Akebia Therapeutics, Inc.
Form 10-K
March 14, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

OR

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

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.)
245 First Street, Suite 1100, Cambridge, MA (Address of principal executive offices)	02142 (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; Common stock 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 x

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

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

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

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

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

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the shares of common stock on The NASDAQ Stock Market on June 30, 2015, was $259,927,754.

The number of shares of Registrant's Common Stock outstanding as of March 1, 2016 was 37,942,946.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement for our 2016 Annual Meeting of Stockholders scheduled to be held June 16, 2016 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 safe harbor provisions of the Private Securities Litigation Reform Act of 1995, or PSLRA, with the intention of obtaining the benefits of the "safe harbor" provisions of the PSLRA. Forward-looking statements involve risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "target," "will," "would," or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the projected timing of (1) commencement of our Phase 3 development program in dialysis patients with anemia related to CKD and full enrollment of such program, (2) initiation of a clinical study of vadadustat in hyporesponsive dialysis-dependent patients, (3) submission of an NDA and an MAA for vadadustat, and (4) commencement of clinical development of AKB-6899 in oncology;
- the projected costs and size of our Phase 3 development program for vadadustat;
- our development plans with respect to vadadustat and AKB-6899;
- the timing or likelihood of regulatory filings and approvals, including any required post-marketing testing or any labeling and other restrictions;
- our business development plans, including our plans to engage collaborators to commercialize vadadustat and to diversify our pipeline by acquiring additional products;
- our plans to commercialize vadadustat, if it is approved;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

All forward-looking statements in this Annual Report on Form 10-K involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, 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.

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PART I

Item 1. Business

Overview

Incorporated in Delaware in 2007, we are a biopharmaceutical company focused on the development of novel proprietary therapeutics based on hypoxia inducible factor, or HIF, biology and the commercialization of these products for patients with serious unmet medical needs. HIF is the primary regulator of the production of red blood cells, or RBCs, in the body and a potentially novel mechanism for the treatment of anemia secondary to chronic kidney disease, or CKD. Pharmacologic modulation of the HIF pathway may also have broader therapeutic applications in acute renal failure, organ protection, ischemia-reperfusion injury, cancer, ophthalmology, and inflammatory diseases.

Anemia is a serious medical condition in which blood is deficient in RBCs and hemoglobin, each of which is critical in delivering oxygen to tissue. Anemia generally exists when hemoglobin, a protein in RBCs that carries oxygen, is less than 13 g/dL in men or 12 g/dL in women. Untreated anemia is associated with chronic fatigue, increased risk of progression of multiple diseases and death. Anemia is common in patients with CKD, cancer, heart failure, inflammatory diseases and other critical illnesses, as well as in the elderly.

More than 30 million people in the United States have CKD, with estimates that over 1.8 million of these patients suffer from anemia. Anemia from these indications is currently treated by injectable recombinant erythropoiesis-stimulating agents, or rESAs,—including Epogen®, Procrit® and Aranesp® — with iron supplementation or RBC transfusion. Based on the reported revenues of companies that market and sell rESAs, we estimate that global sales of injectable rESAs were $7.0 billion in 2014; the vast majority of which were for renal indications.

rESAs are designed to stimulate production of RBCs by binding directly to and saturating erythropoietin, or EPO, receptors. While injectable rESAs and transfusions may be effective in raising hemoglobin levels, they carry significant potential side effects and need to be delivered subcutaneously or intravenously. In particular, injectable rESAs may lead to thrombosis, stroke, myocardial infarction and death. These risks are described in black box warnings on the prescribing information of all products marketed in this class. These safety concerns, which became evident starting in 2006, have led to a significant reduction in the use of injectable rESAs. Today, anemia is either not treated or inadequately treated in the majority of non-dialysis dependent CKD patients. As a result, we believe that a safe, effective, oral therapeutic option will take significant market share and meaningfully grow the market in patients not requiring dialysis.

Given the burdens of the current standard of care and costs associated with administering an injectable rESA, we believe our lead product candidate, vadadustat, formerly known as AKB-6548, is a promising cost-effective alternative for the treatment of anemia in CKD. Vadadustat is being developed as a once-daily, oral therapy and has successfully completed Phase 2 development demonstrating that vadadustat can safely and predictably raise hemoglobin levels in patients with anemia related to CKD. Vadadustat works by a differentiated mechanism of action that we believe has the potential to be safer than that of injectable rESAs and may offer additional beneficial therapeutics effects beyond anemia including delaying CKD progression. This novel mechanism of action is referred to as HIF prolyl-hydroxylase, or HIF-PH, inhibition. Instead of binding directly to the EPO receptors on cells in the bone marrow, vadadustat leads to activation of critical pathways for hemoglobin and RBC production. This approach mimics the physiological adjustment made by the body when exposed to reduced oxygen levels at higher altitudes.

We recently commenced Phase 3 development of vadadustat in non-dialysis patients. Positive results from our Phase 2b study in non-dialysis CKD patients demonstrated that vadadustat raised hemoglobin levels with no safety signal observed. In December 2015, we began dosing patients in our Phase 3 vadadustat program in non-dialysis patients with anemia related to CKD, PRO_2TECT, after obtaining feedback from United States and European regulatory authorities regarding the design of the program. If the results from the PRO_2TECT program support the results observed across our previous clinical studies, including 29,000 days of patient exposure, we anticipate submitting a New Drug Application, or NDA, to the United States Food and Drug Administration, or FDA, for vadadustat in 2019.

We have also completed a Phase 2 study of vadadustat for the treatment of anemia in patients undergoing dialysis, which found that vadadustat, dosed either once daily or three times per week, maintained stable hemoglobin levels following conversion from rESA therapy with no safety signal observed. We expect to initiate our Phase 3 vadadustat program in dialysis-dependent CKD patients, $INNO_2$VATE, in 2016, anticipating full enrollment by early 2018.

We have engaged Quintiles, Inc., or Quintiles, as our primary clinical research organization, or CRO, for the PRO_2TECT and $INNO_2$VATE programs. We expect the cost of the Phase 3 program to be in the range of $80,000 to $85,000 per patient and we plan to enroll approximately 3,100 patients in the PRO_2TECT program and approximately 2,600 patients in the $INNO_2$VATE program.

A subset of dialysis-dependent CKD patients have shown an inadequate hemoglobin response despite receiving high doses of rESAs. Previous studies have shown that rESA hyporesponsiveness is associated with poor clinical outcomes including increased mortality risk. By increasing iron mobilization, in addition to increasing erythropoietin levels, vadadustat may allow for a more consistent hemoglobin response in these patients. We expect to generate clinical data in hyporesponsive dialysis-dependent patients by 2017.

If approved by regulatory authorities, we plan to commercialize vadadustat in the United States for the treatment of anemia in patients with CKD. These patients are primarily treated by approximately 7,000 nephrologists, and we believe we can reach most of this market with a specialty sales force of approximately 125 people. In Japan and certain other Asian countries, we plan to commercialize vadadustat through our recently announced collaboration with Mitsubishi Tanabe Pharma Corporation, or Mitsubishi Tanabe. We intend to seek one or more collaborators to commercialize vadadustat in additional markets.

Our second clinical candidate, AKB-6899, is designed as a small molecule HIF-PH inhibitor with potential therapeutic benefit in oncology and ophthalmology. AKB-6899 has demonstrated the ability in vitro to reduce vascular endothelial growth factor, or VEGF, levels in the presence of hypoxia. In several preclinical mouse models, AKB-6899 has been active in reducing tumor growth and development of metastases. We opened an Investigational New Drug application, or IND, with the FDA at the end of 2015. We expect to commence clinical development of AKB-6899 in 2016 and anticipate completion of the Phase 1 study in oncology in late 2017.

We are led by a team of experienced biopharmaceutical executives with a background in developing and commercializing drugs for the treatment of renal and metabolic disorders. John P. Butler, our CEO, was previously President of Genzyme Corporation’s renal division which grew to over $1 billion in annual revenue under his leadership, and was Chairman of the Board of the American Kidney Fund, the leading patient advocacy organization for kidney disease patients. Earlier in his career, Mr. Butler held sales and marketing positions at Amgen, working on the early commercial launch of injectable rESAs in the renal anemia market.

Our Strategy

Our strategy is to develop and deliver novel therapeutics for patients based on HIF biology, beginning with vadadustat for patients with anemia secondary to CKD. The key elements of our strategy are to:

- Complete the development of vadadustat for anemia secondary to CKD. We initiated our PRO_2TECT program in 2015, and expect to initiate the $INNO_2$VATE program in 2016.
- Obtain regulatory approval of vadadustat for anemia secondary to CKD in the United States, Europe and other markets. We anticipate submitting an NDA in the United States and MAA in Europe for vadadustat by the end of 2019 if the Phase 3 data are favorable.
- Commercialize vadadustat in the United States and other territories. We will establish a specialty sales and marketing organization to commercialize vadadustat in the United States. In Japan and certain other Asian countries, we plan to commercialize vadadustat through our collaboration with Mitsubishi Tanabe. We intend to seek one or more collaborators to commercialize vadadustat in additional markets.
- Advance AKB-6899 into clinical development. We plan to commence clinical development of AKB-6899, a second HIF-PH inhibitor product candidate, with potential therapeutic benefit in oncology and ophthalmology.

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Diversify our pipeline in kidney disease and other HIF-modulated diseases. We expect to grow our pipeline organically and through in-licensing or acquisitions. Reflecting our strategic strengths in both HIF biology and renal disease, we plan to develop therapeutics for the treatment of renal conditions managed by nephrologists, and medical conditions that can be treated or prevented through HIF modulation.

Our Product Candidates

The following chart depicts our HIF-based product candidates, their indications and their current development.

Anemia Overview

Anemia is a serious medical condition in which blood is deficient in RBCs and hemoglobin, leading to inadequate oxygen delivery to tissues and cells throughout the body. RBCs are normally formed in the bone marrow from precursor or progenitor cells. EPO, a hormonal factor primarily produced in the kidney and liver, binds to and activates the EPO receptor on these precursor cells. The activation of the EPO receptor stimulates these cells to divide, differentiate into RBCs that contain hemoglobin, and mobilize into circulation. Hemoglobin is an iron-containing protein in RBCs that transports oxygen to the tissues of the body.

Anemia generally exists when hemoglobin is less than 13 g/dL in men and 12 g/dL in women. Anemia is common in patients with CKD, cancer, heart failure, inflammatory diseases and other critical illnesses, as well as in the elderly. Untreated anemia is associated with chronic fatigue, increased risk of progression of multiple diseases and death. Increased morbidity (largely due to cardiovascular disease) and mortality are well recognized complications of anemia in patients with CKD. 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 and bone disease. CKD patients are classified by the degree of their loss of kidney function as measured by the glomerular filtration rate, or GFR, and albuminuria, the level of protein in urine. As illustrated in the table below, CKD affects more than 30 million people in the United States and the prevalence of anemia increases with the severity of CKD.

There are many causes of CKD, the most common of which are diabetes mellitus and hypertension. The prevalence and incidence of CKD is increasing in all segments of the U.S. population, particularly in patients over 65. Risk factors for the development of CKD include concomitant diseases (hypertension, diabetes mellitus and cardiovascular disease), lifestyle factors (tobacco use and inactivity), family history, aging, and prenatal factors (maternal diabetes mellitus, low birth weight and small-for-gestational-age status). According to a Lancet article published in May 2013, projected worldwide population changes suggest that the potential number of cases of CKD, specifically end-stage, will increase disproportionately in developing countries, such as Japan, China and India, where the numbers of elderly people are expanding. This effect will be enhanced further if the trends of increasing hypertension and diabetes prevalence persist, competing causes of death—such as stroke and cardiovascular diseases—are reduced, and access to treatment does not improve.

The prevalence and severity of anemia in CKD increases as renal function deteriorates. Three principal factors contribute to the development of anemia as CKD progresses:

- Peritubular fibroblasts, a type of cell in the kidney, are designed to sense the amount of oxygen carried by the blood. These cells secrete EPO to adjust the production of RBCs and maintain circulating oxygen levels at normal physiologic levels. As kidney disease progresses, the number of peritubular fibroblasts is reduced and EPO secretion is significantly decreased. This decline in EPO leads to a reduction in RBC production.
- CKD leads to a shorter average life span for RBCs (70 days) as compared to healthy individuals (90 to 120 days), requiring increased RBC production to keep RBC levels consistent with those of a healthy individual.
- The availability of iron to the bone marrow is impaired. Iron is a required component in the formation of hemoglobin, and is essential for the transport of oxygen to the tissues of the body.

As CKD progresses, the combined effect of decreased RBC production from lower EPO signaling, increased rate of RBC destruction, and reduced iron availability to the bone marrow results in the increased prevalence and severity of anemia.

Current Treatments Leave a Substantial Unmet Need

Injectable rESAs are currently the standard of care for treating anemia in patients with CKD and must be administered intravenously or subcutaneously along with iron supplements. Based on the reported revenues of companies that market and sell rESAs, we estimate that global sales of injectable rESAs were $7.0 billion in 2014, as compared to an estimated $12.0 billion in 2006. The 2013 revenues generated in the United States were an estimated $3.6 billion, the vast majority of which were for renal indications. In 2006, data on the risks of rESA use among these patients started to become available, forcing physicians to balance serious safety concerns against the efficacy of rESAs. The safety concerns with injectable rESA use include increased risk of cardiovascular disease as well as a potentially increased rate of tumor progression in patients with cancer. We believe that the decline in market revenue since 2007 is a direct result of these increased safety concerns, as well as reimbursement pressures, and that an opportunity exists for a safer, well-tolerated alternative to replace injectable rESAs as the standard of care for anemia secondary to CKD.

As a result of the safety concerns related to rESA use, patients have been forced to live with lower hemoglobin levels, higher rates of transfusions, and more intravenous iron, or IV iron, use. As a result of the increased use of IV iron and RBC transfusions, patients are also subject to safety risks related to these alternative treatments to injectable rESAs. The risks of RBC transfusions include the development of antibodies to foreign antigens, which may negatively impact candidacy for kidney transplantation, transmission of blood-borne pathogens, and iron overload with chronic transfusions. The risks of IV iron include hypersensitivity reactions, including fatal anaphylactic-type reactions.

Currently, there is no scientific consensus regarding the cause of the adverse cardiovascular outcomes associated with the use of injectable rESAs to normalize hemoglobin levels. The results of the four major randomized, controlled clinical trials on the treatment of anemia secondary to CKD with rESAs and adjunctive iron supplementation (Normal Hematocrit Trial/NHCT, CREATE, CHOIR and TREAT) all showed an increased risk of adverse cardiovascular outcomes. These results were surprising at the time and contradicted the extensive body of data from observational studies that showed reduced mortality and improved health outcomes to be associated with higher hemoglobin levels.

A number of critical post-hoc analyses of the data from randomized controlled clinical trials have shifted attention to the potential of dose-related toxicity of injectable rESAs in CKD patients as a contributing factor to the reported adverse cardiovascular outcomes, instead of the achieved hemoglobin levels. The graphs below highlight these findings. The first chart explores the relative risk of serious cardiovascular adverse events, including death, hospitalization for heart failure, stroke or myocardial infarction based upon the hemoglobin achieved during the study as well as the weekly injectable rESA dose. The data clearly show that the risk of adverse cardiovascular events was greatest in those patients receiving the highest injectable rESA doses, regardless of the hemoglobin level that was achieved.

The second graph explores the probability of reaching one of several adverse events (death, stroke, heart failure or myocardial infarction) over time for two different groups:

- patients who achieve the target hemoglobin level with a low injectable rESA dose, and
- patients who do not reach the target hemoglobin level, but receive a higher injectable rESA dose in an effort to reach the target level.

Both graphs demonstrate that patients achieving higher hemoglobin levels on lower injectable rESA doses have better outcomes than patients receiving higher injectable rESA doses despite lower achieved hemoglobin levels. Therefore, higher injectable rESA doses, not the achieved hemoglobin level, appears to be most strongly correlated with adverse outcomes.

The significant safety risks associated with rESAs are outlined in a black-box warning in their prescribing information. This warning arose from numerous events highlighting the safety concerns of injectable rESAs and the response by the FDA, as highlighted below.

- In 2007, as a result of concerns associated with administering injectable rESAs to target higher hemoglobin levels, the FDA required that revised warnings, including black-box warnings, be added to the labels of marketed injectable rESAs advising physicians to monitor hemoglobin levels and use the lowest dose of injectable rESA, and increase the hemoglobin concentration to the lowest level sufficient to avoid the need for RBC transfusions.
- In November 2007, the FDA found evidence that the use of injectable rESAs to increase hemoglobin to more than 12 g/dL can stimulate progression of some cancers. As a result, injectable rESAs were required to contain black-box labeling for this risk. Following this change in labeling, the use of injectable rESAs in cancer patients has declined significantly.
- In late 2009, Amgen announced the results from the Trial to Reduce Cardiovascular Endpoints with Aranesp Therapy, or TREAT, its large, randomized, double-blind, placebo-controlled Phase 3 study of patients with CKD (not requiring dialysis), anemia and type 2 diabetes mellitus. In this study, Aranesp was used to treat anemia to a target hemoglobin level of 13 g/dL, which was higher than the 10 g/dL - 12 g/dL range previously approved by the FDA in the label. Study results

failed to show a benefit compared to the placebo control group with regard to composite of time to all-cause mortality or cardiovascular morbidity (including heart failure, heart attack, stroke, or hospitalization for myocardial ischemia) and composite of time to all-cause mortality or chronic renal replacement therapy. In addition, higher rates of stroke were reported among patients in the 13 g/dL target group compared to the placebo control group. Finally, among a subgroup of patients with a history of cancer at baseline, a statistically significant increase in deaths from cancer was observed in the Aranesp-treated patients compared to placebo-treated patients.

- In January 2010, FDA officials published an editorial in the New England Journal of Medicine noting that a number of randomized trials, including TREAT, had attempted to show that using injectable rESAs to raise hemoglobin concentrations to higher targets improves clinical outcomes, but instead suggested the opposite. Accordingly, the article indicated that more conservative hemoglobin targets (well below 12 g/dL), more frequent hemoglobin monitoring, and more cautious dosing should be evaluated.
- In February 2010, the FDA required that injectable rESAs be prescribed and used under a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the safe use of the drugs. As part of the REMS, a medication guide explaining the risks and benefits of injectable rESAs must be provided to all patients receiving injectable rESAs for all indications, and the FDA imposed reporting and monitoring obligations on the manufacturers to ensure compliance.
- In June 2011, the FDA cited increased risks of cardiovascular events as a basis for more conservative dosing guidelines for use of injectable rESAs in CKD patients and announced related changes to injectable rESA labeling. The FDA removed the prior target hemoglobin range of 10-12 g/dL, and recommended that CKD patients initiate treatment when the hemoglobin level is less than 10 g/dL and reduce or interrupt dosing if the hemoglobin level approaches or exceeds 10 g/dL for non-dialysis patients and 11 g/dL for dialysis patients. The FDA also required Amgen to conduct additional clinical trials to explore dosing strategies to minimize hemoglobin variability, rates of change and excursions.

We believe there is now substantial evidence to suggest that EPO level, not hemoglobin, is the cause of the safety issues in the above trials.

Vadadustat as a Potential Solution

We are developing our lead product candidate, vadadustat, to be a best-in-class HIF-PH inhibitor for the treatment of anemia secondary to CKD. Vadadustat may potentially offer:

- Once-a-day therapy delivered orally;
- A dosing regimen that restores the normal diurnal EPO pattern;
- Robust pharmacodynamics and substantially lower peak EPO levels than with injectable rESAs;
- Predictable, meaningful and sustained improvements in hemoglobin levels; and
- Reduced administration of IV or oral iron supplementation to patients treated for anemia secondary to CKD.

Novel Mechanism of Action, Which Mimics the Body’s Natural Physiologic Response

Vadadustat is designed to work by a mechanism of action that differs from injectable rESAs. This novel mechanism of action is referred to as HIF-PH inhibition. Instead of binding directly to and saturating the EPO receptors in the bone marrow for prolonged periods of time, HIF-PH inhibitors act by simulating the body’s natural response to anemia. HIF is the primary regulator of the production of RBCs and acts by simulating the body’s natural 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 and enhancement of the delivery of iron to the bone marrow, ensuring the incorporation of iron into hemoglobin necessary for new RBC production. This is very similar to the natural adaptive response that is induced when a person ascends in altitude. At higher altitudes, lower levels of oxygen circulating in the blood stream lead to reduction in HIF-PH activity which increases intracellular levels of HIFa proteins (HIF1a and HIF2a).

Both HIF1a and HIF2a protein levels in cells are adjusted by the activity of the HIF-PH enzymes, which target the HIFa proteins for degradation. HIF1a helps cells survive under very low oxygen conditions, whereas HIF2a helps cells to adapt to modest changes in oxygen, such that would occur with a change in altitude from sea level to up to 7,500 feet.

When HIFa is stabilized, it travels to the nucleus of the cell, where it binds to the protein HIFß. When bound together, they induce the production of EPO and iron transfer proteins. With continued stabilization of HIFa (either by staying at higher altitude or by the

administration of a HIF-PH inhibitor), the level of hemoglobin and RBCs will rise in order to increase the amount of oxygen circulating in the blood.

By inhibiting HIF-PH, vadadustat leads to increased production of hemoglobin and RBCs, while maintaining normal levels of EPO. In addition, we believe that vadadustat's mechanism of action provides for the ability to induce a more prominent HIF2a response (as naturally occurs with a moderate increase in altitude), and restores the normal diurnal pattern of EPO, which is the normal rise and fall of EPO during the each day.

This mechanism of action is illustrated in the graphic below.

Potential Best-in-Class Profile

We believe vadadustat has compelling clinical data demonstrating a potential best-in-class profile with several potential safety and efficacy advantages over current injectable rESA therapy for the treatment of anemia secondary to CKD.

- Vadadustat significantly increases and maintains hemoglobin levels in CKD patients with anemia. We have successfully completed two Phase 2 trials in non-dialysis patients with CKD which demonstrated that vadadustat significantly increased hemoglobin levels. In the first study (CI-0005), vadadustat was shown to raise hemoglobin in a dose-dependent manner compared to baseline and across all treatment arms ($p < 0.0001$). In the second study (CI-0007), vadadustat effectively increased hemoglobin while minimizing hemoglobin excursions ³ 13.0 g/dL. Only 4.3% of patients on vadadustat had any hemoglobin excursion ³ 13.0 g/dL. In addition, a Phase 2 trial (CI-0011) in dialysis patients with CKD who were converted from existing ESA therapy to vadadustat demonstrated the desired outcome of maintaining stable hemoglobin levels.

- Vadadustat restores the normal diurnal variation of EPO. Instead of binding directly to and saturating the EPO receptor for prolonged periods, as is the case with current injectable ESA therapies, vadadustat acts by simulating the body's natural response to hypoxia by stabilizing HIFa. Vadadustat allows for an enhancement in the normal diurnal variation in EPO without continuous elevation of EPO levels. The approximate EPO exposures that are achieved with vadadustat compared with doses of Aranesp® and Epogen® is depicted in the graph below.

- Oral, once-daily dosing. As demonstrated in non-dialysis CKD patients, vadadustat offers flexible once-daily oral dosing that provides a more gradual and reliable means of hemoglobin titration and maintenance. This was demonstrated in the Phase 2 clinical trial in dialysis dependent CKD patients, where vadadustat maintained stable hemoglobin levels in patients converting from ESA therapy. Vadadustat also offers improved convenience for patients as compared to injectable ESAs. This convenience may increase access to anemia therapy and improve patient compliance.
- Improve mobilization of iron supply to the bone marrow for RBC production. In clinical trials, vadadustat has demonstrated improved iron mobilization and an increase in total iron binding capacity. As a result, unlike injectable rESAs which do not increase iron mobilization, vadadustat offers the added potential benefit of reducing the amount of supplemental iron required by anemic CKD patients. The potential for an IV iron sparing effect of vadadustat will be assessed in the INNO$_2$VATE program.
- Differentiated safety profile. Vadadustat's novel mechanism of action offers the potential opportunity to reduce the risk for cardiovascular and thrombotic events relative to injectable ESAs since CV risks have been associated with a supraphysiological increase in EPO levels and excessive hemoglobin fluctuations and/or excursions. The incidence of cardiovascular adverse events on vadadustat as compared with ESAs will be assessed in the global Phase 3 program. Furthermore, the risk of pure red cell aplasia (PRCA) observed with recombinant ESAs is not expected with vadadustat.

Vadadustat Clinical Development Overview

Akebia is developing vadadustat as oral therapy for the treatment of anemia in CKD subjects who are not on dialysis and in subjects who are on dialysis. A summary of completed and ongoing clinical and clinical pharmacokinetic studies is presented in Table 1.

To date, the safety, tolerability, pharmacokinetic and pharmacodynamic responses of vadadustat have been demonstrated in:

- eight completed Phase 1 studies in healthy volunteers (CI 0001, CI 0002, CI 0006, CI 0008, CI 0010, CI 0012, CI 0013 and CI-0019);
- one completed Phase 1 study in dialysis-dependent CKD subjects (CI 0009);
- three completed Phase 2a studies in non-dialysis CKD subjects with GFR Categories G3-G5 CKD (CI 0003, CI 0004, and CI 0005);

- one completed Phase 2b study in non-dialysis CKD subjects with GFR Categories G3-G5 CKD (CI 0007); and
- one completed Phase 2 study in dialysis-dependent CKD subjects (CI 0011).

In the 14 studies completed to date, 512 unique subjects have received vadadustat, including 164 healthy volunteers (male and female) and 348 subjects with CKD (242 with non-dialysis CKD with GFR categories G3a/b, G4, and G5 for up to 20 weeks and 106 subjects with dialysis-dependent CKD for up to 16 weeks). A total of more than 29,000 patient days of exposure to vadadustat has been accrued to date. The adverse effect, or AEs, most frequently reported with vadadustat and which occurred more frequently in subjects on vadadustat than in subjects on placebo have predominantly been nausea and diarrhea. Generally these symptoms have been mild to moderate in severity, non-serious, and resolved on vadadustat therapy, although they have led to discontinuation of vadadustat in some subjects.

Early Clinical Studies (CI-0001 to CI-0004, and CI-0006):

An IND was filed for vadadustat for the treatment of anemia associated with CKD on July 17, 2009. Under the IND, we may investigate vadadustat in subjects who are not on dialysis and in subjects who are on dialysis. The early clinical studies (CI-0001 through CI-0004) for vadadustat were designed to demonstrate the efficacy and safety of the compound, starting in healthy male volunteers and progressing to CKD patients with anemia. In healthy males, we demonstrated that vadadustat can be dosed daily, and that it induces the desired pharmacodynamics effect, specifically:

- the induction of enhanced diurnal EPO secretion from a single dose;
- an increase in new RBC production by day 5 of dosing; and
- an increase in hemoglobin levels by day 10 of dosing.

Subsequently, we demonstrated a similar induction of a diurnal EPO response in CKD patients. This was followed by a 28-day, dose-titration study to establish the necessary dosing information for increasing hemoglobin levels. Throughout these studies, vadadustat was generally well tolerated. There were no serious adverse events, or SAEs, and treatment emergent adverse events, or TEAEs, were limited in number and duration.

The most common potentially drug-related AEs in our clinical trials were gastro-intestinal disorders, including diarrhea, nausea and constipation. The design and results of each of the 14 completed studies is provided in the following table followed by a more detailed description of three Phase 2 studies in non-dialysis (CI-0005 and CI-0007) and dialysis-dependent (CI-0011) CKD patients treated for up to 20 weeks.

The individual design and summary results of each of our completed clinical trials are highlighted below:

	Study Design			Subjects Treated		
Study[a]	Subjects	Design (Endpoint)	Dose, Duration[b]	Vadadustat	Placebo	Key Findings
Phase 1						
0001	Healthy males	Double-blind, placebo-controlled, fasted (Safety/PK/PD)	80 mg, 160 mg, 300 mg, 600 mg, 900 mg, 1200 mg; single dose	6 (80 mg) 6 (160 mg) 6 (300 mg) 6 (600 mg) 6 (900 mg) 6 (1200 mg)	12 (2 per cohort)	Dose responsive increases in EPO levels were demonstrated following a single dose. Half-life ($t_{1/2}$) of the compound at the 600 mg dose was approximately 4.8 hours and was similar across the doses studied. Seven subjects (19.4%) and 3 subjects (25%) had an AE in the total vadadustat and placebo groups, respectively. Mild diarrhea and mild to moderate headache occurred in more than 1 subject (n=2 and n=3, respectively) in the vadadustat groups. There were no discernible trends in the frequency and type of AEs across the dosing groups. No SAE occurred.
CI-0002	Healthy males	Double-blind, placebo-controlled, fasted (Safety/PK/PD)	500 mg, 700 mg, 900 mg; 10 days	8 (500 mg) 9 (700 mg) 8 (900 mg)	9 (3 per cohort)	Dose responsive increases in reticulocytes and HGB levels were demonstrated. EPO levels returned to baseline by 24 hours following each dose. Vadadustat was generally well tolerated. AEs were balanced overall between the total vadadustat dosing groups (76%) and the placebo group (78%), and across vadadustat dosing cohorts. Gastrointestinal AEs occurred in 36% of subjects in the vadadustat groups and in no subjects on placebo, of which mild to moderate diarrhea was the most frequent (24%), but without a discernible dose effect. No SAE occurred.
CI-0006	Healthy males	Randomized, cross-over bioavailability study, fasted (Bioavailability /PK)	315 mg; single dose of capsule and tablet, with three days wash-out period between doses	8	0	Capsules and tablets were shown to be bioequivalent, and vadadustat was well tolerated with both formulations. Nausea was the only AE that occurred in more than in 1 subject (n=2). No SAE occurred.

