceutical compositions, and methods of treating anemia by administration of AKB-5169, respectively, in the United States, and additional patents issued or pending in many other major jurisdictions worldwide, including Europe, Japan, China, Brazil, Russia and India. The expected expiration dates for these patents are between 2029 and 2038 plus any extensions or adjustments of term available under national law.

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.

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 European Opposition Division 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 two to three 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-PHIs.

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 European Opposition Division 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 European Opposition Division 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 European Opposition Division 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

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), Eprex® (epoetin alfa), commercialized by Johnson & Johnson, and Mircera® (methoxy PEG-epoetin beta), commercialized by Vifor Pharma in the United States and Roche Holding Ltd. outside the United States. In Europe and other markets biosimilar versions of injectable ESAs are available and may become available in the United States in the future. 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, in collaboration with AstraZeneca PLC in the United States and China and with Astellas Pharma Inc. in Europe and Asia, Japan Tobacco International, GlaxoSmithKline plc and Bayer HealthCare AG. FibroGen is currently in Phase 3 clinical development of its product candidate, roxadustat, Japan Tobacco International is currently in Phase 3 clinical development of its product candidate, JTZ-951, in Japan. GlaxoSmithKline's product candidate, daprodustat, is also in Phase 3 clinical studies and Bayer HealthCare AG is currently in Phase 3 clinical development of its product

candidate, molidustat, in Japan. Some of these product candidates may launch in certain 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.

Regulatory Matters

The FDA, and comparable regulatory authorities in other countries, impose substantial and extensive requirements upon companies involved in the research, manufacture, recordkeeping, labeling and packaging, storage, distribution, approval, post-approval monitoring and reporting, marketing, advertising and promotion, sampling, pricing, and export and import of drugs. The process of obtaining marketing approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Moreover, failure to comply with applicable regulatory requirements may result in, among other things, warning or untitled letters, clinical holds, civil or criminal penalties, recall or seizure of products, injunction, disbarment, denial of marketing approval, partial or total suspension of production and, for approved products, withdrawal of the product from the market. Any agency or judicial enforcement action could have a material adverse effect on us.

U.S. Government Regulation

In the United States, the FDA regulates drug products under the U.S. Federal Food, Drug, and Cosmetic Act, or FD&C Act, all amendments thereto, and its implementing regulations. If we fail to comply with applicable FDA or other requirements at any time, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, clinical trial hold or suspension, withdrawal of an approval, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement or administrative action could have a material adverse effect on us.

FDA approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States. The process required by the FDA before a drug may be marketed in the United States generally involves:

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

The manufacturing, preclinical testing, clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Preclinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The results of preclinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol, and other information, are submitted to FDA as part of an IND. The central focus of an IND submission is on the general investigational plan and the protocol for first-in-human study. Some preclinical testing may continue even after the IND is submitted, but an IND must become effective before human clinical trials may begin in the United States. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to one or more proposed clinical trials and places the clinical trial on a clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence. A separate amendment to an existing IND must also be made for each successive clinical trial conducted during product development.

Clinical trials involve the administration of the investigational drug to human subjects under the supervision of qualified investigators in accordance with current Good Clinical Practices, or cGCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, the parameters to be used

in monitoring safety, and the effectiveness criteria to be used. Each protocol involving subjects in the United States must be submitted to the FDA as part of the IND. In addition, an IRB or ethics committee for each medical center proposing to conduct a clinical trial must also review and approve a plan for any clinical trial before it can begin at that center and the IRB must monitor the clinical trial until it is completed. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA, if certain requirements are met. Per FDA regulations, the clinical trial must be conducted either: 1) in compliance with an international guideline for the ethical conduct of clinical research known as the Declaration of Helsinki or 2) with the laws and regulations of the country or countries in which the clinical trial is performed, whichever provides the greater protection to the participants in the clinical trial.

Government Regulation Outside the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, the conduct of clinical trials, and the import, export and distribution of drugs used in clinical trials. Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries.

Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND, prior to the commencement of human clinical trials. In Europe, for example, a CTA must be approved by each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the clinical trial may proceed. Outside of the United States, each clinical trial to be conducted in a given country requires submission and approval of a unique CTA.

The requirements and process governing the conduct of clinical trials, marketing and marketing approvals, and pricing and reimbursement requirements vary from country to country. In all cases, the clinical trials are conducted in accordance with cGCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

In the European Union, marketing authorization for a medicinal product can be obtained through a centralized, decentralized, or mutual recognition procedure.

In accordance with the centralized procedure, the applicant can submit a single marketing authorization application, or MAA, to the European Medicines Agency, or EMA. If granted, a centralized marketing authorization permits the marketing of a product in all 28 member states of the European Union, or EU Member States, and three of the four European Free Trade Association, or EFTA, States (Iceland, Liechtenstein and Norway). The centralized procedure is mandatory for certain medicinal products, including orphan medicinal products, medicinal products derived from certain biotechnological processes, advanced therapy medicinal products and certain other medicinal products containing a new active substance for the treatment of certain diseases, and is optional for certain other products, including medicinal products that are a significant therapeutic, scientific or technical innovation, or whose authorization would be in the interest of public or animal health at EU level.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed.

A mutual recognition procedure is used when a product is already authorized in at least one EU Member State and the marketing authorization holder wishes to obtain a marketing authorization for the same product in at least one other EU Member State.

An approved Pediatric Investigation Plan, or PIP, is required in Europe prior to submission of the MAA covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP. Ideally, the pediatric studies in both the U.S. Pediatric Study Plan and the EU PIP will be identical, but some differences may be required to meet the respective regulatory requirements. The PIP outlines the study designs and timing of the pediatric program. The EMA Paediatric Committee and the FDA's Office of Pediatric Therapeutics have frequent joint discussions about pediatric drug development, including discussions about specific drugs. Often, these discussions are conducted in an attempt to harmonize pediatric drug development across the two jurisdictions. However, this cannot be guaranteed.

The process of obtaining approval for a new drug in Japan resembles U.S. and EU procedures in both substance and scope. All NDAs are collected and reviewed by the PMDA. PMDA review typically involves at least two formal evaluations to establish the safety and efficacy of the drug candidate, as well as one cGMP facility inspection. Consultations to correct outstanding issues are conducted as needed. Assuming satisfactory results, these reports are communicated to the Ministry of Health, Labour, and Welfare, or MHLW, which then issues a final approval of the drug.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for approval of generics of these innovative products from referencing the innovator’s data to assess an Abbreviated New Drug Application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator’s data may be referenced, but no generic medicinal product can be marketed in the European Union until the expiration of the market exclusivity. 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 their author