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Study Design				Subjects Treated		
Study[a]	Subjects	Design (Endpoint)	Dose, Duration[b]	Vadadustat	Placebo	Key Findings
CI-0008	Healthy males	Mass Balance (Radioactivity/ PK)	650 mg; single dose (100 mCi ^{14}C-vadadustat)	6	0	Total radioactivity recovery in urine and feces was >85% with approximately 60% in urine and approximately 26% in feces. Majority of the drug-related radioactivity (>75%) in plasma was associated with vadadustat, followed by the AKB 6548-O-glucuronide (~15%) and a very low contribution (<1%) coming from the AKB 6548-acyl-glucuronide. Vadadustat was generally well tolerated, and no SAE occurred.
CI-0009	DD-CKD	Randomized, crossover, pharmacokinetic study with 72-hour wash-out between successive dosing (PK/Safety and tolerability of subjects on chronic dialysis)	450 mg dose four hours prior to start of a dialysis session; 450 mg dose 2 hours after completion of a different dialysis session	12	0	The timing of administration of vadadustat doses (pre- or post-hemodialysis (HD)) did not notably affect pharmacokinetics of vadadustat and two measured glucuronide metabolites. HD procedure had minimal impact on the clearance of vadadustat. AEs assessed as related included diarrhea (n=2), frequent bowel movements (n=2), and abdominal pain (n=1). One subject with a diabetic foot ulcer experienced the SAEs of limb abscess and osteomyelitis, 7 days post dosing, and were assessed as unrelated to vadadustat by the investigator.
CI-0010	Healthy volunteers	Randomized, partially double-blind, single-dose, 4 treatment, 4 period, 4 sequence crossover study to evaluate the effect of vadadustat on cardiac repolarization intervals (Thorough QTc Study)	600 mg vadadustat dose; 1200 mg vadadustat dose; placebo tablets; 400 mg moxifloxacin tablet	49	48[c]	Vadadustat did not have a meaningful effect on any ECG parameters. An effect on the QTcF interval exceeding 10 msec could be confidently excluded and the effects on heart rate, PR interval, and QRS interval were small and clinically not relevant. Vadadustat, at therapeutic (600 mg) and supratherapeutic (1200 mg) doses, was well tolerated, and the number of subjects with at least 1 AE in each of these groups was balanced (24.5% vs 26.5%, respectively). All AEs were mild in severity. Nausea, diarrhea, abdominal pain, headache, and dizziness occurred with a frequency of 5% or more in subjects on vadadustat compared to placebo, but with no apparent dose effect. No discontinuations or SAE occurred.
CI-0012				10	0	

Healthy males	Open-label, randomized, single-dose, two-period crossover relative bioavailability study to evaluate the effects of iron on the PK of vadadustat (Bioavailability /PK)	450 mg vadadustat dose; 325 mg ferrous sulfate tablet (containing 65 mg elemental iron)	Administration of vadadustat + oral iron resulted in ~50% reduction in vadadustat exposure based on C_{max} and AUC. The reduction does not appear to be related to a change in metabolism to glucuronides. No AE occurred. Concomitant administration of oral iron with vadadustat should be avoided.

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Study Design				Subjects Treated		
Study[a]	Subjects	Design (Endpoint)	Dose, Duration[b]	Vadadustat	Placebo	Key Findings
CI-0013	Healthy volunteers	Open-label, randomized, single-dose, three-period crossover relative bioavailability study of Test (Phase 3) and Reference (Phase 2) Formulations of vadadustat tablets and to evaluate the effect of food (high fat meal) on the bioavailability of vadadustat (Bioavailability /PK)	150 mg vadadustat tablet (Reference, used in Phase 2 studies CI 0007 and CI 0011) 150 mg vadadustat film-coated tablet (intended Phase 3 and commercial formulation)	18	0	Vadadustat test and reference tablet formulations demonstrated bioequivalence following administration of a single 150 mg dose under fasting conditions. Vadadustat AUC and C_{max} were reduced by 20% and 28%, respectively, when a single 150 mg dose of the test formulation of vadadustat tablets was administered with food compared to the test tablet formulation administered under fasting conditions. These differences are not considered to be clinically meaningful and, thus, vadadustat Phase 3 tablets can be administered without regard to meals. Both tablet formulations were well tolerated. AEs that occurred in more than 2 subjects included diarrhea. No SAE occurred.
CI-0019	Healthy volunteers	Open-label study to assess the effect of once-daily multiple dosing of vadadustat on the pharmacokinetics of the CYP2C9 substrate celecoxib (Bioavailability /PK)	600 mg vadadustat dose for 7 days 200 mg celecoxib capsule on Days 1 and 8	12	0	The total exposure of celecoxib increased by approximately 12% following co-administration with vadadustat while the C_{max} of celecoxib increased by approximately 60% when co-administered with vadadustat. Since the potential for interaction is based on total exposure (AUC), it was concluded that vadadustat does not inhibit CYP2C9 to any appreciable extent and, therefore, there is no clinically significant effect of vadadustat on drugs that are CYP2C9 substrates. Vadadustat was well-tolerated and no SAE occurred.
Phase 2						
CI-0003	NDD-CKD, GFR categories	Open-label, fed	500 mg; single dose	22	0	Following a single dose of 500 mg of vadadustat, the changes in EPO levels followed a

G3 & G4	(Safety/PK/PD)	similar pattern as that observed in the Phase 1 study at 600 mg in healthy volunteers (CI-0001). In these subjects with CKD, peak levels of EPO were similar to healthy male volunteers, and the $t_{1/2}$ was modestly longer at 7.9 hours. No AE occurred more than once, except nausea (n=2). The majority of AEs were mild or moderate in severity. There were no changes in mean values of heart, blood pressure or ECG over time. No SAE occurred.

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	Study Design			Subjects Treated		
Study[a]	Subjects	Design (Endpoint)	Dose, Duration[b]	Vadadustat	Placebo	Key Findings
CI-0004	NDD-CKD, GFR categories G3 & G4	Open-label (Change in: reticulocyte count, HGB, hematocrit, RBCs/Safety)	Within subject, dose escalation (potential doses of 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, and 700 mg); 28 days of dosing	10	0	Starting doses were 300 mg (CKD GFR category G4) or 400 mg (CKD GFR category G3). Dose adjustments could be made weekly based on reticulocyte count and HGB data. Average HGB levels rose from 9.91 g/dL at baseline to 10.54 g/dL by Day 29. Five subjects experiencing at least 1 AE. Diarrhea was the only AE that occurred in more than 1 subject (n=2). No SAE occurred.
CI-0005	NDD-CKD, GFR categories G3a-G5, not on dialysis	Double-blind, placebo-controlled (Mean absolute change in HGB between the predose average and End of Treatment/ PD/PK)	240 mg, 370 mg, 500 mg, 630 mg; 42 days of dosing	18 (240 mg) 18 (370 mg) 17 (500 mg) 19 (630 mg)	19	Vadadustat significantly increased HGB levels in subjects compared to baseline in all dose groups and compared to placebo. The HGB increase occurred without increasing predose EPO levels (prior to daily vadadustat dose). There were no apparent differences in the types of AEs across dosing groups or with placebo; 9.7% and 5.3% of subjects had an SAE in the total vadadustat and placebo groups, respectively, and all were assessed as unrelated to study drug by investigators. One subject treated with vadadustat had a non-fatal acute myocardial infarction (MI). One subject died of cardiac arrest after being hospitalized for azotemia due to progression of CKD.
CI-0007	NDD-CKD, GFR categories G3a-G5, not on dialysis (naïve to ESA), previously treated with ESA, or actively treated with ESA	Double-blind, placebo-controlled (Achieving or maintaining a mean HGB of ≥11.0 g/dL or increasing HGB by ≥1.2 g/dL)	450 mg starting dose with dose adjustment with allowable dose levels of 150, 300, 450, or 600 mg to maintain HGB <13.0 g/dL; 2:1 active:placebo; 20 weeks of dosing	138	72	The study achieved its primary endpoint, confirming that the once-daily, oral therapy can successfully increase and maintain HGB levels. 54.9% of patients who received vadadustat met the primary endpoint versus 10.3% in the placebo group (p<0.0001; achieving or maintaining a mean HGB ≥11.0 g/dL or increasing HGB by ≥1.2 g/dL above the pre-treatment value as measured by the mean HGB value at weeks 19 and 20). AEs were balanced overall between the vadadustat and placebo treatment groups (74.6% and 73.6%, respectively). Diarrhea, nausea, hyperkalemia, and hypertension were

reported more frequently in the vadadustat than the placebo group. Angioedema occurred in 2 subjects in the vadadustat group. More subjects had SAEs in the vadadustat group than the placebo group (23.9% and 15.3%, respectively), and this difference was explained by differences in how renal events were reported by investigators. One MI occurred in the placebo group, and none in the vadadustat group. One CVA occurred in the vadadustat group and none in the placebo group. Three subjects died, and the causes of death were reported as ischemic heart disease, sudden cardiac death, and cardiac arrest.

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Study Design				Subjects Treated		
Study[a]	Subjects	Design (Endpoint)	Dose, Duration[b]	Vadadustat	Placebo	Key Findings
CI-0011	DD-CKD	Multi-center, open-label study (Change in HGB/ actual values and change from baseline in HGB, HCT, RBC count, and reticulocyte count / rate of transfusion and/or ESA rescue/ analysis of safety)	Three different starting dose regimens (300 mg QD, 450 mg QD, 450 mg TIW) with subsequent dose adjustment with allowable doses of 150, 300, 450, or 600 mg; 16 weeks of dosing	94	0	The study demonstrated that vadadustat once daily or three time weekly maintained HGB levels in ESRD subjects who were converted from existing ESA therapy to vadadustat. Only one subject had a single HGB rise to 13.1 g/dL. Vadadustat was generally well-tolerated and the frequency and type of SAEs were consistent with those expected in a dialysis-dependent population. No SAE was reported as related to vadadustat and no deaths occurred.

AE =adverse event, AUC = area under the curve, CKD = chronic kidney disease, CVA = cerebral vascular accident, ECG = electrocardiogram, EPO = erythropoietin, ESA = erythropoiesis-stimulating agents, ESRD = end-stage renal disease, HCT = hematocrit, HGB = hemoglobin, MI = myocardial infarction, QD = once daily, PK = pharmacokinetics, PD = pharmacodynamics, QTc = corrected QT interval, RBC = red blood cell, SAEs = serious adverse events, TIW = 3 times per week, $t_{1/2}$ = terminal half-life

a. Official study numbers are precursed with “AKB-6548-”, but have been shortened to the last portion of the protocol number for purposes of reporting in this table.
b. Unless otherwise noted, all doses were administered orally, once daily.
c. Subjects who received placebo also received vadadustat as part of the crossover design of the thorough QTc study.

CI-0005: Positive Phase 2a Proof of Concept Trial in Non-Dialysis CKD Patients

CI-0005 was a randomized, double-blind, placebo controlled trial of vadadustat in non-dialysis patients with CKD GFR categories G3, G4 and G5 designed to evaluate the change in hemoglobin levels over 42 days. The study enrolled 91 CKD patients who received either placebo or one of the following 4 vadadustat doses once daily: 240 mg, 370 mg, 500 mg, or 630 mg. The primary endpoint for the trial was the mean absolute change in hemoglobin from baseline.

All doses of vadadustat significantly increased hemoglobin in a dose-dependent manner compared with placebo ($p<0.0001$). The mean increase in hemoglobin in vadadustat treated patients ranged from 0.7 to 1.4 g/dL, while placebo-treated patients experienced a mean decrease in hemoglobin of 0.1 g/dL. The dose-dependent increases in hemoglobin occurred even though, per protocol, 26% of patients receiving the 630 mg vadadustat dose and 11% of patients in the 500 mg vadadustat dose group had their dose reduced due to a hemoglobin increase > 1.5 g/dL by Day 28. No patient's hemoglobin level exceeded 13 g/dL during the study.

Increases in hemoglobin in the vadadustat group were associated with an increase in reticulocytes and total iron binding capacity, or TIBC, and a decrease in serum hepcidin and ferritin as observed in healthy volunteers, serum EPO levels returned to baseline levels prior the next daily dose of vadadustat, indicating that vadadustat increase hemoglobin without chronically elevating EPO.

Vadadustat was generally well tolerated with 34 subjects (47.2%) in the vadadustat groups and 11 subjects (57.9%) in the placebo group reporting an adverse event. Adverse events were evenly distributed across the dose groups. Ten subjects (13.9%) treated with vadadustat and one placebo subject (5.3%) had AEs that were considered study drug related. The most frequently reported adverse events in either treatment group were: anemia (placebo, 10.5%), nausea (500 mg, 11.8%) and placebo, (10.5%), urinary tract infection (240 mg, 11.1%), hyperkalemia (500 mg, 17.6%), hypoglycemia (630 mg, 10.5%), headache (240 mg, 11.1%), hypertension (630 mg, 10.5%) and placebo (15.8%), and hypotension (placebo, 10.5%). There were eight serious adverse events (vadadustat 9.7% vs. placebo 5.3%) reported and all were considered unrelated to the study drug. These included fluid overload (placebo patient), gastroenteritis, hypoglycemic event, dizziness, triple vessel coronary artery disease with non-ST elevation myocardial infarction, hypertensive crisis, ventricular pacemaker lead replacement, and azotemia (uremia). One subject died after being hospitalized with uremia due to progression of her CKD and acute pulmonary edema. Following a complicated hospital course, the patient developed sustained ventricular tachycardia resulting in a cardiac arrest.

VEGF is necessary for the maintenance of healthy kidney function and is regulated by HIF1a. Clinical studies have shown that increased VEGF levels are potentially linked to increased growth of tumors in patients with cancer. Vadadustat provides for the ability to induce a more prominent HIF2a response, and consistent with this mechanism, no change in VEGF levels were observed from baseline for any of the vadadustat dose groups. The results of this study were reported at the American Society of Nephrology meeting in November 2012.

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

We have completed a Phase 2b study of vadadustat in subjects with anemia secondary to CKD not requiring dialysis. 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 3-5. Subjects were enrolled into one of three groups: (1) ESA naïve with hemoglobin ≤10.5 g/dL, (2) previously treated with ESA with hemoglobin ≤10.5 g/dL, or (3) actively treated with ESA with hemoglobin ≥9.5 and ≤12.0 g/dL and randomized (2:1) to once daily vadadustat or placebo. The primary endpoint was the percent 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 mean age was 66 years, ~75% of subjects had diabetes mellitus and the mean estimated glomerular filtration rate, or eGFR, 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. Group 3 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 associated with an increase in reticulocytes and TIBC 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.

Vadadustat was generally well tolerated with similar percentages of subjects experiencing AEs in vadadustat treated and placebo groups (74.6% vs. 73.6%). There was an increase in renal related SAEs reported in the vadadustat-treated subjects (vadadustat 9.4% vs. placebo 2.8%), however, the number of subjects requiring dialysis, an objective measure of the severity of renal disease, was similar in the two treatment groups (vadadustat 8.0% vs. placebo 9.7%). Overall AEs for renal and urinary disorders was balanced (vadadustat 14.5% vs. placebo 13.9%). The disparity in renal SAEs was likely related to variability in reporting between investigators (reasons included proceeding to dialysis in association with a SAE that was not reported in the renal category, or proceeding to

dialysis without being considered an SAE). Other differences, favoring either vadadustat or placebo, in AEs were as follows: nausea and diarrhea (vadadustat 10.1% vs. placebo 4.2%); gastrointestinal hemorrhage (vadadustat 0.0% vs. placebo 5.6%); upper respiratory tract infection (vadadustat 1.4% vs. placebo 6.9%); hyperkalemia (vadadustat 5.1% vs. placebo 0.0%); and hypertension (vadadustat 8.0% vs. placebo 2.8%). There were three deaths in vadadustat-treated subjects and no deaths in the placebo group. This was the expected number of subject deaths based on previous studies in similar populations.

In summary vadadustat achieved the desired outcomes of raising and maintaining hemoglobin and increasing iron mobilization, while minimizing hemoglobin excursions ≥13 g/dL. The results of this study were reported in various scientific meetings in 2015, including the World Congress of Nephrology meeting in March 2015.

Phase 2 Study in Dialysis-Dependent Patients (CI-0011)

We recently completed a multi-center, open-label, 16-week trial to assess the hemoglobin response, safety, and tolerability of vadadustat in dialysis dependent CKD patients. The trial enrolled 94 hemodialysis patients (hemoglobin 9 - 12 g/dL), who were maintained on ESAs prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD; or 450 mg three times weekly (TIW). For each dose cohort, the mean hemoglobin level at study entry was compared to the average at weeks 7 and 8, and to the average at weeks 15 and 16. To evaluate hemoglobin response to each of the dose regimens, during the first eight weeks of this study patients were to remain on the prescribed starting dose, or decreased if necessary to control hemoglobin. Beginning at week eight, the dose of vadadustat could be increased or decreased to maintain hemoglobin levels as needed. Intravenous iron use was allowed.

The underlying patient demographics and profile of these CKD patients were well-balanced across the three cohorts, and reflective of the US dialysis dependent CKD population as reported in the literature. Mean age was 58 years, average time on dialysis was 4.6 years, and the most common cause of end-stage renal disease was diabetes mellitus and/or hypertension. Baseline hemoglobin levels were similar (10.4-10.6 g/dL) in all three cohorts and the serum ferritin levels indicated that the patients were iron replete at study entry and throughout the study.

The trial achieved its primary endpoint of maintaining stable hemoglobin levels over 16 weeks, across all three cohorts of patients converting from ESAs to vadadustat. The study supports both daily and three times weekly vadadustat dosing regimens as viable options for patients. Consistent with previous studies, all three starting dose regimens improved iron mobilization, as reflected by increases in TIBC and serum iron, and decreases in serum ferritin and hepcidin levels. Only one subject in the 300mg QD cohort had a single hemoglobin excursion to 13.1 g/dL.

Mean Hemoglobin Levels (g/dL)*	Baseline	Week 7/8	Week 15/16
300mg Daily Dose	10.4	10.4	10.3
450mg Daily Dose	10.6	10.3	10.5
450mg Three Times per Week Dose	10.5	10.2	10.4

*Modified intent-to-treat (MITT) population, n=94

Adverse events were balanced across the three cohorts. There were no discernible trends in the frequency of AEs or SAEs by dose cohort. SAEs were reported in 13 subjects (13.8%), which was within the expected range (13 - 17 subjects) for this patient population. No SAEs were reported as related to vadadustat and no deaths occurred during

the study.

The results of this trial demonstrate that vadadustat maintained hemoglobin levels in dialysis-dependent CKD subjects who were converted from existing ESA therapy to vadadustat. Only one subject had a single hemoglobin rise to 13.1 g/dL. Vadadustat was generally well tolerated and the frequency and type of SAEs were consistent with those expected in a dialysis-dependent CKD population. The results of this study were reported at the American Society of Nephrology meeting in November 2015.

Phase 3 Clinical Program

Akebia is conducting two global Phase 3 studies to support an indication for the treatment of anemia in non-dialysis dependent patients and two Phase 3 studies to support an indication for the treatment of anemia in dialysis-dependent CKD patients:

1. 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)”
2. 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)”
3. CI-0016: “Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction of Anemia in Subjects with Dialysis-Dependent Chronic Kidney Disease (DD CKD) (INNO$_2$VATE - CORRECTION)”
4. 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 will be the mean change in hemoglobin between baseline (mean pretreatment hemoglobin) and the primary evaluation period, concluding non-inferiority (NI) when the upper 95% confidence interval of the hazard ratio (vadadustat/ESA) 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 major adverse cardiovascular endpoints, or MACE, with a comparison of vadadustat to an ESA. 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 (vadadustat/ESA) does not exceed the NI margin. The assessment of MACE will also allow for determination of superiority for the composite or individual MACE components.

Overall, the non-dialysis dependent CKD and dialysis-dependent CKD Phase 3 programs will enroll approximately 5,700 CKD patients; approximately 2,850 patients receiving vadadustat and approximately 2,850 patients receiving an ESA. We have engaged Quintiles as our primary CRO for the PRO$_2$TECT and INNO$_2$VATE programs. We expect the cost of the Phase 3 program to be in the range of $80,000 to $85,000 per patient and we plan to enroll approximately 3,100 patients in PRO$_2$TECT and approximately 2,600 patients in INNO$_2$VATE.

In December 2015, we began dosing patients in our Phase 3 vadadustat program in non-dialysis patients with anemia related to CKD, PRO$_2$TECT, after obtaining feedback from United States and European regulatory authorities regarding the design of the program. If the results from the PRO$_2$TECT Phase 3 program support the results observed across our previous clinical studies, we anticipate submitting an NDA to the FDA for vadadustat in 2019. We expect to initiate our Phase 3 vadadustat program in dialysis-dependent CKD patients, INNO$_2$VATE, in 2016, and also anticipating submitting an NDA to FDA in 2019.

Additional Studies

We have completed a thorough QT, or TQT, study in accordance with FDA guidance to ensure that vadadustat does not affect the cardiac conduction cycle (CI-0010). A lengthened QT interval is a biomarker for certain ventricular arrhythmias and a risk factor for sudden death. The results from this study confirm that vadadustat does not alter cardiac repolarization intervals in healthy volunteers following a single dose of up to 1200 mg.

In addition, a clinical study was conducted to evaluate the effect of vadadustat on celecoxib, a substrate for the hepatic cytochrome P450 enzyme CYP2C9. The results of the study showed that the co-administration of vadadustat resulted in a minimal (12%) increase in the exposure (AUC) of celecoxib while the C_{max} of celecoxib increased by approximately 60% when co-administered with vadadustat. Since the potential for interaction is based on total exposure (AUC), it was concluded that vadadustat does not inhibit CYP2C9 to any appreciable extent and, therefore, there is no clinically significant effect of vadadustat on drugs that are CYP2C9 substrates (e.g., losartan, rosuvastatin). Vadadustat was well-tolerated and no SAE occurred.

The results of a standard battery of tests that evaluate for mutations in cells or animals have indicated that vadadustat does not cause mutations that could lead to cancer. However, to satisfy the expected regulatory requirement, carcinogenicity assessments (two years of dosing in rats, and six months of dosing in a transgenic mouse model) will be conducted. The 2-year rat carcinogenicity study was initiated in Q2 2015 and the six month transgenic mouse study will commence in Q2 2016. Embryo-fetal development studies have been conducted in rats and rabbits, and a fertility study has been conducted in rats with no notable findings. A peri-postnatal development study in rats is currently ongoing.

In order to complete the registration package for drug approval, we plan to evaluate the pharmacokinetics and safety of vadadustat in subjects with mild and moderate hepatic impairment. In addition clinical studies are also planned to evaluate the potential of vadadustat to interact with drugs that are substrates of enzymes CYP2B6 and CYP2C8. Clinical studies will also be conducted to determine the effect of vadadustat on substrates of transporters such as P-gp, BCRP, OAT1, OAT3 and OATP1B1.

AKB-6899

Our second clinical candidate, AKB-6899, is designed as a small molecule HIF-PH inhibitor with potential therapeutic application in oncology and ophthalmology. AKB-6899 has demonstrated the ability in vitro to reduce VEGF levels in the presence of hypoxia while stimulating the production of soluble vascular endothelial growth factor receptor 1, or sVEGFr1. sVEGFr1 sequesters VEGF to inhibit VEGF signaling and thereby can decrease tumor growth. Moreover, AKB-6899 inhibits the expression of phosphoglycerate kinase, or PGK, which has been associated with the growth of cancerous tumors. In several preclinical mouse models, AKB-6899 has been active in reducing tumor growth and metastases, and has improved survival. We opened an IND with the FDA at the end of 2015. We expect to commence clinical development of AKB-6899 in 2016 and anticipate completion of the Phase 1 study in oncology in late 2017.

Manufacturing and Supply

Vadadustat is a small-molecule that is manufactured from readily available commercial starting materials. We have no internal manufacturing capabilities and rely on third-party contract manufacturers to produce all lots of drug substance and drug products.

We entered into a Master Services Agreement with Evonik Corporation, or Evonik, pursuant to which Evonik shall further develop and manufacture vadadustat drug substance for use in our Phase 3 development program for vadadustat and other clinical trials. Evonik is currently manufacturing vadadustat at commercially relevant scale.

The drug substance can be readily formulated into compressed tablets using common manufacturing processes. Tablets have been made at several different potencies with excellent drug product pharmaceutical properties and a fast, reproducible dissolution rate. We entered into a Master Services Agreement with Gregory Pharmaceutical Holdings, Inc. (d/b/a UPM Pharmaceuticals Inc., or UPM), pursuant to which UPM shall further develop and manufacture the drug product for use in our Phase 3 development program for vadadustat and other clinical trials. UPM is currently manufacturing vadadustat tablets at commercially relevant scale.

In our agreements with third-party manufacturers, we retain ownership of our intellectual property and generally own and/or are licensed rights to processes, developments, data, results and other intellectual property relating to our products and generated during the course of the manufacturer’s performance under the agreement.

AKB-6899 will be entering clinical development in 2016. A scalable manufacturing route has been used to synthesize GMP material required for non-clinical and clinical development. A capsule formulation has been manufactured for use in clinical trials. We have contracted with several contract manufacturing organizations for the supply of drug substance and finished product to meet our needs for pre-clinical toxicology and early clinical development of AKB-6899. We expect to continue to rely on third-party contract manufacturers for the supply of AKB-6899 drug substance and drug product for the foreseeable future.

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 U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on 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.”

Our patent estate, on a worldwide basis, includes 64 allowed applications and issued patents and approximately 81 pending utility and provisional patent applications, with pending and issued claims relating to our current clinical stage candidate vadadustat as well as other product candidates, including AKB-6899. We also hold three patents that claim the crystal of a protein-ligand complex of EGLN-1 as well as methods for identifying compounds that bind to EGLN-1.

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 five issued patents and one pending application covering the composition of matter, method of treating anemia, and pharmaceutical compositions of vadadustat in the United States, one issued patent in Europe (registered in most countries of the European Patent Convention), and additional patents issued or pending in many other major

jurisdictions worldwide, including Japan, China, South Korea, Brazil, Mexico, Russia, Israel and India. The expected expiration date for these composition of matter patents is 2028 plus any extensions or adjustments of term available under national law.

In July of 2011, a third party filed an opposition to our issued European Patent No. 2044005 (the ’005 Patent). During the oral proceedings, which took place on April 10, 2013, the Opposition Division of the European Patent Office maintained the ’005 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 have appealed the decision of the Opposition Division and final resolution of the opposition proceedings will likely take a number of years. We cannot be assured of the breadth of the claims that will remain in the ’005 Patent or that the patent will not be revoked in its entirety.

We also hold patents and patent applications directed to processes for manufacturing vadadustat, dosing regimens, formulations, polymorphs, and various other aspects relating to the treatment of anemia using vadadustat that are expected to expire between 2032 and 2034 exclusive of possible patent term extensions.

AKB-6899 Patent Portfolio

We hold four issued patents and one pending application covering the AKB-6899 composition of matter and pharmaceutical compositions or methods of use 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 and India. The expected expiration date for these composition of matter patents is 2028 plus any extensions or adjustments of term available under national law.

We hold one issued patent that covers the treatment of anemia by administration of AKB-6899, which is expected to expire in 2028. We also hold, either alone or jointly, one issued patent and one pending application covering various methods, including, but not limited to, the treatment of cancer by administration of AKB-6899 in the United States and additional patent applications are pending in many other major jurisdictions worldwide, including Japan, China, South Korea, Mexico, Russia, Israel and India. The expected expiration dates for these method of treatment patent applications are expected to be 2032 exclusive of possible patent term extensions or adjustments. We hold one pending patent application in the United States and approximately 30 pending patent applications worldwide directed to treatment or prevention of ocular conditions using AKB-6899, and one pending patent application in the United States and approximately 30 pending patent applications worldwide directed to dosing regimens of AKB-6899. The expected expiration date of this ocular patent application is 2035, and the expected expiration date of this dosing patent application is 2034, exclusive of possible patent term extensions or adjustments. We also hold two pending patent application directed to polymorphs of vadadustat and AKB-6899 in the United States and various foreign jurisdictions. The expected expiration dates of these polymorph patent applications are 2034 for vadadustat and 2036 for AKB-6899 exclusive of possible patent term extensions or adjustments.

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 U.S. 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 U.S. patents conflict with our intellectual property rights; nor do we make any admission that any of such patents are valid or enforceable. Under U.S. 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 U.S. 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.

As explained in more detail below, we have had some positive developments in our opposition and invalidity proceedings against FibroGen. With regard to the opposition that we filed in Europe against FibroGen's European Patent No. 1463823, or the '823 patent, the European Opposition Division issued a non-binding preliminary opinion that none of FibroGen's '823 patent claims meet the requirements for patentability. In an oral proceeding which took place March 8 and 9, 2016, the European Opposition Division confirmed 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. 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 patent, which is the Japanese counterpart to the '823 patent, the 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 FibroGen '131 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 in Europe and Japan in the '823 and '131 patents. In the event FibroGen were to obtain such patents in the United States, we may decide to challenge them like we have done in Europe and Japan. On May 13, May 20, and July 6, 2015, we also filed oppositions to FibroGen's European Patent Nos. 2322153, 2322155, and 1633333 respectively, requesting the patents be revoked in their entirety.

In June 2013, the European Patent Office granted the ’823 patent to FibroGen. The ’823 patent claims, among other things, the use of a heterocyclic carboxamide compound selected from the group consisting of pyridine carboxamides, quinoline carboxamides, isoquinoline carboxamides, cinnoline carboxamides, and beta-carboline carboxamides that inhibits HIF-PH enzyme activity in the manufacture of a medicament for increasing endogenous EPO in the prevention, pretreatment, or treatment of anemia. On December 5, 2013, we filed an opposition with the European Patent Office to the ’823 patent requesting that the ’823 patent be revoked in its entirety. The European Opposition Division scheduled oral proceedings for March 8, 2016 and also issued a non-binding preliminary opinion that none of the ’823 patent’s claims met the requirements for patentability. In an oral proceeding which took place March 8 and 9, 2016, the European Opposition Division confirmed 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. If FibroGen appeals the decision of the European Opposition Division, final resolution of the appeal will likely take two to three years. While, for the reasons set forth in our opposition, we maintain that the ’823 patent should be revoked in its entirety, the ultimate outcome of any appeal remains uncertain. If FibroGen appeals the decision of the European Opposition Division and the Technical Board of Appeal at the European Patent Office decides not to revoke the ’823 patent in its entirety, or only certain claims of the ’823 patent and any surviving claims are determined to encompass our intended use of vadadustat, we may not be able to commercialize vadadustat in the European Union for its intended use, which could materially adversely affect our business, operating results and financial condition.

In August 2011, the Japanese Patent Office granted the ’131 patent to FibroGen. The ’131 patent claimed, among other things, the use of certain heterocyclic carboxamides selected from the group consisting of pyridine carboxamides, quinoline carboxamides, and isoquinoline carboxamides to treat anemia, wherein the heterocyclic carboxamides also suppress HIF prolyl-hydroxylase. On June 2, 2014, we filed an invalidity proceeding in the Japanese Patent Office challenging the validity of the ’131 patent and requesting that certain claims be revoked in their entirety. An oral hearing before the Japanese Patent Office was held on February 9, 2015, and on May 11, 2015 the Japanese Patent Office issued a preliminary decision finding all of the challenged claims to be invalid. In response, FibroGen filed a request for correction in which it requested that the ’131 patent claims be amended to exclude pyridine carboxamides from their scope. On November 18, 2015, Akebia received the final trial decision from the JPO in which it accepted FibroGen’s requested claim amendments. As a result of the JPO’s decision and FibroGen’s subsequent amendments, the FibroGen ’131 patent does not cover vadadustat or any pyridine carboxamide compounds.

In August 2014, the European Patent Office granted European Patent Nos. 2322153, 2322155, and 1633333 (the ’153 patent, the ’155 patent, and the ’333 patent, respectively) to FibroGen. 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 EPO, and microcytosis in microcytic anemia. On May 13, May 20, and July 6, 2015, we filed oppositions to the ’155 patent, the ’333 patent, and the ’153 patent, respectively, requesting that the patents be revoked in their entireties. While, for the reasons set forth in our oppositions, we believe that the ’153 patent, the ’155 patent, and the ’333 patent should be revoked in their entireties, the ultimate outcomes of the oppositions remains uncertain.

Competition

We operate in highly competitive segments of the biotechnology and biopharmaceutical markets. We face competition from many different sources, including commercial pharmaceutical and biotechnology enterprises, academic institutions, government agencies and private and public research institutions. Many of our competitors have significantly greater financial, product development, manufacturing and marketing resources than us. Large

pharmaceutical companies have extensive experience in clinical testing and obtaining regulatory approval for drugs. These companies also have significantly greater research capabilities than us. Many universities and private and public research institutes are active in CKD research, some in direct competition with us. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. The key competitive factors affecting the success of vadadustat, if approved, are likely to be its efficacy, convenience and safety profile.

If vadadustat is approved and launched commercially, competing drugs may include EPOGEN® and Aranesp® (commercialized by Amgen), Procrit® and Eprex® (commercialized by Johnson & Johnson) and Mircera® (commercialized by Roche Holding Ltd., or Roche). We may face competition from potential new anemia therapies. There are several other HIF 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 partnership 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/Astellas Pharma Inc., in particular, is currently in Phase 3 clinical development of its product candidate, roxadustat (FG-4592). Some of these product candidates may enter the market as early as 2017. In addition, certain companies are developing potential new therapies for renal-related diseases that could potentially reduce rESA utilization and thus

limit the market for vadadustat if and when it is approved and launched commercially. Such therapies include hepcidin lowering therapies, like PRS-080 from Pieris Pharmaceuticals. Other new therapies are in development for the treatment of conditions inclusive of renal anemia, like sotatercept from Acceleron Pharma Inc. that may impact the market for anemia-targeted treatment.

Since rESAs are biologic products, the introduction of biosimilars into the rESA market in the United States will constitute additional competition for vadadustat if we are able to obtain approval for and commercially launch our product. A biosimilar product is a follow-on version of an existing, branded biologic product. The patents for the existing, branded 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 rESA, expired in 2004 in the European Union, and the remaining patents expired between 2012 and 2015 in the United States. Several biosimilar versions of rESAs are available for sale in the European Union and biosimilar versions of rESAs are currently being pursued in the United States, which will compete with vadadustat if it is approved and marketed, and will likely drive down prices for rEPO, which could also adversely affect our reimbursement.

In the dialysis market, it is typical to compete for and enter into long-term supply agreements with the major operators of dialysis clinics in the United States. In particular, two of the largest operators of dialysis clinics in the United States, DaVita Inc., or DaVita, and Fresenius, account for more than half of the rESA sales in the U.S. dialysis market. We believe that it may be challenging to enter into or expand upon long or short-term supply agreements with DaVita, Fresenius or other operators of dialysis clinics.

Regulatory Matters

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing, labeling and packaging, storage, distribution, post-approval monitoring and reporting, advertising and promotion, pricing, and export and import of drugs. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Moreover, failure to comply with applicable regulatory requirements may result in, among other things, warning letters, clinical holds, civil or criminal penalties, recall or seizure of products, injunction, disbarment, partial or total suspension of production or 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 Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the FDA’s implementing regulations. If we fail to comply with applicable FDA or other requirements at any time during the drug development process, clinical testing, approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA’s refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us. FDA approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States.

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

- completion of extensive nonclinical laboratory tests, nonclinical 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 IND application which must become effective before human clinical trials in the United States may begin;
- approval by an IRB or ethics committee at each clinical trial site 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 an NDA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current 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, nonclinical 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. Nonclinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product.

The results of nonclinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol, and other information, are submitted as part of an IND to the FDA. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human studies. Some nonclinical 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 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 in the United States must be submitted to the FDA as part of the IND. In addition, an independent institutional review board, or 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 to public registries.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA so long as the clinical trial is conducted in compliance with an international guideline for the ethical conduct of clinical research known as the Declaration of Helsinki, as set out in the FDA regulations or 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 U.S.

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. 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, product licensing, pricing and reimbursement 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. To obtain regulatory approval of an investigational drug under European Union regulatory systems, we must submit a Marketing Authorization Application (MAA). The application used to file the NDA in the United States is similar to that required in Europe, with the exception of, among other things, country-specific document requirements.

An approved Paediatric Investigation Plan (PIP) is required in Europe prior to submission of the MAA. Ideally, the pediatric studies in both the U.S. PSP and the EU PIP will be identical, but some differences may be required to meet the respective regulatory requirements (e.g., waiver age). The PIP outlines the study designs and timing of the pediatric program. The EMA Pediatric

Committee (PDCO) and the FDA's Office of Pediatric Therapeutics have frequent 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.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Clinical Trials

Clinical trials are typically conducted in three or four phases, which may overlap or be combined:

- Phase 1: Clinical trials are initially conducted in a limited population of subjects to test the drug candidate for safety, dose tolerance, absorption, metabolism, distribution and excretion in healthy humans or, on occasion, in patients with severe problems or life threatening diseases to gain an early indication of its effectiveness.
- Phase 2: Clinical trials are generally conducted in a limited patient population to evaluate dosage tolerance and appropriate dosage, identify possible adverse effects and safety risks, and evaluate preliminarily the efficacy of the drug for specific targeted indications in patients with the disease or condition under study.
- Phase 3: Clinical trials are typically conducted when Phase 2 clinical trials demonstrate that a dose range of the product candidate is effective and has an acceptable safety profile. Phase 3 clinical trials are commonly referred to as "pivotal" studies, which typically denotes a study which presents the data that the FDA or other relevant regulatory agencies will use to determine whether or not to approve a drug. Phase 3 clinical trials are generally undertaken with large numbers of patients, such as groups of several hundred to several thousand, to further evaluate dosage, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse patient population at multiple, geographically-dispersed clinical trial sites.
- Phase 4: In some cases, FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials after NDA approval. In other cases, a sponsor may voluntarily conduct additional clinical trials post-approval to gain more information about the drug. Such post approval trials are typically referred to as Phase 4 clinical trials.

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

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

New Drug Applications

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

Once the NDA submission has been accepted for review, under the Prescription Drug User Fee Act (PDUFA), the FDA has a goal of responding to standard review NDAs within ten months after the 60-day filing review period, but this timeframe is often extended. The first indication of the FDA's review progress is provided at the mid-cycle review. This typically occurs five months after the

NDA is accepted for review. However, the review process is often significantly extended by FDA requests for additional information or clarification. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

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

After the FDA evaluates the NDA and conducts inspections of manufacturing facilities, it may issue an approval letter or a Complete Response Letter (CRL). An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A CRL indicates that the review cycle of the application is complete but the application is not yet ready for approval. A CRL may require additional clinical data and/or other significant, expensive, and time-consuming requirements related to clinical trials, nonclinical studies and/or manufacturing. Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret data. The FDA could also approve the NDA with a REMS to mitigate risks, which could include medication guides, physician communication plans, or elements to ensure safe use, such as restricted distribution programs, patient registries or other risk minimization tools. The FDA may also condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post-market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

An approved Pediatric Study Plan (PSP) is required for vadadustat under the Pediatric Research Equity Act (PREA) prior to submission of the NDA. The PSP outlines the study designs and timing of the pediatric program. Once the PSP is approved, Akebia and FDA will have reached agreement on the pediatric studies necessary for vadadustat, any deferrals from pediatric data to be included in the NDA, and any waivers of pediatric age ranges in which vadadustat need not be studied.

Once the FDA approves an NDA, or supplement thereto, the FDA may withdraw the approval if ongoing regulatory requirements are not met or if safety problems are identified after the drug reaches the market. Where a withdrawal may not be appropriate, the FDA still may seize existing inventory of such drug or request a recall of any drug already on the market. In addition, the FDA has the authority to prevent or limit further marketing of a drug based on the results of post-market studies or surveillance programs.

After regulatory approval of a drug is obtained, companies are subject to a number of post-approval requirements. For example, there are reporting obligations regarding certain adverse events received and production problems. Companies are also required to report updated safety and efficacy information and to comply with requirements concerning advertising and promotional labeling. Drugs may be marketed only for the FDA approved indications and in accordance with the provisions of the approved labeling. The FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet. A company can make only those claims relating to safety and efficacy that are approved by the FDA. Failure to comply with these requirements can result in warning letters, adverse publicity, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available drugs for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does,

however, impose stringent restrictions on manufacturers' communications regarding off-label use.

Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the applicant to develop additional data or conduct additional nonclinical studies and clinical trials. As with new NDAs, the review process is often significantly extended by the FDA requests for additional information or clarification. Also, quality control and manufacturing procedures must continue to conform to cGMP requirements after approval to ensure and preserve the long term identity, strength, quality, and purity of the drug product. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP requirements, which imposes extensive procedural, substantive and record-keeping requirements. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP requirements, and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP requirement and other aspects of regulatory compliance.

The testing and approval processes require substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. Even if we believe a clinical trial has demonstrated safety and efficacy of one of our drug candidates for the treatment of a disease, the results may not be satisfactory to the FDA. Nonclinical and clinical data may be interpreted by the FDA in different ways, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals which could delay or preclude us from marketing drugs. The FDA may limit the indications for use or place other conditions on any approvals that could restrict the commercial application of the drugs.

Fraud and Abuse Laws

In the United States, the research, manufacturing, distribution, sale and promotion of drug products and medical devices are subject to regulation by various federal, state and local authorities in addition to the FDA, including the CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, state Attorneys General, and other state and local government agencies.

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

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

In addition to the laws described above, the PPACA also imposed new reporting requirements on drug manufacturers for payments made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1,

2013 and are required to submit reports to CMS by the 90th day of each subsequent calendar year.

In addition, many states have adopted laws similar to the federal laws discussed above. Some of these state prohibitions apply to the referral of patients for healthcare services reimbursed by any insurer, not just federal healthcare programs such as Medicare and Medicaid. There has also been a recent trend of increased federal and state regulation of payments made to physicians. Certain states mandate implementation of compliance programs, impose restrictions on drug manufacturers' marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians. Because we intend to commercialize products that could be reimbursed under a federal healthcare program and other governmental healthcare programs, we plan to develop a comprehensive compliance program that establishes internal controls to facilitate adherence to the rules and program requirements to which we will or may become subject. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Due to the breadth of and ambiguities in these laws, the absence of guidance in the form of regulations or court decisions, and the potential for additional legal or regulatory change in this area, it is possible that our future sales and marketing practices and/or our future relationships with physicians might be challenged under these laws. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

Third-Party Coverage and Reimbursement

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

Healthcare Reform

In March 2010, the PPACA was enacted, which includes measures that have or will significantly change the way health care is financed by both governmental and private insurers. Among the provisions of PPACA of greatest importance to the pharmaceutical industry are the following:

- Effective in 2010, PPACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic agents from 15.1% of average manufacturer price, or AMP, to 23.1% of AMP and adding a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP.
- PPACA also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization as of 2010 and by expanding the population potentially eligible for Medicaid drug benefits, to be phased-in by 2014. CMS has proposed to expand Medicaid rebate liability to the territories of the United States as well.
- In addition, PPACA provides for the public availability of retail survey prices and certain weighted average AMPs under the Medicaid program. The implementation of this requirement by the CMS may also provide for the public availability of pharmacy acquisition cost data, which could negatively impact our sales.
- Effective in 2010, PPACA expanded the types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs when used for the orphan indication. In addition, as 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could result in an increase in the required 340B discounts.
- Effective in 2011, PPACA imposed a requirement on manufacturers of branded drugs and biologic agents to provide a 50% discount off the negotiated price of branded drugs dispensed to Medicare Part D patients in the coverage gap (i.e., "donut hole").
- Effective in 2011, PPACA imposed an annual, nondeductible fee on any entity that manufactures or imports certain 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.

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As of 2010, a new Patient-Centered Outcomes Research Institute was established pursuant to PPACA to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products.

- PPACA created the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. Under certain circumstances, these recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings.
- PPACA 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.

Certain details regarding the implementation of PPACA are yet to be determined and, the full effect that PPACA would have on our business is not fully understood. In addition, we expect that additional state and federal healthcare reform measures will be adopted in the future. Because we anticipate that a significant proportion of patients eligible for vadadustat will be covered by Medicare Part D, any government healthcare reform measures which limit the amounts that federal and state governments will pay for healthcare products and services could result in reduced demand for our products once approved or additional pricing pressures.

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, 2015, we had 64 employees, 63 of whom were full-time, 13 of whom hold Ph.D. or M.D. degrees, 39 of whom were engaged in research and development activities and 25 of whom were engaged in business development, finance, information systems, facilities, human resources or administrative support. None of our employees are represented by any collective bargaining unit. We believe that we maintain good relations with our employees.

Facilities

Our corporate headquarters are located in Cambridge, Massachusetts. We currently lease approximately 39,411 square feet of office space in Cambridge, Massachusetts under a lease that expires on August 31, 2026. We believe that our existing facilities are adequate to meet our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms for our future growth.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also adversely affect our business. Please reference our "Cautionary Note Regarding Forward-Looking Statements," which identifies certain forward-looking statements contained in this report that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to our Financial Position and Need for Additional Capital

We have incurred significant losses since inception and anticipate that we will continue to incur significant losses for the foreseeable future and may never achieve or maintain profitability.

We have incurred net losses each year since our inception, including net losses of $60.7 million for the year ended December 31, 2015, and $37.0 million for the year ended December 31, 2014. As of December 31, 2015, we had an accumulated deficit of $161.4 million. To date, we have not commercialized any products or generated any revenue from the sale of products, and we do not expect to generate any product revenue in the foreseeable future. We do not know whether or when we will generate revenue or become profitable.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations primarily through our initial public offering, or IPO, completed in March 2014, our follow-on offerings completed in April 2015 and January 2016, our at-the-market offering in 2015 and private placements of our preferred stock. 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 ability to obtain funding through equity or debt financings or strategic collaboration. Our lead product candidate, vadadustat, recently commenced Phase 3 development, and our other product candidate, AKB-6899, may enter clinical development in 2016 with anticipated completion of the Phase 1 study in oncology in late 2017. Therefore, we expect that it will be several years, if ever, before we have a product candidate ready for commercialization. Even if we obtain regulatory approval to market vadadustat, our future revenue will depend upon the size of any markets in which vadadustat has received approval, our ability to achieve sufficient market acceptance, the availability and extent of reimbursement from third-party payors and other factors.

We expect to continue to incur significant expenses and increased operating losses for the foreseeable future. We anticipate that our expenses will increase significantly if and as we:

- conduct our Phase 3 development program of vadadustat for the treatment of anemia secondary to CKD, including the PRO_2TECT and $INNO_2VATE$ programs;
- commence clinical development of AKB-6899 or other product candidates;
- seek regulatory approvals for our product candidates that successfully complete clinical studies;
- have our product candidates manufactured for clinical trials and for commercial sale;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- initiate additional preclinical, clinical or other studies for additional indications for vadadustat, AKB 6899 and other product candidates that we may develop or acquire;
- seek to discover and develop additional product candidates;
- acquire or in-license other commercial products, product candidates and technologies;
- make royalty, milestone or other payments under any future in-license agreements;
- maintain, protect and expand our intellectual property portfolio;

- attract and retain skilled personnel; and
- continue to create additional infrastructure to support our operations as a public company.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, if at all, we will be able to achieve profitability. If we are required by the FDA or EMA, or other regulatory authorities 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, our expenses could increase.

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 or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

To become and remain profitable, we must succeed in developing and commercializing our product candidates, which must generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering or acquiring additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenue that is significant enough to achieve profitability.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable could depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could cause our stockholders to lose all or part of their investment.

We will require substantial additional financing. 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, 2015, our cash and cash equivalents and available for sale securities were $138.5 million. After giving effect to the receipt of the net proceeds of approximately $61.0 million from our January 2016 follow-on offering and $40.0 million received in January 2016 in connection with our collaboration with Mitsubishi, our cash and cash equivalents and available for sale securities would have been approximately $239.5 million. We believe that we will continue to expend substantial resources for the foreseeable future developing vadadustat, AKB-6899 and any other product candidates that we may develop or acquire. These expenditures will include costs associated with research and development, potentially obtaining regulatory 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 as a result of our decision to include certain elements in our 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:

- the results of our meetings with the FDA and the EMA and other regulatory authorities and the consequential effect on study design, study size and resulting operating costs;
- the size, rate of progress, results and costs of initiating and completing our global Phase 3 development of vadadustat;
- difficulties or delays in enrolling patients in our clinical trials;
- significant costs associated with our Phase 3 clinical studies of vadadustat for the treatment of anemia secondary to CKD; we expect the cost of the Phase 3 program to be in the range of $80,000 to $85,000 per patient and we plan to

enroll approximately 3,100 patients in PRO_2TECT and approximately 2,600 patients in $INNO_2VATE$, aggregating in the range of $456.0 million to $484.5 million for the total program;

- assuming favorable Phase 3 clinical results, the timing of, and the costs involved in, obtaining regulatory approvals for vadadustat in dialysis and non-dialysis indications, including to fund the preparation and filing of regulatory submissions for vadadustat with the FDA, the EMA and other regulatory authorities, and whether we will seek regulatory approval for both indications simultaneously;
- 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 additional indications for vadadustat, AKB-6899 and other product candidates that we may develop or acquire;
- the timing of, and the costs involved in, obtaining regulatory approvals for AKB-6899 if clinical studies are successful;

- the cost and timing of future commercialization activities for our products, if any of our product candidates are approved for marketing, including product manufacturing, marketing, sales and distribution costs;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the cost of having our product candidates manufactured for clinical trials and in preparation for commercialization;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such agreements and the level and timing of funding for these agreements;
- 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; and
- the extent to which we acquire or in-license other products, product candidates or technologies.

Based on our current operating plan, and absent any future financings or strategic partnerships, we believe that our existing cash and cash equivalents and available for sale securities at December 31, 2015, together with the net proceeds from our January 2016 offering and the funds received in January 2016 in connection with our collaboration agreement with Mitsubishi Tanabe, will be sufficient to fund our projected operating expenses and capital expenditure requirements through at least the second quarter of 2017.

However, we do not currently estimate that these funds will enable us to complete our Phase 3 development of vadadustat, including both the PRO2TECT and INNO2VATE clinical programs. 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. We intend to secure a second geographic collaboration for the development and commercialization of vadadustat outside the United States with a goal of providing funds sufficient to enable us to complete our Phase 3 development of vadadustat, including both the PRO_2TECT and $INNO_2$ VATE clinical programs. However, there can be no assurance that our development milestones will be achieved, that we will be able to secure a second geographic collaboration for the development and commercialization of vadadustat outside the United States or that we will secure other sources of financing to complete our Phase 3 development of vadadustat.

We will require additional capital for the further development of our existing product candidates and will also need to raise additional funds sooner to pursue other development activities related to additional product candidates. If and until we can generate a sufficient amount of revenue from our products, we expect to finance future cash needs through public or private equity, debt offerings, or strategic transactions. There can be no assurance that additional funds will be available to us on acceptable terms or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates. If we raise additional funds through the issuance of additional debt or equity securities, it could result in dilution to our existing stockholders or increased fixed payment obligations, and any such securities may have rights senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. 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 product candidates on unfavorable terms to us.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings and license, development and commercialization agreements with collaborators. 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, 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 include covenants limiting or restricting our ability to take certain actions,

such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through strategic collaborations with third parties, we may have to relinquish valuable rights to our product candidates, future revenue streams, research programs or product candidates 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 vadadustat, AKB 6899 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.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in 2007, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, identifying potential product candidates, undertaking preclinical studies and conducting clinical trials. We currently have two product candidates. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. Only a small percentage of biopharmaceutical development programs ultimately result in commercial products or even product candidates and a number of events could delay our development efforts and negatively impact our ability to obtain regulatory approval for, and to manufacture, market and sell, a biopharmaceutical product. We have not yet demonstrated our ability to successfully complete later stage clinical trials, obtain regulatory approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization.

In addition, as a relatively young business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to expand our capabilities to support commercial activities. We may not be successful in adding such capabilities.

Risks Related to our Business and the Clinical Development, Regulatory Review and Approval of Vadadustat and AKB-6899

We depend heavily on the success of one product candidate, vadadustat, which is in Phase 3 development. Even if we obtain favorable clinical results in our Phase 3 studies, we may not be able to obtain regulatory approval for, or successfully commercialize, vadadustat.

We currently have only one product candidate, vadadustat, in clinical development, and our business depends almost entirely on the successful clinical development, regulatory approval and commercialization of that product candidate, which may never occur. We currently have no drug products for sale, generate no revenue from sales of any drugs, and may never be able to develop marketable drug products. Vadadustat, which is in Phase 3 development, will require substantial additional clinical development, testing, manufacturing process development, and regulatory approval before we are permitted to commence its commercialization. We expect to commence clinical development of our other product candidate, AKB-6899, in 2016. 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 government authorities in the United States and in other countries where we intend to test and, if approved, market any product candidates. Before obtaining regulatory 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. Of the large number of drugs in development in the United States, only a small percentage successfully complete the FDA regulatory approval process and are commercialized. Accordingly, even if we are able to obtain the requisite capital to continue to fund our development and clinical programs, we may be unable to successfully develop or commercialize vadadustat.

We are not permitted to market vadadustat in the United States until we receive approval from the FDA, or in any jurisdiction outside of the United States until we receive the requisite approval from regulatory authorities in such jurisdiction. As a condition to an NDA to the FDA for vadadustat regarding its ability to treat patients with anemia secondary to CKD, we must complete Phase 3 studies and any additional non-clinical or clinical studies required by the FDA. Vadadustat may not be successful in clinical trials or receive regulatory approval. Further, vadadustat may not receive regulatory approval even if it is successful in clinical trials. Obtaining approval of an NDA is a complex, lengthy, expensive and uncertain process that typically takes many years following the completion of clinical trials

and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, the safety concerns associated with injectable rESAs and the black box warnings in their prescribing information may affect the FDA's review of the safety results of compounds of this class, 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. We have not obtained regulatory approval for any product candidate and it is possible that vadadustat will never obtain regulatory approval. The FDA may delay, limit or deny approval of vadadustat for many reasons, including, among others:

- we may not be able to demonstrate that vadadustat is safe and effective in treating anemia secondary to CKD to the satisfaction of the FDA;
- 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;

- the FDA may approve vadadustat for use only in a small patient population;
- the FDA may require that we conduct additional clinical trials;
- the contract research organizations, or CROs, that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- we may fail to perform in accordance with the FDA's good clinical practice, or GCP, requirements;
- 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 nonclinical studies and clinical trials;
- 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 other regulatory authorities to delay, limit or deny approval of vadadustat outside the United States.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market vadadustat. Because our business is almost entirely dependent upon vadadustat, any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

Alternatively, even if we obtain regulatory approval, that approval may be for indications or patient populations that are not as broad as we intend or desire or may require labeling that includes significant use or distribution restrictions or safety warnings. We may also be required to perform additional, unanticipated clinical trials to obtain approval or be subject to additional post-marketing testing requirements to maintain regulatory approval. In addition, regulatory authorities may withdraw their approval of a product or the FDA may require a risk evaluation and mitigation strategy, or REMS, for a product, which could impose restrictions on its distribution. Any of the foregoing scenarios could materially harm the commercial prospects for vadadustat or our other product candidates.

We have not yet obtained agreement with all regulatory authorities regarding the design of our Phase 3 studies.

We recently obtained agreement with both the FDA and the EMA on vadadustat's global Phase 3 program in non-dialysis patients with anemia related to CKD; however, we have not yet obtained agreement with all regulatory authorities on the design of these studies, nor have we obtained agreement with all regulatory authorities regarding our Phase 3 studies in dialysis patients with anemia related to CKD. A regulatory authority may suggest we include, or we may choose to include, certain elements in our Phase 3 development programs, such as any or all of the following:

- a larger number of subjects in the program;
- certain dosing requirements;
- more subjects from certain geographic regions than currently planned;
- a longer course of treatment than our current expectations;
- additional or different endpoints from those currently planned; or
- the simultaneous submission of Phase 3 data from our studies in dialysis and non-dialysis patients.

If we choose to change some or all of these elements in our Phase 3 development programs, the costs of our vadadustat development program could increase materially and the potential market introduction of vadadustat could be delayed or we could risk not obtaining regulatory authority approval even if the Phase 3 trials meet their primary endpoints. The regulatory authorities also may require that we conduct additional clinical, nonclinical or manufacturing validation studies and submit that data before it will consider an NDA, MAA or other application for regulatory approval. Furthermore, regulatory authorities may differ in terms of their requirements for our Phase 3 program, which would make it difficult for us to conduct a global Phase 3 program and to use the results from such program to support regulatory approval in multiple jurisdictions.

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We cannot predict what additional requirements may be imposed by any regulatory authorities or how such requirements might delay or increase costs for our planned Phase 3 development program. Because our business is almost entirely dependent upon the successful development, regulatory approval, and commercialization of vadadustat, any such delay or increase in costs would have an 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 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 for vadadustat because of concerns from adverse events observed with injectable rESAs, other investigational agents and commercial products in CKD or for other reasons, including competitive clinical studies for similar patient populations. In addition, patients controlling their disease with injectable rESAs 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. As a result, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our development of vadadustat 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;
- 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 vadadustat in relation to available therapies or other products under development;
- efforts to facilitate timely enrollment in clinical studies;
- 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 on-going or planned clinical studies, any of which would have an adverse effect on our business.

We may not be able to obtain regulatory approval in some jurisdictions outside of the United States.

We currently expect to seek regulatory approval of vadadustat for the treatment of anemia secondary to CKD in markets outside the United States, including the European Union and Japan. Our ability to successfully initiate, enroll and complete a clinical study in any country outside of the United States, should we attempt to do so, is subject to numerous risks unique to conducting business in international markets, including:

- difficulty in establishing or managing relationships with qualified CROs, physicians and clinical trial sites;
- different local standards for the conduct of clinical studies;
-

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; and

- the acceptability of using data obtained from studies conducted in the United States with the EMA and other regulatory authorities outside of the United States.

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If we fail to successfully meet requirements for the conduct of clinical trials outside of the United States, we may be delayed in obtaining, or be unable to obtain, regulatory approval for vadadustat in countries outside of the United States.

Regulatory authorities outside of the United States will require compliance with numerous and varying regulatory 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 approved for sale in that country. In some cases, the price that we intend to charge for our drug product is also subject to approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the United States does not ensure approval by regulatory authorities in other countries or by the FDA. However, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval in another jurisdiction. The regulatory approval process in countries outside of the United States may include all of the risks associated with obtaining FDA approval. We may not obtain such regulatory approvals on a timely basis, if at all. We may not be able to file for regulatory approvals and may not receive the necessary approvals to commercialize our product candidates in any market.

Clinical drug development is a lengthy and expensive process with an uncertain outcome, and positive results from the clinical studies of vadadustat thus far are not necessarily predictive of the results of any future clinical studies of vadadustat. If we cannot replicate the positive results observed to date in our Phase 3 clinical studies, we may be unable to successfully develop, obtain regulatory approval for and commercialize vadadustat.

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, and successful results from early or small clinical trials may not be replicated in later and larger clinical trials. 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 vadadustat Phase 3 development program will enroll 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. Many companies in the pharmaceutical and biotechnology industries 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 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.

We could encounter delays if a clinical trial is suspended or terminated by us, by the relevant IRBs at the sites at which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA or other regulatory authorities. Such suspension or termination may be due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of clinical trial operations, clinical trial site or manufacturing facilities by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, changes in laws or regulations, or lack of adequate funding to continue the clinical trial. Any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenue. Any of these occurrences may harm our business, financial condition and prospects significantly.

Even if we receive regulatory approval for our product candidates, such products will be subject to ongoing regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions, and we may be subject to penalties if we fail to comply with regulatory

requirements or experience unanticipated problems with our products.

Any regulatory approvals that we receive for our product candidates 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. In addition, if the FDA approves any of our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, as well as continued compliance with current Good Manufacturing Practices, or cGMPs, and GCPs for any clinical trials that we conduct post-approval.

Post-approval discovery of previously unknown problems with an approved drug 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 or manufacturing of the drug product, withdrawal of the drug product from the market, or drug product recalls;
- fines, warning 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;
- a Risk Evaluation and Mitigation Strategy (REMS) program; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. 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 adversely affect our business.

Risks Related to our Reliance on Third Parties

We rely on third parties to conduct preclinical and clinical studies for our product candidates. If they do not properly and successfully perform their obligations to us, we may not be able to obtain regulatory approvals for our product candidates.

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 clinical trials, including our Phase 3 development program for vadadustat. We compete with many other companies for the resources of these third parties. The third parties on whom we rely may terminate their engagement with us, and having to enter into alternative arrangements would delay development and commercialization of our product candidates.

We entered into an agreement with Quintiles to be our primary CRO for the PRO_2TECT and $INNO_2VATE$ programs. If Quintiles cannot perform as agreed or terminates their engagement with us, the progress of our Phase 3 clinical studies may be impacted and we may incur significant added costs in identifying, qualifying and contracting with a new CRO. We compete with many other companies for the resources of these third parties. The third parties on whom we rely may terminate their engagements with us, and having to enter into alternative arrangements would delay development and commercialization of our product candidates.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, the FDA and equivalent regulatory authorities outside of the United States require compliance with regulations and standards, including GCP requirements, for designing, conducting, monitoring, recording, analyzing and reporting the results of clinical trials to ensure that the data and results are credible and accurate and that the rights, integrity and confidentiality of study subjects are protected. Although we rely on third parties to conduct our clinical trials, we are responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol in compliance with legal and regulatory requirements. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs or clinical trial sites fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or other regulatory authorities may require us to perform additional clinical trials before approving our

marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. In addition, our clinical trials must be conducted with product that meets certain specifications and is manufactured under applicable cGMP regulations. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

If these third parties do not successfully carry out their duties under their agreements, if the quality or accuracy of the data they obtain is compromised due to their failure to adhere to clinical trial protocols or to regulatory requirements, or if they otherwise fail to comply with clinical trial protocols or meet expected deadlines, the clinical trials of our product candidates may not meet regulatory requirements. If clinical trials do not meet regulatory requirements or if these third parties need to be replaced, preclinical development activities or clinical trials may be extended, delayed, suspended or terminated. If any of these events occur, we may not be able to obtain regulatory approval of our product candidates on a timely basis or at all.

We also expect to rely on other 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 losses and depriving us of potential product revenue. In addition, we will be using an active comparator for our Phase 3 clinical trials in CKD patients. If our distributors are unable to obtain sufficient supply of the active comparator for any reason, our clinical trials may be extended, delayed, suspended or terminated.

We intend to rely on third parties to conduct some or all aspects of our product manufacturing, and these third parties may not perform satisfactorily.

We do not have any manufacturing facilities and do not expect to independently manufacture our product candidates for research and preclinical and clinical studies. We currently rely, and expect to continue to rely, on third parties to manufacture and supply drug product for our vadadustat clinical trials, and we expect to rely on third parties for the manufacture of clinical and commercial quantities of our product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

Also, these third parties may terminate their engagement with us. On February 28, 2014, we entered into an agreement with Evonik Corporation, or Evonik, for the manufacture of the drug substance for the Phase 3 development program of vadadustat. If Evonik cannot perform as agreed or terminates their engagement with us, we may be required to find replacement manufacturers. We may incur significant delays and added costs in identifying, qualifying and contracting with any such replacement, as well as producing the drug substance. Also, if we choose to engage a second source for the production of drug substance, we may incur additional costs. We also have an agreement in place with Gregory Pharmaceutical Holdings (d/b/a UPM Pharmaceuticals Inc., or UPM) for the manufacture of finished drug product for the Phase 3 development program. Although we believe that there are several other manufacturers who also could manufacture our drug product if UPM cannot perform as agreed or terminates their engagement with us, we may incur significant delays and added costs in identifying, qualifying, and contracting with another manufacturer. In addition, we have to enter into technical transfer agreements and share our know-how with such third-party manufacturers, which can be time-consuming and may result in delays. These delays could result in a suspension of our clinical trials or, if vadadustat is approved and marketed, a failure to satisfy patient demand.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities, including regulatory compliance and quality assurance;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- disruptions to the operations of our manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of our manufacturers or suppliers or a catastrophic event affecting our manufacturers or suppliers.

Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or affect our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

The facilities and processes used by our contract manufacturers to manufacture our product candidates will be inspected by the FDA prior to or after we submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with cGMP requirements for manufacture of both drug substance and finished drug product. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, we will not be able to secure and/or maintain regulatory approval for our product candidates. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, EMA or other regulatory authorities do not approve these facilities for the manufacture of our product candidates or if they withdraw any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Moreover, our failure, or the failure of our contract 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 product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect the supply of our products or product candidates.

In addition, our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. Certain of these 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 that might be capable of manufacturing for us.

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

If we are unable to manufacture our product candidates in sufficient quantities and at sufficient yields, we may experience delays in product development, clinical trials, regulatory approval and commercial distribution.

Completion of our clinical trials and commercialization of our product candidates require access to facilities to manufacture our product candidates at sufficient yields and at clinical and commercial scale. We have limited experience manufacturing, or managing third parties in manufacturing, any of our product candidates in the volumes that will be necessary to support large-scale clinical trials or commercial sales. Efforts to establish these capabilities may not meet initial expectations as to scheduling, scale-up, reproducibility, yield, purity, cost, potency or quality.

Our reliance on contract manufacturers may adversely affect our operations or result in unforeseen delays or other problems beyond our control. Because of contractual restraints and the limited number of contract manufacturers with the expertise, required regulatory approvals and facilities to manufacture our bulk drug substance and drug product on a commercial scale, replacement of a manufacturer may be expensive and time-consuming and may cause interruptions in the production of our product candidates. A contract manufacturer may also encounter difficulties in production. These problems may include:

- difficulties with production costs, scale-up and yields;
- availability of raw materials and supplies;
- quality control and assurance;
- capacity constraints;
- shortages of qualified personnel;
- compliance with strictly enforced federal, state and international regulations that vary in each country where a product might be sold; and

· lack of capital funding.

Any delay or interruption in our supply of product candidates or products could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We may not be successful in establishing and maintaining strategic collaborations which could adversely affect our ability to develop and commercialize our product candidates, negatively impacting our operating results.

We plan to commercialize vadadustat ourselves in the United States and have entered into a collaboration agreement with Mitsubishi Tanabe to develop and commercialize vadadustat in Japan and certain other Asian countries. We will likely seek one or more strategic

collaborators to commercialize vadadustat in additional markets. We face competition in seeking appropriate collaborators for our product candidates, and the negotiation process is time-consuming and complex. In order for us to successfully collaborate with a third party on our product candidates, potential collaborators must view these product candidates as economically valuable. Even if we are successful in our efforts to establish strategic collaborations, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such strategic collaborations if, for example, development or approval of a product is delayed or sales of an approved product are disappointing. Any delay in entering into strategic collaboration agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness even if they reach the market.

In addition, our strategic collaborators may terminate any agreements they enter into with us, and we may not be able to adequately protect our rights under these agreements. Furthermore, our strategic collaborators will likely negotiate for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we do.

If we fail to maintain our current collaboration with Mitsubishi Tanabe or other strategic collaborations related to our product candidates, we will bear all of the risk and costs related to the development and commercialization of any such product candidate, and we may need to seek additional financing, hire additional employees and otherwise develop expertise. This could negatively affect the development of any such product candidate.

Risks Related to our Intellectual Property

If our efforts to protect our proprietary technologies are not adequate, we may not be able to compete effectively in our market. We are currently involved in an opposition proceeding involving one of our European patents, and the outcome of that proceeding may affect our ability to establish a competitive advantage in the market or successfully commercialize our lead product candidate in the European Union.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technologies. We will only be able to protect our product candidates, proprietary technologies and their uses from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position in the market.

In July 2011, a third party filed an opposition to one of our issued European patents, European Patent No. 2044005, or the ’005 Patent. 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 have appealed the decision of the Opposition Division and final resolution of the opposition proceeding will likely take a year or more. We cannot be assured of the breadth of the claims that will remain in the ’005 Patent or that the patent will not be revoked in its entirety. If the European Patent Office decides to narrow the scope of the claims or revoke the ’005 Patent, we may not be able to establish a competitive advantage in the European Union in our market or successfully commercialize our product candidates in the European Union, which could materially adversely affect our business, operating results and financial condition.

Composition-of-matter patents on the active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. Method-of-use patents protect the use of a product for the specified method. A method-of-use patent does not prevent a competitor from making and marketing a product that is identical to our product for an

indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products “off-label.” Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or license may fail to result in issued patents in the United States or in other countries. Our competitors have and will continue to undertake formal efforts to oppose the issuance of claims in our patent applications. We do not control decisions made by the United States Patent and Trademark Office, or US PTO, or equivalent bodies outside the United States. Even if our patents do 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. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the breadth or strength of protection provided by the patents and patent applications we hold with respect to our product candidates is threatened, it could dissuade companies from collaborating with us to develop, and threaten our ability to commercialize,

our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Furthermore, for applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third-party or instituted by the US PTO to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. For applications containing a claim not entitled to priority before March 16, 2013, there is greater level of uncertainty in the patent law with the passage of the America Invents Act (2011), which brings into effect significant changes to the U.S. patent laws and which introduces new procedures for challenging pending patent applications and issued patents. A primary change under this reform is creating a “first to file” system in the United States. This will require us to be cognizant of the time from invention to filing of a patent application.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we require all of our employees to assign their inventions to us, and require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot be certain that our trade secrets and other confidential or proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of some countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, we will not be able to establish or maintain a competitive advantage in the market, which could materially adversely affect our business, operating results and financial condition.

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 research, develop and manufacture 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, material transfer agreements, consulting agreements, research agreements or other similar agreements with our advisors, employees, third-party contractors 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 trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are 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 that we may collaborate with will usually expect to be granted rights to publish data arising out of such collaboration, 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, in addition to the opportunity to 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, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

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

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 may become a party to, or 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 our product candidates progress toward commercialization, the possibility of a patent infringement claim against us increases. 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 product candidates infringes these patents or intellectual property rights, or that we are employing their proprietary technology without authorization. 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.

In addition, we are aware of subsequent U.S. patents issued to FibroGen directed to purportedly new methods of using such previously known heterocyclic carboxamide compounds for purposes of treating or affecting specified conditions. We do not believe these currently issued FibroGen U.S. patents conflict with our intellectual property rights; nor do we make any admission that any of such patents are valid or enforceable. 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 secondary to CKD.

There may be patents of third parties, including FibroGen, of which we are currently unaware with claims to 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 these patents or others 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 further develop and commercialize vadadustat or AKB-6899. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our 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 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 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 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 opposition and invalidity proceedings and may in the future be involved in 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.

We are currently involved in five opposition proceedings in the European Patent Office. 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 Intellectual Property" and Item 3 – Legal Proceedings.

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 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.

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. 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. An unfavorable outcome could require us to cease using the related 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.

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. 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 various foreign governmental patent agencies 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 can in many cases 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 drug 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. Consequently, the breadth of our intellectual property rights in some countries outside the United States may be less extensive than those in the United States. In addition, the laws of some countries do not protect intellectual property rights to the same extent as laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other countries. Competitors may use our technologies in countries where we have not obtained patent protection to develop their own products and, further, may infringe our patents in territories where we have patent protection, but enforcement is not as strong as in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in countries outside of the United States could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks Related to Commercialization

Our future commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, third-party payors and others in the medical community.

Even if we obtain marketing approval for vadadustat, AKB-6899 or any other product candidates that we may develop or acquire in the future, these product candidates may not gain market acceptance among physicians, third-party payors, patients and others in the medical community. In addition, market acceptance of any approved products depends on a number of other factors, including:

- the safety and efficacy of the product, as demonstrated in clinical trials;
- the clinical indications for which the product is approved and the product label approved by regulatory authorities, including any warnings that may be required on the label;
- 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 availability of adequate coverage and reimbursement by third-party payors and government authorities;
- the ability to contract with dialysis providers;

- relative convenience and ease of administration;
- the prevalence and severity of adverse side effects;
- the effectiveness of our sales and marketing efforts; and
- the restrictions on the use of our products together with other medications, if any.

For example, two of the largest operators of dialysis clinics in the United States, DaVita, Inc., or DaVita, and Fresenius Medical Care, or Fresenius, account for more than half of the injectable rESA sales in the U.S. dialysis market. We believe that it may be challenging to enter into long or short-term supply agreements with DaVita, Fresenius or other operators of dialysis clinics.

Market acceptance is critical to our ability to generate significant revenue. In addition, any product candidate, if approved and commercialized, may be accepted in only limited capacities or not at all. If any approved products are not accepted by the market to the extent that we expect, we may not be able to generate significant revenue and our business would suffer.

If we are unable to establish sales, marketing and distribution capabilities or to enter into agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and we have not yet sold, marketed or distributed any of our products. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish a sales and marketing organization or make arrangements with third parties to perform these services.

There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force are expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to and educate physicians regarding our products;
- our inability to effectively manage a geographically dispersed sales and marketing team;
- the 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
- unforeseen costs and expenses associated with creating a sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and have to enter into arrangements with third parties to perform these services, our profitability, if any, is likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

Coverage and reimbursement may be limited or unavailable in certain market segments for any approved products, which could make it difficult for us to sell our 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 pay for and establish formularies and 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;

- cost-effective; and
- neither experimental nor investigational.

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. Additionally, we may be required to enter into contracts with third-party payors 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 gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available

for any of our product candidates. Even if we obtain coverage for our product candidates, third-party payors may not establish adequate reimbursement amounts, which may reduce the demand for, or the price of, our products. If reimbursement is not available or 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 the level of reimbursement of new drugs. As a result, significant uncertainty exists as to whether and how much third-party payors will provide reimbursement for newly approved drugs, which in turn will put pressure on the pricing of drugs.

In addition, if vadadustat is used in an outpatient dialysis facility, such facilities often receive fixed reimbursement for all dialysis services furnished to patients with end-stage renal disease, or ESRD. For example, Medicare payments to ESRD facilities for such services are based on a prospective payment system known as the basic case-mix adjusted composite payment system. These payments cover a bundle of items and services routinely required for dialysis treatments furnished to Medicare beneficiaries in Medicare-certified ESRD facilities or at their home, including the cost of certain routine drugs such as our product candidates. Patient and provider access to adequate coverage and reimbursement by government and private insurance plans is central to the acceptance of any products for which we receive regulatory approval. We may be unable to sell vadadustat, if approved, to dialysis providers on a profitable basis if third-party payors reduce their current levels of payment or if our costs of production increase faster than increases in reimbursement levels.

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

In some countries, particularly member states of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable 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 European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we 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 within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be adversely affected.

The impact of recent healthcare reform and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model.

Our revenue prospects could be affected by changes in healthcare spending and policy in the United States and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to healthcare availability or method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition.

In the United States, the Medicare Prescription Drug, Improvement and Modernization Act of 2003, also called 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. As a result of this legislation and the expansion of federal coverage

of drug products, we expect that there will be additional pressure to reduce costs. For example, the Centers for Medicare and Medicaid Services, or CMS, has enacted regulations that reduced capitated payments to dialysis providers. These cost reduction initiatives and other provisions of this legislation could decrease the scope of coverage and the price that we receive for any approved products and could seriously harm our business. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may cause a similar reduction in payments from private payors. Similar regulations or reimbursement policies may be enacted in international markets which could similarly impact our business.

In addition, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively PPACA, was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The PPACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D. In addition, other legislative changes have been proposed and

adopted in the United States since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013.

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

- the demand for any drug products for which we may obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to obtain coverage and reimbursement approval for a product;
- our ability to generate revenue and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

If our product candidates obtain marketing approval, we will be subject to healthcare laws, regulation and enforcement and our failure to comply with those laws could have a material adverse effect on our results of operations and financial conditions.

If we obtain approval for any of our product candidates and begin commercializing them, our operations may be directly, or indirectly through our customers, subject to additional healthcare regulation and enforcement by the federal government, states and governments outside of the United States in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security, and transmission of individually identifiable health information;
- the federal physician "sunshine" requirements under PPACA, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to CMS information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report

information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. In addition, recent healthcare reforms have strengthened these laws. For example, the PPACA, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of the statute or specific intent to

violate it. The PPACA also amended the False Claims Act, such that violations of the anti-kickback statute are now deemed violations of the False Claims Act. To constitute a false claim prior to this amendment, an anti-kickback violation had to be accompanied by a false statement, such as false certification of compliance.

If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could materially adversely affect our ability to operate our business and our financial results.

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

If vadadustat is approved and launched commercially, competing drugs may include EPOGEN® and Aranesp®, commercialized by Amgen, Procrit® and Eprex®, commercialized by Johnson & Johnson, and Mircera®, commercialized by Roche Holding Ltd., or Roche. We may face competition from potential new anemia therapies. There are several other HIF 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/Astellas Pharma Inc., in particular, is currently in Phase 3 clinical development of its product candidate, FG-4592 (roxadustat). Some of these product candidates may enter the market as early as 2017. In addition, certain companies are developing potential new therapies for renal-related diseases that could potentially reduce rESA utilization and thus limit the market for vadadustat if and when it is approved and launched commercially. Other new therapies are in development for the treatment of conditions inclusive of renal anemia, like sotatercept from Acceleron Pharma Inc. that may impact the market for anemia-targeted treatment.

Since rESAs are biologic products, the introduction of biosimilars into the rESA market in the United States will constitute additional competition for vadadustat if we are able to obtain approval for and commercially launch our product. A biosimilar product is a follow-on version of an existing, branded biologic product. The patents for the existing, branded 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 rESA, expired in 2004 in the European Union, and the remaining patents expired between 2012 and 2015 in the United States. Several biosimilar versions of rESAs are available for sale in the European Union and biosimilar versions of rESAs are currently being studied in clinical trials in the United States.

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 regulatory 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 anemia. In particular, these companies have greater experience and expertise in securing government contracts and grants to support their research and development efforts, conducting pre-clinical testing and clinical trials,

obtaining regulatory approvals to market products, 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 that we develop obsolete. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing products before, or more effectively than, we do. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and be commercially successful. If we are not able to compete effectively against potential competitors, our business will not grow and our financial condition and operations will suffer.

Our products may cause undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our products or even competing products in development that utilize a common mechanism of action could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. In our Phase 2b study of vadadustat for the treatment of anemia secondary to CKD in patients not on dialysis, the incidence of the most common treatment emergent adverse events were well balanced overall between the vadadustat and placebo treatment groups. There was a higher incidence of serious adverse events (SAEs) reported in the vadadustat treatment group, the most common being renal-related. Serious adverse events deemed to be possibly or probably related to vadadustat could have a material adverse effect on the development of our product candidates and our business as a whole. Our understanding of adverse events in future 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.

If we or others identify undesirable side effects caused by our 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, or enrolled patients may not want to complete a clinical trial;
- we may be unable to obtain regulatory approval for our product candidates or regulatory authorities may withdraw approvals of product candidates;
- regulatory authorities may require additional warnings on the label;
- a medication guide outlining the risks of such side effects for distribution to patients 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 market acceptance of our products and could substantially increase commercialization costs.

Risks Related to our Business and Industry

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our products, conduct our clinical trials and commercialize our product candidates.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We are highly dependent on certain members of our senior management. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. We may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the intense competition among numerous biopharmaceutical companies for similar personnel.

We also experience competition for the hiring of scientific and clinical personnel from universities, research institutions and other biopharmaceutical companies. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may become employed by companies other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to

continue to attract and retain high quality personnel, our ability to grow and pursue our business strategy will be limited.

Our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate (1) FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, (2) quality standards, including Good Laboratory Practices (GLP), GCP and GMP, (3) federal

and state healthcare fraud and abuse laws and regulations, (4) laws that require the reporting of true and accurate financial information and data or (5) securities laws and regulations. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. It is not always possible to identify and deter misconduct by employees and third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials and commercialization, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic collaborators, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management. Our future financial performance and our ability to commercialize vadadustat, if approved, and any other product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company.

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

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

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to study participants or patients;
- product recalls or withdrawals, or labeling, marketing or promotional restrictions;
- loss of revenue;
- the inability to commercialize any product candidates that we may develop; and

·a decline in our stock price.

Failure to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to marketing any of our product candidates. Although we maintain product liability insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which

we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

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 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 Common Stock

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012. As a result, we intend to continue to take advantage of certain reduced disclosure requirements.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and obtaining shareholder approval of any golden parachute payments not previously approved.

Investors may find our common stock less attractive if we continue to rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We could be an emerging growth company for up to five years from our initial public offering in March 2014, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have total annual gross revenue of $1 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company immediately.

Our stock price has been and may continue to be volatile, and, as a result you may not be able to resell your shares at or above the public offering price.

Our stock price has been and may continue to be volatile. Since our IPO in March 2014, the price of our common stock as reported on The NASDAQ Global Market has ranged from a low of $5.91 on August 25, 2015 to a high of $31.00 on June 20, 2014. The market price of shares of our common stock could be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control.

In addition, the stock market has recently experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks. The volatility of pharmaceutical, biotechnology and other life sciences company stocks often does not relate to the operating performance of the companies represented by the stock. As we operate in a single industry, we are especially vulnerable to the factors listed above to the extent that they affect our industry, markets or products. In the past, securities class action litigation has often been initiated against companies following periods of volatility in their stock price, and such an action has recently been filed against us. This type of litigation could result in substantial costs and divert our management’s attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation.

We and certain of our directors and executive officers are currently subject to securities class action litigation in connection with our initial public offering, which could result in substantial costs and divert management's attention.

A purported securities class action was filed against us and certain of our directors and executive officers alleging violation of federal securities laws. We believe such claims are without merit, and will engage in a vigorous defense of such litigation. In connection with such litigation, we could incur substantial costs and such costs and any related settlements or judgments may not be covered by insurance. We could also suffer an adverse impact on our reputation and a diversion of management's attention and resources, which could have a material adverse effect on our business.

Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

Our executive officers, directors and principal stockholders, together with their respective affiliates, collectively control a majority of our common stock. Accordingly, these stockholders will be able to exert a significant degree of influence over our management and affairs and over matters requiring stockholder approval, including the election of our Board of Directors and approval of significant corporate transactions. This concentration of ownership could have the effect of entrenching our management and/or the Board of Directors, delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us, which in turn could have a material and adverse effect on the fair market value of our common stock.

Provisions in our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our Amended and Restated Certificate of Incorporation and Amended and Restated By-Laws contain provisions that may have the effect of discouraging, delaying or preventing a change in control of us or changes in our management. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our Board of Directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our Board of Directors. Among other things, these provisions:

- authorize “blank check” preferred stock, which could be issued by our Board of Directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified Board of Directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our Board of Directors pursuant to a resolution adopted by a majority of the total number of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our Board of Directors;
- provide that our directors may be removed only for cause;

- provide that vacancies on our Board of Directors may be filled only by a majority of directors then in office, even though less than a quorum;
- require a supermajority vote of the holders of our common stock or the majority vote of our Board of Directors to amend our Amended and Restated By-Laws; and
- require a supermajority vote of the holders of our common stock to amend the classification of our Board of Directors into three classes and to amend certain other provisions of our Amended and Restated Certificate of Incorporation.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Any provision of our Amended and Restated Certificate of Incorporation, our Amended and Restated By-Laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our ability to use net operating losses to offset future taxable income may be subject to certain limitations.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses, or NOLs, to offset future taxable income. Our existing NOLs may be subject to substantial limitations arising from previous ownership changes and our ability to utilize NOLs could be further limited by Section 382 of the Code. Future changes in our stock ownership, many of which are outside of our control, could result in an ownership change under Section 382 of the Code. Our NOLs may also be impaired under state law. Accordingly, we may not be able to utilize a material portion of our NOLs. Furthermore, our ability to utilize our NOLs is conditioned upon our attaining profitability and generating U.S. federal taxable income. As described above under "—Risks related to our financial position and need for additional capital," we have incurred significant net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future; thus, we do not know whether or when we will generate the U.S. federal taxable income necessary to utilize our NOLs. A full valuation allowance has been provided for the entire amount of our NOLs.

Our Amended and Restated Certificate of Incorporation designates the state or federal courts located in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our Amended and Restated Certificate of Incorporation provides that, subject to limited exceptions, the state and federal courts located in the State of Delaware will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our Amended and Restated Certificate of Incorporation or our Amended and Restated By-Laws or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our Amended and

Restated Certificate of Incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our Amended and Restated Certificate of Incorporation inapplicable to, or unenforceable with respect to, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Item 1B. Unresolved Staff Comments
None

Item 2. Properties
Our corporate headquarters are located in Cambridge, Massachusetts. We currently lease approximately 39,411 square feet of office space in Cambridge, Massachusetts under a lease that expires on August 31, 2026. We believe that our existing facilities are adequate to meet our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms for our future growth.

Item 3. Legal Proceedings
Shareholder Litigation

In September 2015, a purported securities class action lawsuit was filed against the Company, including its Chief Executive Officer, its Chief Financial Officer, and members of its Board of Directors, in the Business Litigation Section of the Suffolk County Superior Court of Massachusetts. The complaint is brought on behalf of an alleged class of those who purchased common stock of the Company pursuant or traceable to our initial public offering, and purports to allege claims arising under Sections 11, 12(a)(2) and 15 of the Securities Act of 1933, as amended (the "Securities Act"). The complaint generally alleges that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning the Phase 2b clinical study of vadadustat. The complaint seeks, among other relief, unspecified compensatory damages, rescission of certain stock purchases, attorneys' fees, and costs. In October 2015, we removed the case to the United States District Court for the District of Massachusetts, and the plaintiff filed a motion to remand the case back to the Business Litigation Section of the Suffolk County Superior Court of Massachusetts. The plaintiff's motion to remand is currently pending. We believe such claims are without merit, and we will engage in a vigorous defense of such litigation.

Opposition Proceeding Against Our '005 Patent

In July 2011, a third party filed an opposition to our issued European Patent No. 2044005, or the '005 Patent. During the oral proceedings, which took place on April 10, 2013, the Opposition Division of the European Patent Office maintained the '005 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 have appealed the decision of the Opposition Division and final resolution of the opposition proceedings will likely take a year or more. We cannot be assured of the breadth of the claims that will remain in the '005 Patent or that the patent will not be revoked in its entirety.

Opposition and Invalidity Proceedings Against FibroGen Inc.

As explained in more detail below, we have had some positive developments in our opposition and invalidity proceedings against FibroGen, Inc., or FibroGen. With regard to the opposition that we filed in Europe against FibroGen's European Patent No. 1463823, or the '823 patent, the European Opposition Division issued a non-binding

preliminary opinion that none of FibroGen's '823 patent claims meet the requirements for patentability. In an oral proceeding which took place March 8 and 9, 2016, the European Opposition Division confirmed 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. 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 patent, which is the Japanese counterpart to the '823 patent, the 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 FibroGen '131 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 in Europe and Japan in the '823 and '131 patents. In the event FibroGen were to obtain such patents in the United States, we may decide to challenge them like we have done in Europe and Japan. On May 13, May 20, and July 6, 2015, we also filed oppositions to FibroGen's European Patent Nos. 2322153, 2322155, and 1633333 respectively, requesting the patents be revoked in their entirety.

In June 2013, the European Patent Office granted the '823 patent, to FibroGen. The '823 patent claims, among other things, the use of a heterocyclic carboxamide compound selected from the group consisting of pyridine carboxamides, quinoline carboxamides, isoquinoline carboxamides, cinnoline carboxamides, and beta-carboline carboxamides that inhibits HIF-PH enzyme activity in the manufacture of a medicament for increasing endogenous EPO in the prevention, pretreatment or treatment of anemia. On December 5,

2013, we filed an opposition to the ’823 patent requesting that the ’823 patent be revoked in its entirety. The European Opposition Division scheduled oral proceedings for March 8, 2016 and also issued a non-binding preliminary opinion that none of the ’823 patent’s claims met the requirements for patentability. In an oral proceeding which took place March 8 and 9, 2016, the European Opposition Division confirmed 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. If FibroGen appeals the decision of the European Opposition Division, final resolution of the appeal will likely take two to three years. While, for the reasons set forth in our opposition, we maintain that the ’823 patent should be revoked in its entirety, the ultimate outcome of any appeal remains uncertain. If FibroGen appeals the decision of the European Opposition Division and the Technical Board of Appeal at the European Patent Office decides not to revoke the ’823 patent in its entirety, or only certain claims of the ’823 patent and any surviving claims are determined to encompass our intended use of vadadustat, we may not be able to commercialize vadadustat in the European Union for its intended use, which could materially adversely affect our business, operating results and financial condition.

In August 2011, the Japanese Patent Office granted the ’131 patent, to FibroGen. The ’131 patent claims, among other things, the use of certain heterocyclic carboxamides selected from the group consisting of pyridine carboxamides, quinoline carboxamides, and isoquinoline carboxamides to treat anemia, wherein the heterocyclic carboxamides also suppress HIF prolyl hydroxylase. On June 2, 2014, we filed an invalidity proceeding in the Japanese Patent Office challenging the validity of the ’131 patent and requesting that certain claims be revoked in their entirety. An oral hearing before the Japanese Patent Office was held on February 9, 2015, and on May 11, 2015 the Japanese Patent Office issued a preliminary decision finding all of the challenged claims to be invalid. In response, FibroGen filed a request for correction in which it requested that the ’131 patent claims be amended to exclude pyridine carboxamides from their scope. On November 18, 2015, Akebia received the final trial decision from the JPO in which it accepted FibroGen’s requested claim amendments. As a result of the JPO’s decision and FibroGen’s subsequent amendments, the FibroGen ’131 patent does not cover vadadustat or any pyridine carboxamide compounds.

In August 2014, the European Patent Office granted European Patent Nos. 2322153, 2322155, and 1633333, or the ’153 patent, the ’155 patent, and the ’333 patent, respectively, to FibroGen. 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 EPO, and microcytosis in microcytic anemia. On May 13, May 20, and July 6, 2015, we filed oppositions to the ’155 patent, the ’333 patent, and the ’153 patent, respectively, requesting that the patents be revoked in their entireties. While, for the reasons set forth in our oppositions, we believe that the ’153 patent, the ’155 patent, and the ’333 patent should be revoked in their entireties, the ultimate outcomes of the oppositions remains uncertain. If the European Patent Office decides not to revoke the ’153 patent, the ’155 patent, or the ’333 patent in their entireties, or only certain claims of those patents, and any surviving claims are determined to encompass our intended use of our lead product candidate, we may not be able to commercialize our lead product candidate in the European Union for its intended use, which could materially adversely affect our business, operating results and financial condition.

Item 4. Mine Safety Disclosures
Not applicable.

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PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Price Information

Our common stock began trading on the NASDAQ Global Market on March 20, 2014 under the symbol "AKBA". Prior to that date, there was no established public trading market for our common stock. The following table sets forth, for the periods indicated, the high and low intraday sales prices of our common stock as reported by the NASDAQ Global Market:

	High	Low
2015		
First Quarter	$13.90	$8.47
Second Quarter	$11.12	$7.27
Third Quarter	$14.20	$5.91
Fourth Quarter	$13.20	$7.91

	High	Low
2014		
First Quarter from and after March 20th	$28.50	$18.75
Second Quarter	$31.00	$16.41
Third Quarter	$28.33	$20.10
Fourth Quarter	$21.75	$8.60

Holders

At March 1, 2016, there were approximately 28 holders of record of our common stock.

Dividends

We have never declared or paid any cash dividends on our common stock and our ability to pay cash dividends is currently prohibited by the terms of our debt financing arrangements. We currently intend to retain earnings, if any, for use in our business and do not anticipate paying cash dividends on our common stock in the foreseeable future. Payment of future dividends, if any, on our common stock will be at the discretion of our board of directors after taking into account various factors, including our financial condition, operating results, anticipated cash needs, and plans for expansion.

Issuer Purchases of Equity Securities

There were no repurchases of shares of common stock made during the year ended December 31, 2015.

Comparative Stock Performance Graph

The information included under the heading “Comparative Stock Performance Graph” in this Item 5 of Part II of this annual report on Form 10-K shall not be deemed to be “soliciting material” or subject to Regulation 14A or 14C, shall not be deemed “filed” for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act.

Set forth below is a graph comparing the total cumulative returns of Akebia Therapeutics, Inc., the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes $100 was invested on March 20, 2014 in our common stock and each of the indices and that all dividends, if any, are reinvested.

Equity Compensation Plan Information

We have two equity compensation plans, which have both been approved by our shareholders: the 2014 Incentive Plan and the 2014 Employee Stock Purchase Plan.

The following table sets forth the number and weighted-average exercise price of ordinary shares to be issued upon exercise of outstanding options and the number of securities remaining available for future issuance under all of our equity compensation plans, at December 31, 2015.

Plan Category	Number of securities to be issued upon exercise of outstanding options, warrants and rights (a)	Weighted-average exercise price of outstanding options, warrants and rights (b)	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a)) (c)
Equity compensation plans approved by security holders	2,206,635	$ 9.04	1,759,036
Total	2,206,635	$ 9.04	1,759,036

Item 6. Selected Financial Data

The selected statements of operations data for the years ended December 31, 2015, 2014 and 2013 and the balance sheet data as of December 31, 2015 and 2014 are derived from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. The balance sheet data as of December 31, 2013 is derived from our audited consolidated financial statements not included in this Annual Report. You should read this data together with our consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K under the captions "Consolidated Financial Statements and Supplementary Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our interim period results are not necessarily indicative of results to be expected for a full year or any other interim period.

	Year Ended December 31,			
	2015	2014	2013	2012
	(in thousands, except share and per share data)			
Consolidated statements of operations data:				
Operating expenses:				
Research and development	$43,016	$23,263	$8,902	$5,032
General and administrative	18,497	14,677	$7,031	3,491
Total operating expenses	61,513	37,940	15,933	8,523
Loss from operations	(61,513)	(37,940)	(15,933)	(8,523)
Other income, net	797	906	2,766	327
Net loss	$(60,716)	$(37,034)	$(13,167)	$(8,196)
Accretion on preferred stock	-	(86,899)	(55,886)	(3,323)
Net loss applicable to common shareholders	$(60,716)	$(123,933)	$(69,053)	$(11,519)
Net loss per share applicable to common stockholders—basic and diluted[1]	$(2.29)	$(8.04)	$(126.94)	$(27.82)
Weighted-average number of common shares used in net loss per share applicable to common stockholders—basic and diluted	26,469,170	15,406,386	544,002	414,107

(1) See Note 2 within the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a description of the method used to calculate basic and diluted net loss per share of common stock.

	December 31,		
	2015	2014	2013
	(in thousands)		
Balance Sheet Data:			
Cash and cash equivalents and available for sale securities	$138,454	$108,918	$32,556
Working capital	129,149	103,595	29,529

Total assets	142,940	110,995	34,665
Redeemable convertible preferred stock	-	-	157,827
Accumulated deficit	(161,389)	(100,673)	(127,072)
Total stockholders' equity (deficit)	130,998	104,078	(127,072)

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing in this annual report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this annual report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this annual report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Operating Overview

We are a biopharmaceutical company focused on the development of novel proprietary therapeutics based on hypoxia inducible factor, or HIF, biology and the commercialization of these products for patients with serious unmet medical needs. HIF is the primary regulator of the production of red blood cells, or RBCs, in the body and a potentially novel mechanism for the treatment of anemia secondary to chronic kidney disease, or CKD. Pharmacologic modulation of the HIF pathway may also have broader therapeutic applications in acute renal failure, organ protection, ischemia-reperfusion injury, cancer, ophthalmology, and inflammatory diseases.

Anemia is a serious medical condition in which blood is deficient in RBCs and hemoglobin, each of which is critical in delivering oxygen to tissue. Anemia generally exists when hemoglobin, a protein in RBCs that carries oxygen, is less than 13 g/dL in men or 12 g/dL in women. Untreated anemia is associated with chronic fatigue, increased risk of progression of multiple diseases and death. Anemia is common in patients with CKD, cancer, heart failure, inflammatory diseases and other critical illnesses, as well as in the elderly.

More than 30 million people in the United States have CKD, with estimates that over 1.8 million of these patients suffer from anemia. Anemia from these indications is currently treated by injectable recombinant erythropoiesis-stimulating agents, or rESAs,—including Epogen®, Procrit® and Aranesp® — with iron supplementation or RBC transfusion. Based on the reported revenues of companies that market and sell rESAs, we estimate that global sales of injectable rESAs were $7.0 billion in 2014; the vast majority of which were for renal indications.

rESAs are designed to stimulate production of RBCs by binding directly to and saturating erythropoietin, or EPO, receptors. While injectable rESAs and transfusions may be effective in raising hemoglobin levels, they carry significant potential side effects and need to be delivered subcutaneously or intravenously. In particular, injectable rESAs may lead to thrombosis, stroke, myocardial infarction and death. These risks are described in black box warnings on the prescribing information of all products marketed in this class. These safety concerns, which became evident starting in 2006, have led to a significant reduction in the use of injectable rESAs. Today, anemia is either not treated or inadequately treated in the majority of non-dialysis dependent CKD patients. As a result, we believe that a safe, effective, oral therapeutic option will take significant market share and meaningfully grow the market in patients not requiring dialysis.

Given the burdens of the current standard of care and costs associated with administering an injectable rESA, we believe our lead product candidate, vadadustat, formerly known as AKB-6548, is a promising cost-effective alternative for the treatment of anemia in CKD. Vadadustat is being developed as a once-daily, oral therapy and has successfully completed Phase 2 development demonstrating that vadadustat can safely and predictably raise hemoglobin levels in patients with anemia related to CKD. Vadadustat works by a differentiated mechanism of action that we believe has the potential to be safer than that of injectable rESAs and may offer additional beneficial therapeutics effects beyond anemia including delaying CKD progression. This novel mechanism of action is referred to as HIF prolyl-hydroxylase, or HIF-PH, inhibition. Instead of binding directly to the EPO receptors on cells in the bone marrow, vadadustat leads to activation of critical pathways for hemoglobin and RBC production. This approach

mimics the physiological adjustment made by the body when exposed to reduced oxygen levels at higher altitudes.

We recently commenced Phase 3 development of vadadustat in non-dialysis patients. Positive results from our Phase 2b study in non-dialysis CKD patients demonstrated that vadadustat raised hemoglobin levels with no safety signal observed. In December 2015, we began dosing patients in our Phase 3 vadadustat program in non-dialysis patients with anemia related to CKD, PRO_2TECT, after obtaining feedback from United States and European regulatory authorities regarding the design of the program. If the results from the PRO_2TECT program support the results observed across our previous clinical studies, including 29,000 days of patient exposure, we anticipate submitting a New Drug Application, or NDA, to the United States Food and Drug Administration, or FDA, for vadadustat in 2019.

We have also completed a Phase 2 study of vadadustat for the treatment of anemia in patients undergoing dialysis, which found that vadadustat, dosed either once daily or three times per week, maintained stable hemoglobin levels following conversion from rESA therapy with no safety signal observed. We expect to initiate our Phase 3 vadadustat program in dialysis-dependent CKD patients, $INNO_2VATE$, in 2016, anticipating full enrollment by early 2018.

We have engaged Quintiles, Inc., or Quintiles, as our primary clinical research organization, or CRO, for the PRO_2TECT and $INNO_2VATE$ programs. We expect the cost of the Phase 3 program to be in the range of $80,000 to $85,000 per patient and we plan to enroll approximately 3,100 patients in the PRO_2TECT program and approximately 2,600 patients in the $INNO_2VATE$ program.

A subset of dialysis-dependent CKD patients have shown an inadequate hemoglobin response despite receiving high doses of rESAs. Previous studies have shown that rESA hyporesponsiveness is associated with poor clinical outcomes including increased mortality risk. By increasing iron mobilization, in addition to increasing erythropoietin levels, vadadustat may allow for a more consistent hemoglobin response in these patients. We expect to generate clinical data in hyporesponsive dialysis-dependent patients by 2017.

If approved by regulatory authorities, we plan to commercialize vadadustat in the United States for the treatment of anemia in patients with CKD. These patients are primarily treated by approximately 7,000 nephrologists, and we believe we can reach most of this market with a specialty sales force of approximately 125 people. In Japan and certain other Asian countries, we plan to commercialize vadadustat through our recently announced collaboration with Mitsubishi Tanabe Pharma Corporation, or Mitsubishi Tanabe. We intend to seek one or more collaborators to commercialize vadadustat in additional markets.

Our second clinical candidate, AKB-6899, is designed as a small molecule HIF-PH inhibitor with potential therapeutic benefit in oncology and ophthalmology. AKB-6899 has demonstrated the ability in vitro to reduce vascular endothelial growth factor, or VEGF, levels in the presence of hypoxia. In several preclinical mouse models, AKB-6899 has been active in reducing tumor growth and development of metastases. We opened an Investigational New Drug application, or IND, with the FDA at the end of 2015. We expect to commence clinical development of AKB-6899 in 2016 and anticipate completion of the Phase 1 study in oncology in late 2017.

Since our inception in 2007, we have devoted the largest portion of our resources to our development efforts relating to vadadustat, including preparing for and conducting clinical studies of vadadustat, providing general and administrative support for these operations and protecting our intellectual property. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations primarily through our IPO, our follow-on public offering, our at-the-market offering and the private placements of preferred stock, common stock and convertible notes.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were $60.7 million and $37.0 million for the year ended December 31, 2015 and 2014, respectively. Substantially all of our net losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations.

We expect to continue to incur significant operating expenses and increased operating losses for at least the next several years. We expect our expenses will increase substantially in connection with our ongoing activities, as we:

- conduct a global Phase 3 development program of vadadustat for the treatment of anemia secondary to CKD;
- seek regulatory approvals for our product candidates that successfully complete clinical trials;
- have our product candidates manufactured for clinical trials and for commercial sale;
-

establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;

- continue preclinical and clinical development of AKB-6899;
- initiate additional preclinical, clinical or other studies for additional indications for vadadustat, AKB 6899 and other product candidates that we may develop or acquire;
- seek to discover and develop additional product candidates;
- acquire or in-license other commercial products, product candidates and technologies;
- make royalty, milestone or other payments under any future in-license agreements;
- maintain, protect and expand our intellectual property portfolio;

- attract and retain skilled personnel; and
- create additional infrastructure to support our operations as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which we expect will take a number of years and is subject to significant uncertainty. We have no manufacturing facilities, and all of our manufacturing activities are contracted out to third parties. Additionally, we currently utilize third-party contract research organizations, or CROs, to carry out our clinical development activities, and we do not yet have a sales organization. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, we will seek to fund our operations through public or private equity or debt financings or other sources including geographic partnerships. However, we may be unable to raise additional funds or enter into other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our products.

On March 6, 2014, we effected a 1.75-for-1 stock split of our outstanding common stock. Our historical share and per share information have been retroactively adjusted to give effect to this stock split. Shares of common stock underlying outstanding stock options and other equity instruments were proportionately increased and the respective exercise prices, if applicable, were proportionately reduced in accordance with the terms of the agreements governing such securities. Shares of common stock reserved for issuance upon the conversion of our Series A Redeemable Convertible Preferred Stock, Series B Redeemable Convertible Preferred Stock and Series C Redeemable Convertible Preferred Stock were proportionately increased, and the respective conversion prices were proportionately reduced.

On March 25, 2014, we completed our IPO whereby we sold 6,762,000 shares of common stock, including 879,647 shares of common stock pursuant to the full exercise of an over-allotment option granted to the underwriters, at a price of $17.00 per share. The shares began trading on the NASDAQ Global Market on March 20, 2014. The aggregate net proceeds received by us from the offering were approximately $104.4 million, net of underwriting discounts and commissions and estimated offering expenses. Upon the closing of the IPO, all of our outstanding shares of convertible redeemable preferred stock converted into 12,115,183 shares of common stock. Additionally, we are now authorized to issue 175,000,000 shares of common stock and 25,000,000 shares of preferred stock.

On April 22, 2015, we completed a follow-on public offering whereby we sold 8,363,636 shares of common stock, including 1,090,909 share of common stock pursuant to the full exercise of an over-allotment granted to the underwriters in connection with the offering, at a price of $8.25 per share. The aggregate net proceeds received by us from the offering were approximately $64.6 million, net of underwriting discounts and commissions and estimated offering expenses.

In August 2015, we entered into a Sales Agreement with Cantor Fitzgerald & Co. to periodically sell up to $50 million of shares of our common stock in an at-the-market, or ATM, offering. In January 2016, we terminated the Sales Agreement in order to use the shares for the January 2016 follow-on offering. During 2015, prior to the termination, we sold 1,719,434 shares of common stock pursuant to the Sales Agreement. The aggregate net proceeds received by the Company were approximately $18.4 million, net of commissions. No additional shares of our common stock will be sold pursuant to the Sales Agreement.

In December 2015, we entered into a collaboration agreement with Mitsubishi Tanabe to develop and commercialize vadadustat in Japan and certain other countries in Asia for total milestone payments of up to $350 million, including up to $100 million in upfront and development payments, of which $40 million was received in January 2016. Of the $40.0 million received, $20.0 million is subject to refund to Mitsubishi depending on the outcome of discussions with the Japanese regulator about the global trial design. In addition, we will receive tiered double-digit royalty payments on vadadustat sales.

In January 2016, we completed a follow-on public whereby we sold 7,250,000 shares of common stock at a price of $9.00 per share. The aggregate net proceeds received by us from the offering were approximately $61.0 million, net of underwriting discounts and commissions and estimated offering expenses payable by us.

Financial Overview

In the quarter ended December 31, 2015, we identified and corrected an error in the historical classification of certain operating costs between research and development and general and administrative expenses. We concluded the effect of this classification error was not material to our consolidated financial statements for any prior period. The classification correction had no effect on our current or historical total operating expenses or net loss.

Revenue

To date, we have not generated any revenue from the sales of products or other means. Our ability to generate product revenue and become profitable depends upon our ability to successfully develop and commercialize products. We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates and begin to commercialize any approved products. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenue from the sale of our products, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

We will begin to recognize revenue starting in 2016 related to our agreement with Mitsubishi Tanabe (see Note 12).

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with the CROs and investigative sites that conduct our clinical studies;
- the cost of acquiring, developing and manufacturing clinical study materials;
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies; and
- costs associated with preclinical and clinical activities.

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites.

We cannot determine with certainty the duration and completion costs of the current or future clinical studies of our product candidates or if, when, or to what extent we will generate revenue from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

The duration, costs and timing of clinical studies and development of our product candidates will depend on a variety of factors, including:

- the results of our meetings with the FDA and the EMA and other regulatory authorities and the consequential effect on our study design, study size and resulting operating costs;
- the size, rate of progress, results and costs of initiating and completing our global Phase 3 development of vadadustat; difficulties or delays in enrolling patients in our clinical trials;
- assuming favorable Phase 3 clinical results, the timing or, and the costs involved in, obtaining regulatory approvals for vadadustat in dialysis and non-dialysis indications, including to fund the preparation and filing of regulatory submissions for vadadustat with the FDA, the EMA and other regulatory authorities, and whether we will seek regulatory approval for both indications simultaneously;
- 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 additional indications for vadadustat, AKB-6899 and other product candidates that we may develop or acquire;

- the timing of, and the costs involved in, obtaining regulatory approvals for AKB-6899 if clinical studies are successful;
- the cost and timing of future commercialization activities for our products, if any of our product candidates are approved for marketing, including product manufacturing, marketing, sales and distribution costs;
- the cost of having our product candidates manufactured for clinical trials;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such agreements; and

- unanticipated changes to laws or regulations applicable to our clinical trials;

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA, EMA or another regulatory authority were to require us to conduct clinical studies in addition to or different from those that we currently anticipate, or if we experience significant delays in enrollment in any of our clinical studies, we could be required to expend significant additional financial resources and time on the completion of clinical development.

From inception through December 31, 2015, we have incurred $116.1 million in research and development expenses. We plan to increase our research and development expenditures for the foreseeable future as we continue the development of vadadustat and AKB-6899. Our current and/or planned research and development activities include the following:

- global Phase 3 development of vadadustat, including the PRO2TECT and INNO2VATE clinical programs; and
- the initiation of a Phase 1 study of AKB-6899 in 2016.

Our direct research and development expenses consist principally of external costs, such as startup fees paid to investigators, consultants, central laboratories and CROs in connection with our clinical studies, and costs related to acquiring and manufacturing clinical study materials.

We currently have two programs to which our research and development costs are attributable. Historically, we have not accumulated and tracked our research and development costs or our personnel and personnel-related costs on a program-by-program basis. Our employee and infrastructure resources, and many of our costs, were directed broadly to applicable research endeavors. As a result, we are unable to specify precisely the historical costs incurred for each of our programs on a program-by-program basis.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs for personnel, including stock-based compensation and travel expenses. Other general and administrative expense include facility-related costs, fees for directors, accounting and legal services fees, recruiting fees and expenses associated with obtaining and maintaining patents.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research and development and potential commercialization of our product candidates. We also anticipate increased expenses related to finance, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, and our other costs associated with being a public company. Additionally, we anticipate an increase in payroll and related expenses if and when we prepare for commercial operations, especially in sales and marketing.

Critical Accounting Policies and Significant Judgments and Estimates

Our management’s discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to prepaid and accrued research and development expenses and stock-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying

values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Prepaid and Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our prepaid and accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers

invoice us monthly in arrears for services performed. We make estimates of our prepaid and accrued research and development expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated prepaid and accrued research and development expenses include expenses for:

- CROs in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to product manufacturing, development and distribution of clinical materials.

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. The scope of services under these contracts can be modified and some of the agreements may be cancelled by either party upon written notice. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed we may report amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates and the amount actually incurred.

Stock-Based Compensation

Stock-Based Awards

We issue stock-based awards to employees and non-employees, generally in the form of stock options, restricted stock, RSUs and shares of common stock. We account for our stock-based compensation awards in accordance with Financial Accounting Standards Board, ("FASB") ASC Topic 718, Compensation—Stock Compensation, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock and modifications to existing stock awards, to be recognized in the statements of operations and comprehensive loss based on their fair values. We account for stock-based awards to non-employees in accordance with FASB ASC Topic 505-50, Equity-Based-Payments to Non-Employees, or ASC 505-50, which requires the fair value of the award to be re-measured at fair value until a performance commitment is reached or counterparty performance is complete. Described below is the methodology we have utilized in measuring stock-based compensation expense. Since the consummation of our IPO, stock option, common stock and restricted stock values are determined based on the quoted market price of our comparable public companies.

We estimate the fair value of our stock-based awards of options to purchase shares of common stock to employees and non-employees using the Black-Scholes option pricing model, which requires the input of highly subjective assumptions, including (a) the expected stock price volatility, (b) the calculation of the expected term of the award, (c) the risk-free interest rate and (d) expected dividends. Due to the lack of a public market for the trading of our common stock and a lack of company-specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The computation

of expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to our company, including stage of product development and life science industry focus. We are a company in the product development stage with no revenue and the representative group of companies has certain similar characteristics. We believe the group selected has sufficient similar economic and industry characteristics, and includes companies that are most representative of our company. We use the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, Share-Based Payment, to calculate the expected term for options granted to employees as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The expected term is applied to the stock option grant group as a whole, as we do not expect substantially different exercise or post-vesting termination behavior among our employee population. For options granted to non-employees, we utilize the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected life of the stock options. The expected dividend yield is assumed to be zero as we have never paid dividends and have no current plans to pay any dividends on our common stock, similar to our peer group. We estimate grant date fair value of restricted stock awards with corresponding promissory notes

using the Black-Scholes option pricing model. Post IPO, the grant date fair value of restricted stock awards and awards of common stock has been based on the estimated value of our common stock at the date of grant.

Our stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Consistent with the guidance in ASC 505-50, compensation expense related to awards to non-employees with service-based vesting conditions is recognized on a straight-line basis based on the then-current fair value at each financial reporting date prior to the measurement date over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable. Consistent with the guidance in ASC 505-50, compensation expense related to awards to non-employees with performance-based vesting conditions is recognized based on the then-current fair value at each financial reporting date prior to the measurement date over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

We are also required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from our estimates. We use historical data to estimate pre-vesting forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from our estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the consolidated financial statements is based on awards that are ultimately expected to vest.

In June 2011, certain of our employees purchased shares of our restricted stock in exchange for promissory notes. Although these notes were 50% recourse to the employees, we have accounted for the promissory notes as nonrecourse in their entirety since the promissory notes are not aligned with a corresponding percentage of the underlying shares. Accordingly, we have accounted for the combination of the promissory note and restricted stock as a grant of an option, as the substance is similar to the grant of an option. The exercise price of this stock option is the principal and interest due on the promissory note. The fair value of the stock option is recognized over the requisite service period (not the term of the promissory note) through a charge to compensation cost. The maturity date of the promissory notes reflects the legal term of the stock option for purposes of valuing the award. The outstanding principal and interest on the promissory notes was paid in full during the third quarter of 2014.

Stock-based compensation expense totaled approximately $4.7 million and $6.0 million for the years ended December 31, 2015 and 2014, respectively.

We expect the impact of our stock-based compensation expense for stock options and restricted stock granted to employees and non-employees to grow in future periods due to the potential increases in the fair value of our common stock and the increase in the number of grants as a result of an increase in headcount.

Emerging Growth Company Status

The JOBS Act permits an “emerging growth company” to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies. We chose to “opt out” of this provision and, as a result, we will comply with new or revised accounting standards as required when they are adopted. This decision to opt out of the extended transition period under the JOBS Act is irrevocable.

Results of Operations

Comparison of the Years Ended December 31, 2015 and 2014

	Year ended December 31,		Increase (Decrease)
	2015	2014	
	(In Thousands)		
Operating expenses:			
Research and development	$43,016	$23,263	$ 19,753
General and administrative	18,497	14,677	3,820
Total operating expenses	61,513	37,940	23,573
Loss from operations	(61,513)	(37,940)	23,573
Other income, net	797	906	(109)
Net loss	$(60,716)	$(37,034)	$ 23,682

Research and Development Expenses. Research and development expenses were $43.0 million for the year ended December 31, 2015, compared to $23.3 million for the year ended December 31, 2014. The increase of $19.7 million was primarily due to the following:

	(in millions)
Preparation for the PRO$_2$TECT Phase 3 program	$ 14.2
Other clinical and non-clinical	2.7
Regulatory activities	1.2
Completion of Phase 2b study in non-dialysis patients with anemia related to CKD	(4.8)
Ongoing Phase 2 study for the treatment of anemia in patients undergoing dialysis	(0.8)
Total increase related to the continued development of vadadustat	12.5
Headcount and consulting	4.6
Drug development for AKB-6899	2.2
Other	1.2
Stock compensation	(0.7)
Total net increase	$ 19.8

General and Administrative Expenses. General and administrative expenses were $18.5 million for the year ended December 31, 2015, compared to $14.7 million for the year ended December 31, 2014. The increase of $3.8 million was primarily due to the following expense increases: $1.2 million of wage and personnel-related costs due to additional headcount, $1.4 million in commercial planning costs, $0.7 million in legal costs and $0.7 million related to facilities.

Other Income, Net. Other income, net, was $0.8 million for the year ended December 31, 2015, compared to $0.9 million for the year ended December 31, 2014. Other income, net for the year ended December 31, 2015, is primarily related to reimbursements under a services agreement for employee-related costs of approximately $0.3 million and interest income of approximately $0.5 million. Other income, net for the year ended December 31, 2014 is primarily related to reimbursements under a services agreement for employee-related costs of approximately $0.7 million and interest income of approximately $0.2 million. The decrease in reimbursements related to the services agreement for employee-related costs is principally the result of reduced time spent by our employees on the services agreement related activities.

Comparison of the Years Ended December 31, 2014 and 2013

	Year ended December 31,		Increase (Decrease)
	2014	2013	
	(In Thousands)		
Operating expenses:			
Research and development	$23,263	$8,902	$ 14,361
General and administrative	14,677	7,031	7,646

Total operating expenses	37,940	15,933	22,007
Loss from operations	(37,940)	(15,933)	22,007
Other income, net	906	2,766	(1,860)
Net loss	$(37,034)	$(13,167)	$ 23,867

Research and Development Expenses. Research and development expenses were $23.3 million for the year ended December 31, 2014, compared to $8.9 million for the year ended December 31, 2013. The increase of $14.4 million was primarily due to the following:

	(in millions)
Ongoing Phase 2 study for the treatment of anemia in patients undergoing dialysis	$ 2.9
Completion of Phase 2b study in non-dialysis patients with anemia related to CKD	1.7
Other clinical and non-clinical	3.3
Preparation for the PRO_2TECT Phase 3 program	0.3
Total increase related to the continued development of vadadustat	8.2
Stock compensation	2.7
Headcount and consulting	3.0
Drug development for AKB-6899	0.3
Other	0.2
Total net increase	$ 14.4

General and Administrative Expenses. General and administrative expenses were $14.7 million for the year ended December 31, 2014, compared to $7.0 million for the year ended December 31, 2013. The increase of $7.6 million was primarily due to the following expense increases: $1.8 million of stock-based compensation, $0.7 million of professional fees, $2.7 million related to additional headcount, severance and consulting costs, $1.1 million related to insurance and facilities, $0.7 million in commercial planning costs and $0.7 million in legal costs.

Other Income, Net. Other income, net, was $0.9 million for the year ended December 31, 2014, compared to $2.8 million for the year ended December 31, 2013. Other income, net for the year ended December 31, 2014, is primarily related to reimbursements under a services agreement for employee-related costs of approximately $0.7 million and interest income of approximately $0.2 million. Other income, net for the year ended December 31, 2013 included $1.0 million in reimbursements under a services agreement for employee-related costs and a $2.4 million gain on the extinguishment of debt, partially offset by net interest expense of $0.7 million. The decrease in reimbursements related to the services agreement for employee-related costs is principally the result of reduced time spent by our employees on services agreement related activities.

Liquidity and Capital Resources

We have incurred losses and cumulative negative cash flows from operations since our inception in February 2007, and as of December 31, 2015, we had an accumulated deficit of $161.4 million. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through a combination of equity offerings, debt financings, other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements.

We have funded our operations principally from the sale of common stock and preferred stock. As of December 31, 2015, we had cash and cash equivalents and available for sale securities of approximately $138.5 million. We also received approximately $61.0 million of net proceeds from our follow-on public offering of common stock in January 2016 and $40.0 million from Mitsubishi in January 2016 in connection with our collaboration agreement. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to

liquidity and capital preservation. Accordingly, available for sale securities, consisting principally of corporate and government debt securities stated at fair value, are also available as a source of liquidity.

Cash Flows

The following table sets forth the primary sources and uses of cash for each of the periods set forth below:

	Year ended December 31,		
	2015	2014	2013
	(In Thousands)		
Net cash provided by (used in):			
Operating activities	$(52,407)	$(27,483)	$(11,332)
Investing activities	(13,688)	(65,352)	(11,425)
Financing activities	83,093	104,400	42,331
Net increase in cash and cash equivalents	$16,998	$11,565	$19,574

Operating Activities. During the years ended December 31, 2015, 2014 and 2013, our operating activities used net cash of $52.4 million, $27.5 million and $11.3 million respectively. The net cash used in operating activities in these periods primarily resulted from our net losses and changes in our working capital accounts. The increase in net cash used in operations for the year ended December 31, 2015 as compared to the year ended December 31, 2014 was due primarily to higher operating expenses during the year ended December 31, 2015 of $61.5 million as compared to $37.9 million for the year ended December 31, 2014 adjusted for non-cash items, including stock-based compensation of $4.7 million in 2015. The increase in net cash used in operations for the year ended December 31, 2014 as compared to the year ended December 31, 2013 was due primarily to higher operating expenses during the year ended December 31, 2014 of $37.9 million as compared to $15.9 million for the year ended December 31, 2013 adjusted for non-cash items, including stock-based compensation of $6.0 million in 2014.

Investing Activities. During the years ended December 31, 2015, 2014 and 2013, our investing activities used net cash of $13.7 million, $65.4 million and $11.4 million, respectively. Net cash used in investing activities for the years ended December 31, 2015, 2014 and 2013 was comprised primarily of purchases of available for sale securities and purchases of equipment, offset by proceeds from the maturities of available for sale securities.

Financing Activities. During the years ended December 31, 2015, 2014 and 2013 our net cash provided by financing activities was $83.1 million, $104.4 million and $42.3 million, respectively. Net cash provided by financing activities for the year ended December 31, 2015 consisted primarily of net proceeds from the issuance of common stock from our follow-on public offerings and ATM offering. Net cash provided by financing activities for the year ended December 31, 2014 consisted primarily of net proceeds from the issuance of common stock in connection with our IPO. Net cash provided by financing activities for the year ended December 31, 2013 consisted primarily of net proceeds from the issuance of preferred stock.

Operating Capital Requirements

To date, we have not generated any revenue from product sales. We do not know when, or if, we will generate revenue from product sales. We do not expect to generate significant revenue from product sales unless and until we obtain regulatory approval of and commercialize one of our current or future product candidates. We anticipate that we will continue to generate losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. We are subject to all risks incident to the development and commercialization of novel therapeutics, and we

may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. We expect to incur additional costs associated with operating as a public company also, we anticipate that we will need substantial additional funding in connection with our continuing operations.

Our existing cash and cash equivalents and available for sale securities of $138.5 million at December 31, 2015, the net proceeds from our January 2016 public offering of approximately $61.0 million, together with the $40.0 million received in January 2016 in connection with our collaboration with Mitsubishi, are sufficient to fund our projected operating requirements through at least the second quarter of 2017.

However, we do not currently estimate that these funds will enable us to complete our Phase 3 development of vadadustat, including both the PRO2TECT and INNO2VATE clinical programs. 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. We intend to secure a second geographic collaboration for the development and commercialization of vadadustat outside the United States with a goal of providing funds sufficient to enable us to complete our Phase 3 development of vadadustat, including both the PRO_2TECT and $INNO_2$ VATE clinical programs. However, there can be no assurance that our development milestones will be achieved, that we will be able to secure a second geographic collaboration for the development and commercialization of vadadustat outside the United States or that we will secure other sources of financing to complete our Phase 3 development of vadadustat.

We will require additional capital for the further development of our existing product candidates and will also need to raise additional funds sooner to pursue other development activities related to additional product candidates. If and until we can generate a sufficient amount of revenue from our products, we expect to finance future cash needs through public or private equity, debt offerings, or strategic transactions. There can be no assurance that additional funds will be available to us on acceptable terms or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates. If we raise additional funds through the issuance of additional debt or equity securities, it could result in dilution to our existing stockholders or increased fixed payment obligations, and any such securities may have rights senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Any of these events could significantly harm our business, financial condition and prospects.

Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may be substantially different than actual results, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements, both near- and long-term, will depend on many factors, including, but not limited to those described under Part II, Item 1A Risk Factors of this Annual Report on Form 10-K.

If we cannot expand our operations or otherwise capitalize on our business opportunities because we lack sufficient capital, our business, financial condition and results of operations could be materially adversely affected.

Contractual Obligations and Commitments

In December 2013, we entered into a three-year lease for 6,837 square feet of office space in Cambridge, Massachusetts. The lease has monthly lease payments of approximately $31,000 for the first twelve months, with annual rent escalation thereafter, and provides a rent abatement of approximately $31,000 for the first full calendar month of the lease term. The lease term commenced and rental payments began in January 2014. We recorded a deferred lease obligation in 2014 which represents the cumulative difference between actual facility lease payments and lease expense recognized ratably over the lease period. In accordance with the lease, we entered into a cash-collateralized irrevocable standby letter of credit in the amount of $125,345, naming the landlord as beneficiary.

In December 2014, we entered into a First Amendment to Lease for additional office space contiguous to its current office space in Cambridge, Massachusetts. The First Amendment included leasing an additional 8,530 square feet of office space, or the Expansion Space, with an occupancy date of March 13, 2015. The First Amendment provided for additional monthly lease payments of approximately $45,000 for the 8,530 square feet for the first twelve months and provided for annual rent escalations thereafter. The monthly rent on the existing 6,837 square feet remained at approximately $32,000 through December 31, 2016, the expiration of the lease. The First Amendment included a Landlord’s contribution for leasehold improvements in the amount of approximately $100,000 which was accounted for as a deferred lease incentive and reduction in monthly rent expense over the term of the lease. We recorded an additional deferred lease obligation for the Expansion Space which represented the cumulative difference between actual facility lease payments and lease expense recognized ratably over the lease period. We had an existing cash-collateralized irrevocable standby letter of credit of $125,345, naming the landlord as beneficiary. In connection with the First Amendment, we paid an additional cash security deposit to the landlord of $179,130.

In November 2015, we entered into a Second Amendment to Lease amending the Lease to extend its existing lease for 16,222 square feet on the 11th floor, which was due to expire on December 31, 2016, and lease an additional 23,189

square feet of office space on the 11th and 14th floors. Monthly lease payments for the existing 16,222 square feet on the 11th floor remain unchanged until December 31, 2016 and will be approximately $107,000 per month commencing on May 1, 2017. The new space leased by the Company under the Second Amendment includes (i) 3,066 square feet on the 14th floor which was delivered on November 23, 2015 and additional monthly lease payments of approximately $20,000 commencing on March 1, 2016, (ii) 16,739 square feet on the 14th floor with an estimated delivery date of April 1, 2016 and additional monthly lease payments of approximately $110,000 commencing September 1, 2016 and (iii) 3,384 square feet on the 1th floor with an estimated delivery date of January 1, 2017 and additional monthly lease payments of approximately $23,000 commencing May 1, 2017. The above rents are subject to annual rent escalations, commencing on either February 1, 2017 or February 1, 2018 depending upon the delivery date of each respective suite. The Second Amendment includes a Landlord's contribution for leasehold improvements for both the new leased space and our existing premises. The term of the lease, as amended, expires on the later of August 31, 2026 or 10 years after the Landlord delivers the entirety of the 14th floor to us. In connection with the Second Amendment, we paid an additional cash security deposit to the landlord of $976,382. Total cash security deposits of $1,280,857 and $304,475 are included in other assets in our consolidated balance sheets as of December 31, 2015 and 2014, respectively.

We lease office equipment under two three year capital leases with payments commencing in February 2014 and April 2015, respectively. The capital lease amounts are included in accrued expenses and other liabilities.

At December 31, 2015, our future minimum payments required under these leases are as follows:

	Payments due by period (in thousands)				
	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Capital Lease Obligations	$14	$8	$6	$—	$—
Operating Lease Obligations	32,697	2,522	9,365	9,365	11,445
Total	$32,711	$2,530	$9,371	$9,365	$11,445

Under our agreement with Quintiles for the PRO_2TECT and $INNO_2$VATE programs, the total cost of committed work not yet paid as of December 31, 2015 was approximately $246.0 million. The estimated period of performance for the committed work is through the third quarter of 2019. The scope of the services under this agreement can be modified and the agreement cancelled by the Company upon written notice.

Off-Balance Sheet Arrangements

As of December 31, 2015 we did not have any off-balance sheet arrangements as defined in the rules and regulations of the SEC.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2015 and 2014, we had cash and cash equivalents and available for sale securities of $138.5 million and $108.9 million, respectively, primarily money market mutual funds consisting of U.S. government debt securities, certificates of deposit and corporate debt securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our investments are subject to interest rate risk and will fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our portfolio.

Item 8. Financial Statements and Supplementary Data
Akebia Therapeutics, Inc.

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Shareholders of

Akebia Therapeutics, Inc.

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

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

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

/s/ Ernst & Young LLP

Boston, Massachusetts

March 14, 2016

AKEBIA THERAPEUTICS, INC.

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$49,778	$32,780
Available for sale securities	88,676	76,138
Prepaid expenses and other current assets	2,563	1,562
Total current assets	141,017	110,480
Property and equipment, net	540	210
Deferred offering costs	102	—
Other assets	1,281	305
Total assets	$142,940	$110,995
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$2,313	$2,021
Accrued expenses	9,555	4,864
Total current liabilities	11,868	6,885
Other liabilities	74	32
Total liabilities	11,942	6,917
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Preferred stock $0.00001 par value, 25,000,000 shares authorized at December 31, 2015 and 2014; 0 shares issued and outstanding at December 31, 2015 and 2014	—	—
Common stock: $0.00001 par value; 175,000,000 shares authorized at December 31, 2015 and 2014; 30,662,218 and 20,370,624 shares issued and outstanding at December 31, 2015 and 2014, respectively	—	—
Additional paid-in capital	292,783	204,969
Treasury stock, at cost, 8,463 shares	(162)	(162)
Accumulated other comprehensive loss	(234)	(56)
Accumulated deficit	(161,389)	(100,673)
Total stockholders' equity	130,998	104,078
Total liabilities and stockholders' equity	$142,940	$110,995

See accompanying notes to consolidated financial statements.

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AKEBIA THERAPEUTICS, INC.

Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except share and per share data)

	Years ended December 31,		
	2015	2014	2013
Operating expenses:			
Research and development	$43,016	$23,263	$8,902
General and administrative	18,497	14,677	7,031
Total operating expenses	61,513	37,940	15,933
Operating loss	(61,513)	(37,940)	(15,933)
Other income (expense):			
Interest income (expense), net	510	206	(704)
Extinguishment of debt and other liabilities	—	—	2,420
Other income	287	700	1,050
Net loss	$(60,716)	$(37,034)	$(13,167)
Reconciliation of net loss to net loss applicable to common stockholders:			
Net loss	$(60,716)	$(37,034)	$(13,167)
Accretion on preferred stock	—	(86,899)	(55,886)
Net loss applicable to common stockholders	$(60,716)	$(123,933)	$(69,053)
Net loss per share applicable to common stockholders—basic and diluted	$(2.29)	$(8.04)	$(126.94)
Weighted-average number of common shares used in net loss per share applicable to common stockholders—basic and diluted	26,469,170	15,406,386	544,002
Comprehensive loss:			
Net loss	$(60,716)	$(37,034)	$(13,167)
Other comprehensive loss - unrealized loss on securities	(234)	(56)	—
Comprehensive loss	$(60,950)	$(37,090)	$(13,167)

See accompanying notes to consolidated financial statements.

Akebia Therapeutics, Inc.

Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)

(in thousands, except share and per share data)

Redeemable Convertible Preferred Stock								Stockholders' Equity (Deficit)					
ies A		Series B		Series C		2012 Series X							
leemable nvertible ferred Stock mber		Redeemable Convertible Preferred Stock		Redeemable Convertible Preferred Stock		Redeemable Convertible Preferred Stock		Common Stock	Additional $0.00001				
res	Amount	Number of Shares	Amount	Number of Shares	Amount	Number of Shares	Amount	Number of Shares	Paid-In Par Value	Capital	Treasury Stock	Unrealized Gain/Loss	Ac De
4,538	37,092	1,287,525	19,816	—	—	—	—	615,757	——		—	—	(5
	—	—	—	—	—	—	—	583,126	——		—	—	—
	—	—	—	—	—	—	—	176,717	——		—	—	—
	—	—	—	—	—	—	—	14,357	—5		—	—	—
	—	—	—	—	—	—	—	(6,612)	——		—	—	—
	—	—	—	—	—	25,000	2,486	—	——		—	—	—
	—	—	—	—	—	25,000	2,458	—	——		—	—	—
	—	—	—	2,945,742	40,088	—	—	—	——		—	—	—

—	—	—	357,143	4,944	(50,000)	(4,944)	—	—	—	—	—	—
2,275	—	1,441	—	52,170	—	—	—	—	(1,569)	—	—	(5
—	—	—	—	—	—	—	—	—	1,564	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	(1
4,538	39,367	1,287,525	21,257	3,302,885	97,203	—	—	1,383,345	—	—	—	—	(1
—	—	—	—	—	—	—	6,762,000	—	114,954	—	—	—
—	—	—	—	—	—	—	56,000	—	—	—	—	—
—	—	—	—	—	—	—	(53,835)	—	—	—	—	—
—	—	—	—	—	—	—	—	—	237	—	—	—
—	—	—	—	—	—	—	116,394	—	89	—	—	—
34,821	—	24,257	—	27,822	—	—	—	—	(85,663)	—	—	(1

34,538)	(74,188)	(1,287,525)	(45,514)	(3,302,885)	(125,025)	—	—	12,115,183	—180,057	—	—	64
	—	—	—	—	—	—	—	—	—6,010	—	—	—
	—	—	—	—	—	—	—	—	—(10,715)	—	—	—
	—	—	—	—	—	—	—	—	——	—	(56)	—
	—	—	—	—	—	—	—	(2,553)	——	(94)	—	—
	—	—	—	—	—	—	—	(5,910)	——	(68)	—	—
	—	—	—	—	—	—	—	—	——	—	—	(3
	—	—	—	—	—	—	—	20,370,624	—204,969	(162)	(56)	(1
	—	—	—	—	—	—	—	10,083,070	—82,750	—	—	—
	—	—	—	—	—	—	—	25,903	—220	—	—	—
	—	—	—	—	—	—	—	(36,053)	——	—	—	—
	—	—	—	—	—	—	—	218,674	—130	—	—	—
	—	—	—	—	—	—	—	—	—4,714	—	—	—
	—	—	—	—	—	—	—	—	——	—	(178)	—
	—	—	—	—	—	—	—	—	——	—	—	(6

—	—	—	—	—	—	—	30,662,218	—292,783	(162)	(234)	(1

See accompanying notes to consolidated financial statements

AKEBIA THERAPEUTICS, INC.

Consolidated Statements of Cash Flows

(in thousands)

	Year ended December 31,		
	2015	2014	2013
Operating activities:			
Net loss	$(60,716)	$(37,034)	$(13,167)
Adjustments to reconcile net loss to net cash used in operating activities:			
Gain on extinguishment of debt and other liabilities	—	—	(2,420)
Depreciation expense	96	49	1
Amortization of debt issuance costs	—	—	8
Amortization of premium/discount on investments	558	268	752
Stock-based compensation expense	4,714	6,010	1,564
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(1,001)	(686)	(217)
Other assets	(976)	(179)	(125)
Accounts payable	231	1,307	296
Accrued expenses	4,646	2,754	1,976
Other liabilities	41	28	—
Net cash used in operating activities	(52,407)	(27,483)	(11,332)
Investing activities:			
Purchase of equipment	(414)	(229)	(19)
Proceeds from maturities of available for sale securities	63,901	12,585	1,990
Purchases of available for sale securities	(77,175)	(77,708)	(13,396)
Net cash used in investing activities	(13,688)	(65,352)	(11,425)
Financing activities:			
Proceeds from the issuance of redeemable convertible preferred stock, net of issuance costs	—	—	40,047
Proceeds from the issuance of 2012 Series X preferred stock, net of issuance costs	—	—	2,279
Proceeds from the issuance of common stock, net of issuance costs	82,750	104,328	5
Proceeds from sale of stock under employee stock purchase plan	220	—	—
Proceeds from the exercise of stock options	130	—	—
Repurchase of treasury stock	—	(162)	—
Payments received on promissory notes issued in exchange for shares of common stock	—	237	—
Payments on capital lease obligations	(7)	(3)	—
Net cash provided by financing activities	83,093	104,400	42,331
Increase in cash and cash equivalents	16,998	11,565	19,574
Cash and cash equivalents at beginning of period	32,780	21,215	1,641
Cash and cash equivalents at end of period	$49,778	$32,780	$21,215

Non-cash financing activities:			
Conversion of series A, series B and series C preferred stock into common stock	$—	$244,727	$—
Accretion of preferred stock to redemption value	$—	$86,899	$55,886
Unpaid initial public offering issuance costs	$—	$—	$857
Unpaid follow-on offering costs	$102	$—	$—
Assets acquired under capital lease	$12	$—	$12
Reclassification of 2012 Series X preferred stock from debt to preferred stock	$—	$—	$2,486
Conversion of 2012 Series X preferred stock into Series C preferred stock	$—	$—	$4,944

See accompanying notes to consolidated financial statements.

Akebia Therapeutics, Inc.

Notes to Consolidated Financial Statements

1. Nature of Organization and Operations

Akebia Therapeutics, Inc. (Akebia, or the Company) is a biopharmaceutical focused on the development of novel proprietary therapeutics based on hypoxia inducible factor, or HIF, biology and the commercialization of these products for patients with serious unmet medical needs. HIF is the primary regulator of the production of red blood cells, or RBCs, in the body and a potentially novel mechanism for the treatment of anemia secondary to chronic kidney disease, or CKD. Pharmacologic modulation of the HIF pathway may also have broader therapeutic applications in acute renal failure, organ protection, ischemia-reperfusion injury, cancer, ophthalmology, and inflammatory diseases. The Company's lead product candidate, vadadustat, formerly known as AKB-6548, is a promising cost-effective alternative for the treatment of anemia. Vadadustat is being developed as a once-daily, oral therapy and has successfully completed Phase 2 development demonstrating that vadadustat can safely and predictably raise hemoglobin levels in patients with anemia related to CKD.

The Company's operations to date have been limited to organizing and staffing the Company, business planning, raising capital, acquiring and developing its technology, identifying potential product candidates and undertaking preclinical and clinical studies. The Company has not generated any product revenue to date, nor is there any assurance of any future product revenue. The Company's product candidates are subject to long development cycles and there is no assurance the Company will be able to successfully develop, obtain regulatory approval for or market its product candidates.

The Company is subject to a number of risks including, but not limited to, the need to obtain adequate additional funding including the resources necessary to fund its recently commenced global Phase 3 development of vadadustat, in dialysis and non-dialysis patients. In December 2015, the Company began dosing patients in its Phase 3 vadadustat program in non-dialysis patients with anemia related to CKD, PRO_2TECT, after obtaining feedback from United States and European regulatory authorities regarding the design of the program. The Company also expects to initiate its Phase 3 vadadustat program in dialysis-dependent CKD patients, $INNO_2VATE$, in 2016, anticipating full enrollment by early 2018. The Company has engaged a clinical research organization for the PRO_2TECT and $INNO_2VATE$ programs. The Company expects the cost of the Phase 3 program to be in the range of $80,000 to $85,000 per patient and it plans to enroll approximately 3,100 patients in PRO_2TECT and approximately 2,600 patients in $INNO_2VATE$.

The Company is also subject to a number of risks including the need to obtain adequate additional funding, possible failure of preclinical testing or clinical trials, the need to obtain marketing approval for its product candidates, the development of new technological innovations by competitors, the need to successfully commercialize and gain market acceptance of any of the Company's products that are approved and the ability to protect its proprietary technology. If the Company does not successfully commercialize any of its products, it will be unable to generate product revenue or achieve profitability.

On March 25, 2014, the Company completed its initial public offering, or IPO, whereby the Company sold 6,762,000 shares of common stock, including 879,647 shares of common stock pursuant to the full exercise of an over-allotment option granted to the underwriters in connection with the offering, at a price of $17.00 per share. The shares began trading on the NASDAQ Global Market on March 20, 2014. The aggregate net proceeds received by the Company from the offering were $104.4 million, net of underwriting discounts and commissions and estimated offering

expenses. Upon the closing of the IPO, all outstanding shares of convertible redeemable preferred stock converted into 12,115,183 shares of common stock. Additionally, the Company is now authorized to issue up to 175,000,000 shares of common stock and 25,000,000 shares of undesignated preferred stock.

In April 2015, the Company completed a follow-on public offering whereby the Company sold 8,363,636 shares of common stock, including 1,090,909 share of common stock pursuant to the full exercise of an over-allotment granted to the underwriters in connection with the offering, at a price of $8.25 per share. The aggregate net proceeds received by the Company from the offering were approximately $64.6 million, net of underwriting discounts and commissions and estimated offering expenses.

In August 2015, the Company entered into a Sales Agreement with Cantor Fitzgerald & Co. to periodically sell up to $50 million of shares of the Company's common stock in an "at-the-market" (ATM) offering. In January 2016, the Company terminated the Sales Agreement in order to use the shares for the January 2016 follow-on offering. During 2015, prior to the termination, the Company sold 1,719,434 shares of common stock pursuant to the Sales Agreement. The aggregate net proceeds received by the Company were approximately $18.4 million, net of commissions. No additional shares of the Company's common stock will be sold pursuant to the Sales Agreement.

In December 2015, we entered into a collaboration agreement with Mitsubishi Tanabe to develop and commercialize vadadustat in Japan and certain other countries in Asia for total milestone payments of up to $350 million, including up to $100 million in upfront

and development payments, of which $40.0 million was received in January 2016. Of the $40.0 million received, $20.0 million is subject to refund to Mitsubishi depending on the outcome of discussions with the Japanese regulator about the global trial design. In addition, we will receive tiered double-digit royalty payments on sales of vadadustat.

In January 2016, the Company completed a follow-on public whereby the Company sold 7,250,000 shares of common stock at a price of $9.00 per share. The aggregate net proceeds received by the Company from the offering were approximately $61.0 million, net of underwriting discounts and commissions and estimated offering expenses payable by the Company.

The Company believes that it can continue as a going concern as its cash resources of approximately $138.5 million at December 31, 2015 will be sufficient to allow the Company to fund its current operating plan through at least the next twelve months. There can be no assurance, however, that the current operating plan will be achieved in the timeframe anticipated by the Company, or that its cash resources will fund the Company's operating plan for the period anticipated by the Company or that additional funding will be available on terms acceptable to the Company, or at all.

Unless otherwise indicated, all information in these condensed consolidated financial statements gives retrospective effect to the 1.75-for-1 stock split of the Company's common stock (the Stock Split) that was effected on March 6, 2014 (see Note 6), as well as any other stock-splits in historical periods.

The Company was incorporated on February 27, 2007 under the laws of the State of Delaware.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Akebia Therapeutics Securities Corporation and Akebia Europe Limited. All intercompany balances and transactions have been eliminated in consolidation. These consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("U.S. GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

In the quarter ended December 31, 2015, the Company identified and corrected an error in the historical classification of certain operating costs between research and development and general and administrative expenses. The Company concluded the effect of this classification error was not material to its consolidated financial statements for any prior period. The classification correction had no effect on the Company's current or historical total operating expenses or net loss.

Recent Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB or other standard-setting bodies and adopted by the Company as of the specified effective date. Unless otherwise discussed, the Company believes the

impact of recently issued standards that are not yet effective will not have a material impact on its financial position or results of operations upon adoption.

In November 2015, the FASB issued ASU No. 2015-17, to simplify the presentation of deferred income taxes. The new standard requires that all deferred tax assets and liabilities, along with any related valuation allowance, be classified as noncurrent on the balance sheet. The standard is effective for interim and annual periods beginning after December 15, 2016 and allows for early adoption using a full retrospective method or a prospective method for all periods presented. The Company has elected to early adopt the provisions of this new standard in the fourth quarter of 2015 using a full retrospective method. The accounting standard did not have any impact on the Company's consolidated financial statements since a full valuation allowance has been provided on the Company's deferred tax assets (see Note 7).

In August 2014, the FASB issued ASU 2014-15, which requires management of public and private companies to evaluate whether there is substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued. Management's evaluation should be based on relevant conditions and events that are known and reasonably knowable at the date that the financial statements are issued. If conditions or events raise substantial doubt about an entity's ability to continue as a going concern, and substantial doubt is not alleviated after consideration of management's plans, an entity should include a statement in the footnotes indicating that there is substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued. The new standard is effective for annual periods ending after December 15, 2016, and for annual periods and interim periods thereafter. Early application is permitted. The Company has concluded, that if this standard had been adopted as of December 31, 2015, substantial doubt about the Company's ability to continue as a going concern does not exist.

In May 2014, the FASB, issued a new revenue recognition standard which amends revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. The new standard provides a five step framework whereby revenue is recognized when promised goods or services are transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The standard also requires enhanced disclosures pertaining to revenue recognition in both interim and annual periods. In August 2015, the FASB deferred the effective date of the new revenue standard from January 1, 2017 to January 1, 2018. Early adoption is permitted any time after the original effective date, which for us is January 1, 2017. The standard allows for adoption using a full retrospective method or a modified retrospective method. We are currently evaluating the timing, method of adoption and the expected impact that the standard could have on our consolidated financial statements and related disclosures.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment, which is the business of developing and commercializing proprietary therapeutics based on HIF biology.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results may differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes, and management must select an amount that falls within that range of reasonable estimates. Estimates are used in the following areas, among others: prepaid and accrued research and development expense, stock-based compensation expense, accrued expenses and income taxes.

Prior to the IPO, the Company utilized significant estimates and assumptions in determining the fair value of its common stock. The Company granted stock options at exercise prices not less than the fair market value of its

common stock as determined by the Board of Directors contemporaneously at the date such grants were made, with input from management. Prior to the Company's IPO in March 2014, the fair value of common stock at the grant date was adjusted in connection with the Company's retrospective fair value assessment for financial reporting purposes. Accordingly, the Board of Directors determined the estimated fair value of the Company's common stock based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector and the prices at which the Company sold shares of preferred stock, the superior rights and preferences of securities senior to the Company's common stock at the time and the likelihood of achieving a liquidity event, such as an IPO or sale of the Company.

The Company utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants Technical Practice Aid, Valuation of Privately-Held Company Equity Securities Issued as Compensation, to estimate the fair value of its common stock in periods prior to March 2014. The methodologies included a probability analysis including both a potential public trading scenario and potential sale scenario. In both scenarios, value is estimated using the guideline public company method. The sale scenario includes an adjustment for a market participant acquisition premium. Value is allocated among the preferred and common shares according to the rights associated with each type of security. Valuation methodologies

include estimates and assumptions that require the Company's judgment. These estimates include assumptions regarding future performance, including the successful completion of a public offering. Significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date.

Cash and Cash Equivalents

Cash and cash equivalents consist of all cash on hand, deposits and funds invested in available-for-sale securities with original maturities of three months or less at the time of purchase. At December 31, 2015, the Company's cash is primarily in money market funds. The Company may maintain balances with its banks in excess of federally insured limits.

Investments

Management determines the appropriate classification of securities at the time of purchase and reevaluates such designation as of each balance sheet date. Currently, the Company classifies all securities as available-for-sale which are included in current assets as they are intended to fund current operations. The Company carries available-for-sale securities at fair value. The Company conducts periodic reviews to identify and evaluate each investment that has an unrealized loss, in accordance with the meaning of other-than-temporary impairment and its application to certain investments. When assessing whether a decline in the fair value of a security is other-than-temporary, the Company considers the fair market value of the security, the duration of the security's decline, and prospects for the underlying business. Based on these considerations, the Company did not identify any other-than-temporary unrealized losses at December 31, 2015. Unrealized losses on available-for-sale securities that are determined to be temporary, and not related to credit loss, are recorded in accumulated other comprehensive loss, a component of stockholders' equity. The amortized cost of debt securities in this category reflects amortization of premiums and accretion of discounts to maturity computed under the effective interest method. The Company includes this amortization in the caption "Interest income, net" within the Consolidated Statements of Operations and Comprehensive Loss. We also include in net investment income, realized gains and losses and declines in value determined to be other than temporary. The Company bases the cost of securities sold upon the specific identification method, and includes interest and dividends on securities in interest income.

Patents

Costs incurred in connection with the application for and issuance of patents are expensed as incurred.

Income Taxes

Income taxes are recorded in accordance with FASB Topic 740, Income Taxes (ASC 740), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The Company has elected to early adopt the provisions of ASU No. 2015-17 in the fourth quarter of 2015 using a full retrospective method. As a result, all deferred taxes as of December 31, 2015 and 2014 are classified as noncurrent within the income tax provision (see Note 7), however as we record a full valuation allowance against the Company's net deferred tax assets, the adoption of this standard has no impact on our consolidated balance sheets as of December 31, 2015 and 2014.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position, as well as consideration of the available facts and circumstances. As of December 31, 2015 and 2014, the Company does not have any significant uncertain tax positions. The Company recognizes interest and penalties related to uncertain tax positions in income tax expense.

Stock-Based Compensation

The Company accounts for its stock-based compensation awards in accordance with FASB ASC Topic 718, Compensation—Stock Compensation (ASC 718). ASC 718 requires all stock-based payments to employees, including grants of employee stock options, restricted stock, restricted stock units, or RSUs, and modifications to existing stock awards, to be recognized in the statements of operations and comprehensive loss based on their fair values. The Company accounts for stock-based awards to non-employees in accordance with FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees (ASC 505-50), which requires the fair value of

the award to be re-measured at fair value until a performance commitment is reached or counterparty performance is complete. The Company's stock-based awards are comprised of stock options, shares of restricted stock and shares of common stock. The Company estimates the fair value of options granted using the Black-Scholes option pricing model. The Company uses the quoted market price of comparable public companies to determine the fair value of restricted stock awards and common stock awards.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (a) the expected stock price volatility, (b) the calculation of expected term of the award, (c) the risk-free interest rate and (d) expected dividends. Due to the lack of a public market for the trading of the Company's common stock and a lack of company-specific historical and implied volatility data, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The computation of expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including stage of product development and life science industry focus. The Company is in the product development stage with no revenue and the representative group of companies has certain similar characteristics to the Company. The Company believes the group selected has sufficient similar economic and industry characteristics, and includes companies that are most representative of the Company. The Company uses the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, Share-Based Payment, to calculate the expected term for options granted to employees as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The expected term is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. For options granted to non-employees, the Company utilizes the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected life of the stock options. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on its common stock, which is similar to the Company's peer group.

The Company's stock-based awards are subject to either service- or performance-based vesting conditions. Compensation expense related to awards to employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Consistent with the guidance in ASC 505- 50, compensation expense related to awards to non-employees with service-based vesting conditions is recognized on a straight-line basis based on the then-current fair value at each financial reporting date prior to the measurement date over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable. Consistent with the guidance in ASC 505-50, compensation expense related to awards to non-employees with performance-based vesting conditions is recognized based on the then-current fair value at each financial reporting date prior to the measurement date over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company is also required to estimate forfeitures at the time of grant, and revise those estimates in the subsequent periods if actual forfeitures differ from its estimates. The Company uses historical data to estimate pre-vesting forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from the Company's estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the condensed consolidated financial statements is based on awards that are ultimately expected to vest.

Fair Value of Financial Instruments

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. FASB ASC Topic 820, Fair Value Measurements and Disclosures (ASC 820), establishes a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available.

Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments, and is not a measure of the investment credit quality. The three levels of the fair value hierarchy are described below:

- Level 1 – Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.
- Level 2 – Valuations based on quoted prices for similar assets or liabilities in markets that are not active, or for which all significant inputs are observable, either directly or indirectly.
- Level 3 – Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Items measured at fair value on a recurring basis include short-term investments (see Note 4). The carrying amounts of accounts receivable, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair values due to their short-term maturities. The rate implicit within the Company's capital lease obligation approximates market interest rates.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Cash, investments and accounts receivable are the only financial instruments that potentially subject the Company to concentrations of credit risk. The Company maintains its cash with high quality, accredited financial institutions and, accordingly, such funds are subject to minimal credit risk. The Company has no significant off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts or other hedging arrangements.

Net Loss per Share

Basic net loss per share is calculated by dividing net loss attributable to common stockholders by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by adjusting weighted-average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury-stock method. For purposes of the diluted net loss per share calculation, preferred stock, stock options, unvested restricted stock and RSUs are considered to be common stock equivalents, but have been excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive for all periods presented. Therefore, basic and diluted net loss per share were the same for all periods presented.

Property and Equipment

Property and equipment is stated at cost, less accumulated depreciation. Assets under capital lease are included in property and equipment. Property and equipment is depreciated using the straight-line method over the estimated useful lives of the assets, generally three to seven years. Such costs are periodically reviewed for recoverability when impairment indicators are present. Such indicators include, among other factors, operating losses, unused capacity, market value declines and technological obsolescence. Recorded values of asset groups of equipment that are not

expected to be recovered through undiscounted future net cash flows are written down to current fair value, which generally is determined from estimated discounted future net cash flows (assets held for use) or net realizable value (assets held for sale).

The following is the summary of property and equipment and related accumulated depreciation as of December 31, 2015 and 2014.

	Useful Life	2015	2014
		(in thousands)	
Computer equipment and software	3	$300	$99
Furniture and fixtures	5	243	117
Equipment	7	50	6
Leasehold improvements	Shorter of the useful life or remaining lease term (3 years)	70	27
Office equipment under capital lease	3	24	12
		687	261
Less accumulated depreciation		(147)	(51)
Net property and equipment		$540	$210

Depreciation expense, including expense associated with assets under capital leases, was approximately $96,000, $49,000 and $1,000 for the years ended December 31, 2015, 2014 and 2013, respectively.

3. Available for sale securities

Available for sale securities at December 31, 2015 and 2014 consist of the following:

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
December 31, 2015				
Cash and cash equivalents	$49,778	$ —	$ —	$49,778
Available for sale securities:				
Certificates of deposit	$21,505	—	—	$21,505
U.S. Government debt securities	46,461	—	(185)	46,276
Corporate debt securities	20,944	1	(50)	20,895

Total available for sale securities	$88,910	$ 1	$ (235)	$88,676
Total cash, cash equivalents, and available for sale securities	$138,688	$ 1	$ (235)	$138,454

The estimated fair value of the Company's available-for-sale securities balance at December 31, 2015, by contractual maturity, is as follows:

Due in one year or less	$39,075
Due after one year	49,601
Total available for sale securities	$88,676

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
December 31, 2014				
Cash and cash equivalents	$32,780	$ —	$ —	$32,780
Available for sale securities:				
Certificates of deposit	$13,429	—	—	$13,429
U.S. Government debt securities	38,412	1	(28)	38,385
Commercial paper	2,499	—	—	2,499
Corporate debt securities	21,854	3	(32)	21,825
Total available for sale securities	$76,194	$ 4	$ (60)	$76,138
Total cash, cash equivalents, and available for sale securities	$108,974	$ 4	$ (60)	$108,918

4. Fair Value of Financial Instruments

The Company utilizes a portfolio management company for the valuation of the majority of its investments. This company is an independent, third-party vendor recognized to be an industry leader with access to market information that obtains or computes fair market values from quoted market prices, pricing for similar securities, recently executed transactions, cash flow models with yield curves and other pricing models. For valuations obtained from the pricing service, the Company performs due diligence to understand how the valuation was calculated or derived, focusing on the valuation technique used and the nature of the inputs.

Based on the fair value hierarchy, the Company classifies its cash equivalents and available-for-sale securities within Level 1 or Level 2. This is because the Company values its cash equivalents and available-for-sale securities using quoted market prices or alternative pricing sources and models utilizing market observable inputs.

Assets measured or disclosed at fair value on a recurring basis as of December 31, 2015 are summarized below:

	Fair Value Measurements Using			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Assets:				
Cash and cash equivalents	$49,778	$—	$ —	$49,778
Certificates of deposit	—	21,505	—	21,505
U.S. Government debt securities	—	46,276	—	46,276
Corporate debt securities	—	20,895	—	20,895
	$49,778	$88,676	$ —	$138,454

The Company’s corporate debt securities are all investment grade.

Assets measured or disclosed at fair value on a recurring basis as of December 31, 2014 are summarized below:

	Fair Value Measurements Using			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Assets:				
Cash and cash equivalents	$32,780	$—	$ —	$32,780
Certificates of deposit	—	13,429	—	13,429
U.S. Government debt securities	—	38,385	—	38,385
Commercial paper	—	2,499	—	2,499
Corporate debt securities	—	21,825	—	21,825
	$32,780	$76,138	$ —	$108,918

The Company had no assets or liabilities measured at fair value on a recurring basis using significant unobservable inputs (Level 3) at December 31, 2015 and December 31, 2014.

Investment securities are exposed to various risks such as interest rate, market and credit. Due to the level of risk associated with certain investment securities and the level of uncertainty related to changes in the value of investment securities, it is at least reasonably possible that changes in risks in the near term would result in material changes in the fair value of investments.

5. Accrued Expenses

Accrued expenses are as follows:

	December 31,	
	2015	2014
	(in thousands)	
Accrued clinical	$4,536	$2,132
Accrued bonus	2,178	1,286
Professional fees	647	328
Accrued payroll	518	213
Accrued vacation	310	177
Accrued severance	—	179
Other	1,366	549
Total accrued expenses	$9,555	$4,864

In February 2014, the Company entered into a separation agreement with an employee primarily as a result of the transition to the Company's Cambridge, Massachusetts location. During the first quarter of 2014, the Company recorded severance expense in the amount of approximately $0.3 million, which was recorded to general and administrative expense. During the year ended December 31, 2014, approximately $0.3 million was paid out of the severance accrual and the remainder was paid during the first quarter of 2015. At December 31, 2015 and 2014, approximately $0 and $45,890, respectively, remained in accrued expenses in relation to the unpaid severance costs.

In August 2014, the Company entered into a separation agreement with an employee, which became effective on August 13, 2014. The Company will record the expense and liability associated with the separation agreement ratably over the period from August 5, 2014 through December 31, 2015 because the severance payments are subject to continued service and forfeiture until December 31, 2015. During the year ended 2015 and 2014, the Company recorded severance expense in the amount of approximately $0.3 million and $0.1 million respectively, which was recorded to research and development expense. At December 31, 2015 and 2014, approximately $0 and $0.1 million, respectively, remained in accrued expense in relation to the unpaid severance costs.

6. Stockholders' Equity

Authorized and Outstanding Capital Stock

As of December 31, 2014, the authorized capital stock of the Company included 175,000,000 shares of common stock, par value $0.00001 per share, of which 30,662,218 and 20,370,624 shares are issued and outstanding at December 31, 2015 and December 31, 2014, respectively; and 25,000,000 shares of undesignated preferred stock, par value $0.00001 per share, of which 0 shares are issued and outstanding at December 31, 2015 and December 31, 2014.

On March 6, 2014, the Company effected a 1.75-for-1 stock split of its outstanding common stock. Unless otherwise indicated, all share data and per share amounts in these financial statements have been retroactively adjusted to reflect the stock split, as well as any stock splits that occurred in periods prior to March 6, 2014.

Upon the closing of the IPO on March 25, 2014, all of the outstanding shares of the Company's redeemable convertible preferred stock were converted into 12,115,183 shares of its common stock. As of December 31, 2014, the Company does not have any redeemable convertible preferred stock issued or outstanding.

Equity Plans

On February 28, 2014, the Company's Board of Directors adopted its 2014 Incentive Plan (2014 Plan) and its 2014 Employee Stock Purchase Plan (ESPP), which were subsequently approved by its stockholders and became effective upon the closing of the Company's IPO on March 25, 2014. The 2014 Plan replaces the 2008 Equity Incentive Plan (2008 Plan), however, any options or awards outstanding under the 2008 Plan at the time of adoption of the 2014 Plan remain outstanding and effective.

The 2014 Plan allows for the granting of stock options, stock appreciation rights, or SARs, restricted stock, unrestricted stock, stock units, performance awards and other awards convertible into or otherwise based on shares of our common stock. Dividend equivalents may also be provided in connection with an award under the 2014 Plan. The Company's employees, officers, directors and consultants and advisors are eligible to receive awards under the 2014 Plan. The Company initially reserved 1,785,000 shares of its common stock for the issuance of awards under the 2014 Plan. The 2014 Plan provides that the number of shares reserved and available for issuance under the 2014 Plan will automatically increase annually on January 1st of each calendar year, by an amount equal to three percent (3%) of the number of shares of stock outstanding on a fully diluted basis as of the close of business on the immediately preceding December 31st (2014 Plan Evergreen Provision). The Company's Board of Directors may act prior to January 1st of any year to provide that there will be no automatic increase in the number of shares available for grant under the 2014 Plan for that year (or that the increase will be less than the amount that would otherwise have automatically been made). Subject to adjustment, no more than 1,131,937 shares of our common stock may be delivered in satisfaction of incentive stock options awarded under the 2014 Plan. During the year ended December 31, 2015, the Company granted 957,050 stock options to employees, 27,875 restricted stock units to employees and 35,000 stock options to directors under the 2014 Plan.

The ESPP authorizes the initial issuance of up to a total of 262,500 share of the Company's common stock to participating employees. The maximum aggregate number of shares of common stock available for purchase pursuant to the exercise of options granted under the ESPP will be the lesser of (a) 262,500 shares, increased on each anniversary of the adoption of the ESPP by one percent (1%) of the total shares of common stock then outstanding and (b) 739,611 shares (which is equal to five percent (5%) of the total shares of common stock outstanding on the date of the adoption of the ESPP on a fully diluted, as converted basis (ESPP Evergreen Provision). Under the ESPP, each offering period is six months, at the end of which employees may purchase shares of common stock through payroll deductions made over the term of the offering. The per-share purchase price at the end of each offering period is equal to the lesser of 85% of the closing price of our common stock at the beginning or end of the offering period.

Shares Reserved for Future Issuance

The Company has reserved for future issuance the following number of shares of common stock:

	December 31,	
	2015	2014
Unvested restricted common stock	216,716	422,145
Common stock options and RSU's outstanding	2,231,057	1,526,346
Shares available for issuance under the 2014 Plan [1]	1,318,732	1,549,154
Shares available for issuance under the ESPP	440,304	262,500
Total	4,206,809	3,760,145

[1] On January 1, 2016, the shares reserved for future grants under the 2014 Plan increased by 986,800 shares pursuant to the 2014 Plan Evergreen Provision.

[2] On February 28, 2016, the shares reserved for future issuance under the ESPP increased by 379,430 shares pursuant to the ESPP Evergreen Provision.

Stock-Based Compensation

Stock Options

On March 6, 2015, the Company issued 479,750 stock options to employees. Options granted by the Company vest over periods of between 12 and 48 months. Options vest in installments of (i) 25% at the one year anniversary and (ii) in either 36 or 48 equal monthly or 12 equal quarterly installments beginning in the thirteenth month after the initial Vesting Commencement Date (as defined) or grant date, subject to the employee's continuous service with the Company. Options generally expire ten years after the date of grant.

The assumptions used in the Black-Scholes pricing model to estimate the grant date fair value of options granted to employees are as follows:

	Year ended December 31,	
	2015	2014
Risk-free interest rate	1.44% - 1.95%	1.63% - 2.06%
Dividend yield	0.00%	0.00%
Volatility	62.47% - 81.25%	67.97% - 77.00%
Expected term (years)	5.51 - 6.25	6.25

The following table summarizes the Company's stock option activity:

	Shares	Weighted-Average Exercise Price	Weighted-Average Contractual Life (in years)	Aggregate Intrinsic Value
Outstanding, December 31, 2014	1,526,349	$ 7.57		$11,523,531
Granted	992,050	$ 9.81		
Exercised	(218,674)	$ 0.60		$2,047,507
Forfeited	(93,090)	$ 12.96		$107,384
Expired/cancelled	—			
Outstanding, December 31, 2015	2,206,635	$ 9.04	8.20	$13,114,811
Options exercisable, December 31, 2015	610,696	$ 6.20	6.63	$5,620,564
Expected to vest, December 31, 2015	1,958,808	$ 9.71	8.56	$10,737,600

As of December 31, 2015, there was approximately $9.7 million of unrecognized compensation cost related to stock options, which is expected to be recognized over a weighted average period of 2.62 years.

Restricted Stock

On December 23, 2013, the Company issued 450,224 shares of restricted stock to employees and 79,067 shares of restricted stock to non-employees at a grant date fair value of $7.42 per share. The aggregate grant date fair value for the shares of restricted stock issued on December 23, 2013 totaled approximately $3.9 million. The awards of restricted stock contained a performance condition wherein vesting is contingent upon the Company's consummation of a liquidity event, as defined, prior to the fifth anniversary of the date of grant. Certain of the awards of restricted stock have a requisite service period that was complete upon grant. The remainder of the awards of restricted stock have a requisite service period of four years whereby the award vests 25% on the one year anniversary of the Vesting Commencement Date (as defined), then ratably on the first day of each calendar quarter for 12 quarters, subject to continuous service by the individual and achievement of the performance target. Due to the nature of the performance condition, the Company had concluded that the performance condition was not probable of achievement and therefore, recognition of compensation cost had been deferred until the occurrence of a liquidity event, as defined. The liquidity event occurred upon the closing of the Company's IPO on March 25, 2014. Accordingly, the Company recognized $0.1 million of compensation expense on March 25, 2014 related to the restricted stock awards with a requisite service period that was complete upon grant. Compensation expense related to the remainder of the restricted stock awards is being recognized over the associated requisite service period commencing on March 25, 2014. The Company recorded approximately $0.9 million of stock-based compensation expense related to restricted stock during 2015.

A summary of the Company's restricted stock activity is as follows:

	Shares	Weighted-Average Grant Date Fair Value
Unvested balance, December 31, 2014	422,145	$ 8.39
Granted	-	
Vested	(169,376)	$ 8.87
Forfeited	(36,053)	$ 8.93
Outstanding, December 31, 2015	216,716	$ 7.97

As of December 31, 2015, there was approximately $0.4 million of unrecognized compensation cost related to the restricted stock awards granted on December 23, 2013 with a performance condition. The recognition of the compensation cost for these awards did not begin until the closing of the IPO on March 25, 2014. The unrecognized compensation cost is expected to be recognized over a weighted average period of 1.08 years.

Common Stock Awards

In connection with the termination of a former employee in September 2013, the Company granted the former employee stock awards totaling 70,964 shares in September 2013 and 105,753 shares in December 2013 of Common Stock, at a fair value of $3.77 per share and $7.42 per share, respectively. The fair value of the awards are based on the estimated fair value of the Company's Common Stock at the date of grant. Accordingly, compensation cost was recognized in full on the date of grant. The associated common shares immediately vested, and were not subject to any other restriction. Accordingly, the compensation cost was recognized in full on the date of grant. Total compensation cost of approximately $1.1 million was recognized during the year ended December 31, 2013 related to these awards.

Restricted Stock Units

On March 6, 2015, the Company issued 27,875 RSUs to employees. The RSUs vest 100% on the three year anniversary. Total stock-compensation expense to be recognized over the life of the RSUs is $0.3 million and will be recognized on a straight-line basis over the vesting period. The Company recorded approximately $62,000 of stock-based compensation expense related to the RSUs during 2015.

	Shares	Weighted-Average Grant Date Fair Value
Unvested balance, December 31, 2014	-	$ -
Granted	27,875	$ 11.15
Vested	-	$ -
Forfeited	(3,450)	$ 11.15
Outstanding, December 31, 2015	24,425	$ 11.15

As of December 31, 2015, there was approximately $0.2 million of unrecognized compensation cost related to restricted stock units, which is expected to be recognized over a weighted average period of 2.18 years.

ESPP

The first offering period under the ESPP opened on January 2, 2015. The Company issued 25,903 shares during the year ended December 31, 2015. The Company recorded approximately $83,000 of stock-based compensation expense related to ESPP during 2015.

Compensation Expense Summary

The Company has recognized the following compensation cost related to share-based awards:

	Year ended December 31,	
	2015	2014
	(in thousands)	
Research and development	$2,079	$2,766
General and administrative	2,635	3,244
Total	$4,714	$6,010

Compensation expense by type of award:

	Year ended December 31,	
	2015	2014
	(in thousands)	
Stock options	$3,660	$1,925
Restricted stock	909	4,085
Restricted stock units	62	—
Employee stock purchase plan	83	—
Total	$4,714	$6,010

Included in the compensation expense for the year ended December 31, 2014, is approximately $1.0 million related to the modification of awards in connection with an employee separation agreement in the first quarter of 2014.

7. Income Taxes

The Company's income tax provision was computed based on the federal statutory rate and the average state statutory rates, net of the related federal benefit. There was no current or deferred income tax expense or benefit for the years ended December 31, 2015 and 2014, due to the Company's net losses and increases in its deferred tax asset valuation allowance. Following is a reconciliation of the statutory federal income rate to the Company's effective tax rate:

	Year ended December 31,	
	2015	2014
Federal tax at statutory rate	34.0 %	34.0 %
State and local tax at statutory rate	3.0	5.5
Research and development tax credits	0.4	(0.6)
Equity compensation	(0.6)	(1.6)
Other permanent differences and credits	—	(0.1)
Change in valuation allowance	(36.8)	(37.2)
Effective tax rate	0.0 %	0.0 %

The Company's income tax provision was computed based on the federal statutory rate and the average state statutory rates, net of the related federal benefit.

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Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. When realization of the deferred tax asset is more likely than not to occur, the benefit related to the deductible temporary differences attributable to operations is recognized as a reduction of income tax expense. Valuation allowances are provided against deferred tax assets when, based on all available evidence, it is considered more likely than not that some portion or all of the recorded deferred tax assets will not be realized in future periods. The Company cannot be certain that future taxable income will be sufficient to realize its deferred tax assets, and accordingly a full valuation allowance has been provided on its deferred tax assets. The Company continues to maintain the underlying tax benefits to offset future taxable income and to monitor the need for a valuation allowance based on the profitability of its future operations. The valuation allowance increased by approximately $22.3 million and $13.8 million, during the years ended December 31, 2015 and 2014, respectively, primarily as a result of increases in unbenefited deferred tax assets such as tax losses and stock-based compensation. Significant components of the Company's deferred tax assets and liabilities are as follows:

	December 31,	
	2015	2014
	(in thousands)	
Deferred tax assets:		
Accrued expenses	$912	$559
Intangible assets	527	$603
Restricted stock	301	$436
Fixed assets	—	$2
Non-qualified stock options [1]	1,558	$440
Research and development credits	1,829	$1,589
Net operating loss carryforward	51,356	$30,559
Other	64	$39
Total deferred tax assets	56,547	$34,227
Less valuation allowance	(56,545)	(34,227)
Total deferred tax assets, net of valuation allowance	2	—
Deferred tax liabilities:		
Fixed assets	(2)	—
Restricted stock	—	—
Total deferred tax liabilities	(2)	—
Net deferred tax asset	$—	$—

[1] This amount was reclassified from "other" in 2014 for comparability.

At December 31, 2015 and December 31, 2014, the Company has approximately $1.0 million (after amortization of $0.9 million) and $1.2 million (after amortization of $0.8 million), respectively, of start-up expenses capitalized for income tax purposes with amortization available to offset future federal, state and local income tax. At December 31, 2015 and 2014, the Company has approximately $140.5 million and $84.2 million, respectively, of federal net operating loss (NOL) carry-forwards. Additionally, at December 31, 2015 and 2014, the Company has approximately $111.9 million and $83.7 million, respectively, of state net operating loss (NOL) carry-forwards which expire through 2035. Included in the 2015 and 2014 NOLs are approximately $0.9 million of tax deductions related to equity compensation in excess of book compensation expense. Pursuant to the realization requirements in ASC 718, these tax deductions are not included in the NOL deferred tax asset above. The Company also has approximately $2.0 million of federal and state research and development tax credit carry-forwards. The NOL and research and

development tax credit carry-forwards begin to expire in 2027 through 2035, and will be utilized for tax purposes at such time the Company generates taxable income. The NOL and research and development tax credit carry-forwards may be limited in certain circumstances, including ownership changes.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carry-forwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception, which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future. The Company has not yet analyzed whether there has been a change in control.

For applicable years, the Company generated research credits but has not conducted a study to document its qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carry-forwards and the valuation allowance.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2015, 2014 and 2013, the Company had no accrued uncertain tax positions or associated interest or penalties and no amounts have been recognized in the Company's consolidated statements of operations.

The Company files income tax returns in the U.S. federal jurisdiction, and various state jurisdictions. The Company's 2012 through 2014 tax years remain open and subject to examination by federal and state taxing authorities. However, federal and state net operating losses from 2008 through 2014 are subject to review by taxing authorities in the year utilized.

8. Commitments and Contingencies

In December 2013, the Company entered into a three-year lease for 6,837 square feet of office space in Cambridge, Massachusetts. The lease has monthly lease payments of approximately $31,000 for the first twelve months, with annual rent escalation thereafter, and provides a rent abatement of approximately $31,000 for the first full calendar month of the lease term. The lease term commenced and rental payments began in January 2014. The Company recorded a deferred lease obligation in 2014 which represents the cumulative difference between actual facility lease payments and lease expense recognized ratably over the lease period, which is included in other liabilities. In accordance with the lease, the Company entered into a cash-collateralized irrevocable standby letter of credit in the amount of $125,345, naming the landlord as beneficiary.

In December 2014, the Company entered into a First Amendment to Lease, or the Amendment, for additional office space contiguous to its current office space in Cambridge, Massachusetts. The Amendment included leasing an additional 8,530 square feet of office space, or the Expansion Space, with an occupancy date of March 13, 2015. The Amendment provided for additional monthly lease payments of approximately $45,000 for the 8,530 square feet for the first twelve months and provided for annual rent escalations thereafter. The monthly rent on the existing 6,837 square feet remained at approximately $32,000 through December 31, 2016, the expiration of the lease. The Amendment included a Landlord's contribution for leasehold improvements in the amount of approximately $100,000 which was accounted for as a deferred lease incentive and reduction in monthly rent expense over the term of the lease. The Company recorded an additional deferred lease obligation for the Expansion Space which represented the cumulative difference between actual facility lease payments and lease expense recognized ratably over the lease period. The Company had an existing cash-collateralized irrevocable standby letter of credit of $125,345, naming the landlord as beneficiary. In connection with the Amendment, the Company paid an additional cash security deposit to the landlord of $179,130. These amounts are included in other assets.

In November 2015, the Company entered into a Second Amendment to Lease amending the Lease to extend its existing lease for 16,222 square feet on the 11th floor, which was due to expire on December 31, 2016, and lease an additional 23,189 square feet of office space on the 11th and 14th floors. Monthly lease payments for the existing 16,222 square feet on the 11th floor remain unchanged until December 31, 2016 and will be approximately $107,000

per month commencing on May 1, 2017. The new space leased by the Company under the Second Amendment includes (i) 3,066 square feet on the 14th floor which was delivered on November 23, 2015 and additional monthly lease payments of approximately $20,000 commencing on March 1, 2016, (ii) 16,739 square feet on the 14th floor with an estimated delivery date of April 1, 2016 and additional monthly lease payments of approximately $110,000 commencing September 1, 2016 and (iii) 3,384 square feet on the 1th floor with an estimated delivery date of January 1, 2017 and additional monthly lease payments of approximately $23,000 commencing May 1, 2017. The above rents are subject to annual rent escalations, commencing on either February 1, 2017 or February 1, 2018 depending upon the delivery date of each respective suite. The Second Amendment includes a Landlord's contribution for leasehold improvements for both the new leased space and the Company's existing premises. The Landlord's contribution will be accounted for as a deferred lease incentive and reduction in monthly rent expense over the term of the lease. In connection with the Second Amendment, the Company paid an additional cash security deposit to the Landlord of $976,382. The term of the lease, as amended, expires on the later of August 31, 2026 or 10 years after the Landlord delivers the entirety of the 14th floor to the Company. In connection with the Second Amendment, the Company paid an additional cash security deposit to the landlord of $976,382. Total cash security deposits of $1,280,857 and $304,475 are included in other assets in the Company's consolidated balance sheets as of December 31, 2015 and 2014, respectively.

The Company leases office equipment under a two three year capital leases with payments commencing in February 2014 and April 2015, respectively. The capital lease amounts are included in accrued expenses and other liabilities.

At December 31, 2015, the Company's future minimum payments required under these leases are as follows:

	Operating Lease	Capital Lease	Total
	(in thousands)		
2016	$2,522	$ 8	$2,530
2017	3,122	5	3,127
2018	3,122	1	3,123
2019	3,122	—	3,122
2020	3,122	—	3,122
Thereafter	17,687	—	17,687
Total	$32,697	14	$32,711
Less amount representing interest		—	
Present value of minimum lease payments at December 31, 2015		$ 14	

The Company recorded approximately $0.9 million and $0.4 million in rent expense for the years ended December 31, 2015 and 2014 respectively.

Under the Company's agreement with Quintiles to conduct the PRO$_2$TECT and INNO$_2$VATE programs, the total cost of committed work not yet paid as of December 31, 2015 was approximately $246.0 million. The estimated period of performance for the committed work with Quintiles is through the third quarter of 2019. The Company contracts with various other organizations to conduct research and development activities with remaining contract costs to the Company of approximately $5.2 million and $4.3 million at December 31, 2015 and December 31, 2014, respectively. The scope of the services under the research and development contracts can be modified and the contracts cancelled by the Company upon written notice. In some instances the contracts may be cancelled by the third party upon written notice.

In September 2015, a purported securities class action lawsuit was filed against the Company, including its Chief Executive Officer, its Chief Financial Officer, and members of its Board of Directors, in the Business Litigation Section of the Suffolk County Superior Court of Massachusetts. The complaint is brought on behalf of an alleged class of those who purchased common stock of the Company pursuant or traceable to our initial public offering, and purports to allege claims arising under Sections 11, 12(a)(2) and 15 of the Securities Act of 1933, as amended (the "Securities Act"). The complaint generally alleges that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning the Phase 2b clinical study of vadadustat. The complaint seeks, among other relief, unspecified compensatory damages, rescission of certain stock purchases, attorneys' fees, and costs. In October 2015, we removed the case to the United States District Court for the District of Massachusetts, and the plaintiff filed a motion to remand the case back to the Business Litigation Section of the Suffolk County Superior Court of Massachusetts. The plaintiff's motion to remand is currently pending. The Company believes such claims are without merit, and will engage in a vigorous defense of such litigation.

As explained in more detail below, we have had some positive developments in our opposition and invalidity proceedings against FibroGen, Inc., or FibroGen. With regard to the opposition that we filed in Europe against FibroGen's European Patent No. 1463823, or the '823 patent, the European Opposition Division issued a non-binding preliminary opinion that none of FibroGen's '823 patent claims meet the requirements for patentability. In an oral proceeding which took place March 8 and 9, 2016, the European Opposition Division confirmed 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. 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 patent, which is the Japanese counterpart to the '823 patent, the 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 FibroGen '131 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 in Europe and Japan in the '823 and '131 patents. In the event FibroGen were to obtain such patents in the United States, we may decide to challenge them like we have done in Europe and Japan. On May 13, May 20, and July 6, 2015, we also filed oppositions to FibroGen's European Patent Nos. 2322153, 2322155, and 1633333 respectively, requesting the patents be revoked in their entirety.

In June 2013, the European Patent Office granted the '823 patent, to FibroGen. The '823 patent claims, among other things, the use of a heterocyclic carboxamide compound selected from the group consisting of pyridine carboxamides, quinoline carboxamides, isoquinoline carboxamides, cinnoline carboxamides, and beta-carboline carboxamides that inhibits HIF-PH enzyme activity in the manufacture of a medicament for increasing endogenous EPO in the prevention, pretreatment or treatment of anemia. On December 5,

2013, we filed an opposition to the ’823 patent requesting that the ’823 patent be revoked in its entirety. The European Opposition Division scheduled oral proceedings for March 8, 2016 and also issued a non-binding preliminary opinion that none of the ’823 patent’s claims met the requirements for patentability. In an oral proceeding which took place March 8 and 9, 2016, the European Opposition Division confirmed 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. If FibroGen appeals the decision of the European Opposition Division, final resolution of the appeal will likely take two to three years. While, for the reasons set forth in our opposition, we maintain that the ’823 patent should be revoked in its entirety, the ultimate outcome of any appeal remains uncertain. If FibroGen appeals the decision of the European Opposition Division and the Technical Board of Appeal at the European Patent Office decides not to revoke the ’823 patent in its entirety, or only certain claims of the ’823 patent and any surviving claims are determined to encompass our intended use of vadadustat, we may not be able to commercialize vadadustat in the European Union for its intended use, which could materially adversely affect our business, operating results and financial condition.

In August 2011, the Japanese Patent Office granted the ’131 patent, to FibroGen. The ’131 patent claims, among other things, the use of certain heterocyclic carboxamides selected from the group consisting of pyridine carboxamides, quinoline carboxamides, and isoquinoline carboxamides to treat anemia, wherein the heterocyclic carboxamides also suppress HIF prolyl hydroxylase. On June 2, 2014, we filed an invalidity proceeding in the Japanese Patent Office challenging the validity of the ’131 patent and requesting that certain claims be revoked in their entirety. An oral hearing before the Japanese Patent Office was held on February 9, 2015, and on May 11, 2015 the Japanese Patent Office issued a preliminary decision finding all of the challenged claims to be invalid. In response, FibroGen filed a request for correction in which it requested that the ’131 patent claims be amended to exclude pyridine carboxamides from their scope. On November 18, 2015, Akebia received the final trial decision from the JPO in which it accepted FibroGen’s requested claim amendments. As a result of the JPO’s decision and FibroGen’s subsequent amendments, the FibroGen ’131 patent does not cover vadadustat or any pyridine carboxamide compounds.

In August 2014, the European Patent Office granted European Patent Nos. 2322153, 2322155, and 1633333, or the ’153 patent, the ’155 patent, and the ’333 patent, respectively, to FibroGen. 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 EPO, and microcytosis in microcytic anemia. On May 13, May 20, and July 6, 2015, we filed oppositions to the ’155 patent, the ’333 patent, and the ’153 patent, respectively, requesting that the patents be revoked in their entireties. While, for the reasons set forth in our oppositions, we believe that the ’153 patent, the ’155 patent, and the ’333 patent should be revoked in their entireties, the ultimate outcomes of the oppositions remains uncertain. If the European Patent Office decides not to revoke the ’153 patent, the ’155 patent, or the ’333 patent in their entireties, or only certain claims of those patents, and any surviving claims are determined to encompass our intended use of our lead product candidate, we may not be able to commercialize our lead product candidate in the European Union for its intended use, which could materially adversely affect our business, operating results and financial condition.

The Company is not able to predict the outcome of the lawsuit described above or estimate the amount or range of any possible loss the Company might incur if the Company does not prevail in the final, non-appealable determination of this lawsuit. Therefore, we have not accrued any amounts in connection with this lawsuit.

9. Employee Retirement Plan

During 2008, the Company established a retirement plan (the Plan) authorized by Section 401(k) of the Internal Revenue Code. In accordance with the Plan, all employees who have attained the age of 21 are eligible to participate in the Plan as of the first Entry Date, as defined, following their date of employment. Each employee can contribute a percentage of compensation up to a maximum of the statutory limits per year. Company contributions are discretionary and contributions in the amount of approximately $0.1 million and $0 were made during the year ended December 31, 2015 and 2014, respectively.

10. Net Loss per Share

The following table presents the calculation of basic and diluted net loss per share applicable to common stockholders:

	Year ended December 31,	
	2015	2014
	(in thousands, except share and per share data)	
Numerator:		
Net loss	$(60,716)	$(37,034)
Accretion on preferred stock	—	(86,899)
Net loss applicable to common stockholders	$(60,716)	$(123,933)
Denominator:		
Weighted-average number of common shares – basic and diluted	26,469,170	15,406,386
Net loss per share applicable to common stockholders – basic and diluted	$(2.29)	$(8.04)

The amounts in the table below were excluded from the calculation of diluted net loss per share, prior to the use of the treasury stock method, due to their anti-dilutive effect:

	Year ended December 31,	
	2015	2014
Outstanding stock options	2,206,635	1,526,346
Unvested restricted stock	216,716	422,145
Unvested restricted stock units	24,425	—
Total	2,447,776	1,948,491

11. Quarterly Results (unaudited)

	Three Months Ended June 30,

	March 31, 2015	2015	September 30, 2015	December 31, 2015
	(in thousands, except per share data) (unaudited)			
Operating expenses	$10,896	$10,889	$19,678	$20,050
Loss from operations	$(10,896)	$(10,889)	$(19,678)	$(20,050)
Other income (expense), net	$201	$200	$203	$193
Net loss	$(10,695)	$(10,689)	$(19,475)	$(19,857)
Net loss per share applicable to common stockholders—basic and diluted	$(0.53)	$(0.40)	$(0.68)	$(0.66)

	Three Months Ended			
	March 31, 2014	June 30, 2014	September 30, 2014	December 31, 2014
	(in thousands, except per share data) (unaudited)			
Operating expenses	$9,909	$7,840	$9,584	$10,607
Loss from operations	$(9,909)	$(7,840)	$(9,584)	$(10,607)
Other income (expense), net	$212	$222	$236	$237
Net loss	$(9,697)	$(7,618)	$(9,348)	$(10,370)
Net loss per share applicable to common stockholders—basic and diluted	$(43.37)	$(0.39)	$(0.47)	$(0.52)

12. Subsequent Event

In January 2016, in connection with the Company's Collaboration Agreement which was signed with Mitsubishi Tanabe in December 2015, the Company received a $40.0 million up-front payment. The $40.0 million up-front payment was contingent upon the Company providing certain tax documentation to Mitsubishi which was completed in January 2016. The Company therefore did not have a contractual right to bill until the tax documents were provided in January 2016. Of the $40.0 million received, $20.0 million is subject to refund to Mitsubishi depending on the outcome of discussions with the Japanese regulator about the global trial design.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure
None.

Item 9A. Controls and Procedures
Controls and Procedures

Management's Annual Report on Internal Control over Financial Reporting

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rule 13a-15(f) under the Exchange Act). Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policy or procedures may deteriorate. Management conducted an assessment of the effectiveness of our internal control over financial reporting based on the criteria set forth in Internal Control - Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework). Based on the assessment, management has concluded that its internal control over financial reporting was effective as of December 31, 2015 to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with U.S. GAAP.

Management's Evaluation of our Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Securities Exchange Act of 1934 is (1) recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, to allow timely decisions regarding required disclosure.

As of December 31, 2015, our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934). Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial officer have concluded based upon the evaluation described above that, as of December 31, 2015, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting

During the quarter ended December 31, 2015, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information
Other Information

The following disclosure is provided in accordance with and in satisfaction of the requirements of Item 2.02 “Results of Operations and Financial Condition” of Form 8-K:

On March 14, 2016, Akebia announced its financial results for the quarter ended December 31, 2015 and commented on certain corporate accomplishments and plans. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 hereto.

The information furnished in Item 9B (including Exhibit 99.1) shall not be deemed “filed” for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K and is incorporated herein by reference from our definitive proxy statement relating to our 2016 Annual Meeting of Stockholders (the "Definitive Proxy Statement"), which we expect to file with the SEC no later than April 30, 2016.

Item 10. Director, Executive Officers and Corporate Governance

John P. Butler joined Akebia as director in July 2013 and was appointed as the President and Chief Executive Officer of Akebia in August 2013. Prior to joining Akebia, from 2011 until 2013, Mr. Butler served as the Chief Executive Officer of Inspiration Biopharmaceuticals, Inc., a company focused on developing products for patients with hemophilia. Mr. Butler led the transactions that resulted in the sale of hemophilia assets to Cangene Corporation and Baxter International in early 2013 for total aggregate consideration that could exceed $1 billion. From 1997 to 2011, Mr. Butler held various positions at Genzyme Corporation, a biopharmaceutical company, most recently serving as President of the company's rare genetic diseases business. From 2002 until 2010, Mr. Butler led Genzyme's renal division. Prior to his work at Genzyme, Mr. Butler held sales and marketing positions at Amgen and Hoffmann-La Roche. Mr. Butler currently serves as a member of the Board of Trustees for the American Kidney Fund and a member of the board of directors of Relypsa, Inc. and Keryx Biopharmaceuticals, Inc. Mr. Butler received a B.A. in Chemistry from Manhattan College and an M.B.A. degree from Baruch College, City University of New York. We believe that Mr. Butler is qualified to serve on our board of directors due to his industry experience in the biotechnology sector, particularly his experience working in the renal disease market.

Jason A. Amello joined Akebia as Senior Vice President, Chief Financial Officer and Treasurer in 2013. Prior to joining Akebia, Mr. Amello served as Executive Vice President, Chief Financial Officer and Treasurer of ZIOPHARM Oncology, Inc., a biopharmaceutical company, from 2012 to 2013. From 2000 to 2011, Mr. Amello held various positions at Genzyme Corporation, most recently as Senior Vice President, Corporate Controller and Chief Accounting Officer, and led the Strategic Financial Services group through which he served as a key advisor on all of Genzyme's M&A and strategic transactions. Earlier in his career, Mr. Amello spent 10 years in the business advisory and assurance practice of Deloitte, serving in various roles of increasing responsibility through senior manager. Mr. Amello currently serves on the Board of Directors of the New England Baptist Hospital and is a member of the Quality of Care Committee and the Finance and Investment Committee. Mr. Amello holds a B.A. from Boston College and is a Certified Public Accountant in the Commonwealth of Massachusetts.

Brad Maroni, M.D. joined Akebia as Senior Vice President and Chief Medical Officer in August 2014. Dr. Maroni most recently served as Vice President, Medical Research at Biogen Idec. Prior to that role, Dr. Maroni served as Chief Medical Officer of Stromedix, Inc. until the company was acquired by Biogen Idec in 2012. His previous experience also includes serving as Executive Vice President and Chief Medical Officer at RenaMed Biologics, as well as multiple roles at Amgen Inc., including Vice President, Clinical Development and Anemia/Nephrology Therapeutic Area Head. At Amgen, Dr. Maroni led the cross-functional team responsible for the registration program and global regulatory approval of Aranesp®, a novel long-acting recombinant erythropoietic protein, indicated for the treatment of anemia in chronic kidney disease. During his tenure, Amgen also received approval for Sensipar®, a first-in-class small molecule for the treatment of bone disease in dialysis patients. Dr. Maroni trained as a nephrologist at Brigham and Women's Hospital in Boston, Massachusetts, after which he spent 10 years in academia at Emory University.

Nicole R. Hadas joined Akebia in 2013 and is Senior Vice President, General Counsel and Secretary. Prior to joining Akebia, Ms. Hadas was Vice President and General Counsel at OvaScience, Inc., a biopharmaceutical company, in 2013. Ms. Hadas served as the Senior Vice President and General Counsel at Inspiration Biopharmaceuticals, Inc.,

where she managed the successful sale of its hemophilia assets to Cangene Corporation and Baxter International in early 2013. From 2001 to 2011, Ms. Hadas worked at Genzyme Corporation, most recently as Senior Corporate Counsel. Prior to Genzyme, she was an associate at Foley Hoag representing biopharmaceutical companies and healthcare providers in a wide variety of matters. Ms. Hadas received a B.A. from the University of Michigan and a J.D. from Boston College Law School.

Michel Dahan joined Akebia in 2013 and is the Senior Vice President, Chief Business Officer. Prior to joining Akebia, from 2010 to 2013, Mr. Dahan held various positions at Inspiration Biopharmaceuticals, Inc., most recently as Vice President, Commercial Development and Strategic Planning, and led the global marketing and commercial development in preparation for two global launches. Prior to that, from 2003 to 2010, Mr. Dahan served in various roles for Ipsen, most recently as Senior Director, Strategic Planning, working on global marketing and strategic planning for their hemophilia franchise. He began his career at BNP Paribas in 2002 as an analyst on the Business Valuation Team working on mergers and acquisitions and investment banking. He earned his graduate degree in business administration at HEC Paris (France), his maitrise in mathematics from University Paris VI (France), and his executive education program (PLD) at Harvard Business School.

The remaining information required by this Item 10 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this Item 11 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item 12 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Person Transactions, and Director Independence

The information required by this Item 13 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services

The information required by this Item 14 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

Exhibits and Financial Statement Schedules

(a) Documents filed as part of Form 10-K.

(1) Financial Statements

Report of Independent Registered Public Accounting Firm

Consolidated Balance Sheets

Consolidated Statements of Operations and Comprehensive Loss

Consolidated Statements of Stockholders' Equity (Deficit)

Consolidated Statements of Cash Flows

Notes to Consolidated Financial Statements

(2) Schedules

Schedules have been omitted as all required information has been disclosed in the financial statements and related footnotes.

(3) Exhibits

The Exhibits listed in the Exhibit Index are filed as a part of this Form 10-K.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

AKEBIA THERAPEUTICS, INC.

Date: March 14, 2016

By: /s/ John P. Butler
John P. Butler
Chief Executive Officer and President (Principal Executive Officer)

Date: March 14, 2016

By: /s/ Jason A. Amello
Jason A. Amello
Senior Vice President, Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer)

Date: March 14, 2016 By: /s/ Muneer Satter
Muneer Satter
Chairman

Date: March 14, 2016 By: /s/ Anupam Dalal
Anupam Dalal
Director

Date: March 14, 2016 By: /s/ Duane Nash
Duane Nash
Director

Date: March 14, 2016 By: /s/ Michael Wyzga
Michael Wyzga
Director

Date: March 14, 2016 By: /s/ Maxine Gowen
Maxine Gowen
Director

Date: March 14, 2016 By: /s/ Michael Clayman

Michael Clayman
Director

Date: March 14, 2016 By: /s/ Ronald Renaud
Ronald Renaud
Director

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Ninth Amended and Restated Certificate of Incorporation (incorporated by reference to exhibit 3.1 to the Company's Current Report on Form 8-K, filed on March 28, 2014)
3.2	Amended and Restated Bylaws (incorporated by reference to exhibit 3.2 to the Company's Current Report on Form 8-K, filed on March 28, 2014)
4.1	Form of Common Stock Certificate (incorporated by reference to exhibit 4.1 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
4.2	Third Amended and Restated Voting Agreement, dated May 10, 2013 (incorporated by reference to exhibit 4.2 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
4.3	Amendment No. 1 to the Third Amended and Restated Voting Agreement, dated May 31, 2013 (incorporated by reference to exhibit 4.3 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
4.4	Fourth Amended and Restated Investors' Rights Agreement, dated March 5, 2014 (incorporated by reference to exhibit 4.4 to the Company's 10-K for the year ending December 31, 2014 and filed on March 4, 2015)
10.1	Form of Director and Officer Indemnification Agreement (incorporated by reference to exhibit 10.1 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.2	Office Lease Agreement Between MA-Riverview/245 First Street, L.L.C. and Akebia Therapeutics, Inc., dated December 3, 2013 (incorporated by reference to exhibit 10.2 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.3	First Amendment to Office Lease Agreement Between Jamestown Premier 245 First, LLC and Akebia Therapeutics, Inc., dated December 15, 2014 (incorporated by reference to exhibit 10.3 to the Company's 10-K for the year ending December 31, 2014 and filed on March 4, 2015)
10.4*	Second Amendment to Office Lease Agreement Between Jamestown Premier 245 First, LLC and Akebia Therapeutics, Inc., dated November 23, 2015
10.5	Amended and Restated Administrative Services Agreement, between Akebia Therapeutics, Inc. and Aerpio Therapeutics, Inc., dated August 27, 2012 (incorporated by reference to exhibit 10.3 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.6	Administrative Services Agreement, between Akebia Therapeutics, Inc. and Aerpio Therapeutics, Inc., dated November 1, 2012 (incorporated by reference to exhibit 10.4 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.7†	

	Amended and Restated 2008 Equity Incentive Plan (incorporated by reference to exhibit 10.5 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.8†	Amendment No. 1 to Amended and Restated 2008 Equity Incentive Plan (incorporated by reference to exhibit 10.6 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.9†	Executive Employment Agreement with John P. Butler, dated September 16, 2013 (incorporated by reference to exhibit 10.7 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.10†	Executive Employment Agreement with Jason A. Amello, dated September 23, 2013 (incorporated by reference to exhibit 10.8 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.11†	Offer Letter to Nicole R. Hadas, dated November 13, 2013 (incorporated by reference to exhibit 10.9 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.12†	Executive Employment Agreement with Dr. Robert Shalwitz, dated April 6, 2011 (incorporated by reference to exhibit 10.10 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.13†	Separation Agreement with Dr. Robert Shalwitz, dated August 5, 2014 (incorporated by reference to exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed on November 10, 2014)

Exhibit Number	Description of Exhibit
10.14†	Consulting Agreement with Dr. Robert Shalwitz, dated August 5, 2014 (incorporated by reference to exhibit 10.2 to the Company's Quarterly Report on Form 10-Q, filed on November 10, 2014)
10.15†	Amended and Restated Partial Recourse Promissory Note, dated May 9, 2013, with Robert Shalwitz (incorporated by reference to exhibit 10.20 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.16†	Amended and Restated Partial Recourse Promissory Note, dated June 15, 2013, with Robert Shalwitz (incorporated by reference to exhibit 10.21 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.17†	Forgiveness and Release Agreement with Robert Shalwitz, dated January 30, 2014, (incorporated by reference to exhibit 10.22 to the Company's Registration Statement on Form S-1 (333-193969), filed on February 14, 2014)
10.18†	Offer Letter with Bradley Maroni, M.D., dated July 21, 2014 (incorporated by reference to exhibit 10.17 to the Company's 10-K for the year ending December 31, 2014 and filed on March 4, 2015)
10.19†	Form of Non-Statutory Stock Option Agreement for officers (incorporated by reference to exhibit 10.24 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.20†	Form of Non-Statutory Stock Option Agreement for non-employee directors (incorporated by reference to exhibit 10.25 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.21†	Non-Employee Director Compensation Program (incorporated by reference to exhibit 10.26 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.22†	Form of Executive Severance Agreement for officers (incorporated by reference to exhibit 10.27 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.23†	2014 Incentive Plan (incorporated by reference to exhibit 10.29 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.24†	2014 Employee Stock Purchase Plan (incorporated by reference to exhibit 10.30 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.25†	Cash Incentive Plan (incorporated by reference to exhibit 10.31 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.26#	Master Services Agreement by and between Evonik Corporation and Akebia Therapeutics, Inc., dated February 28, 2014 (incorporated by reference to exhibit 10.32 to the Company's Registration Statement on Form S-1/A (333-193969), filed on March 4, 2014)
10.27†	Form of Restricted Stock Unit Award Agreement under 2014 Incentive Plan (incorporated by reference to exhibit 10.26 to the Company's 10-K for the year ending December 31, 2014 and filed on March 4, 2015)

10.28#	Master Services Agreement, between Akebia Therapeutics, Inc., and Quintiles, Inc., dated as of June 8, 2015 (incorporated by reference to exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed on August 11, 2015)
10.29#*	Collaboration Agreement, between Akebia Therapeutics, Inc. and Mitsubishi Tanabe Pharma Corporation, dated December 11, 2015
21.1*	List of Subsidiaries
23.1*	Consent of Ernst & Young LLP
31.1*	Certification of Principal Executive Officer Required Under Rule 13a-14(a) of the Securities Exchange Act of 1934, as amended
31.2*	Certification of Principal Financial Officer Required Under Rule 13a-14(a) of the Securities Exchange Act of 1934, as amended
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. 1350
99.1	Press Release issued by Akebia Therapeutics, Inc. on March 10, 2016 (furnished herewith)
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document

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Exhibit Number	Description of Exhibit
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	XBRL Taxonomy Extension Labels Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document

* Filed, or submitted electronically, herewith
† Indicates management contract or compensatory plan
# Indicates portions of the exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment