Akebia Therapeutics, Inc.
Form 10-K
March 06, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

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

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

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

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

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

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

Large accelerated filer Accelerated filer

Non-accelerated filer (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

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, 2016, was $264,950,830.

The number of shares of Registrant's Common Stock outstanding as of March 1, 2017 was 38,829,563.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement for our 2017 Annual Meeting of Stockholders scheduled to be held June 15, 2017 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," 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) our PRO_2TECT and $INNO_2$VATE clinical programs, and (2) our Phase 2 hyporesponder study, (3) our Phase 3 TIW dosing study, (4) submission of marketing applications for vadadustat, and (5) filing an IND for AKB-5169;
- enrollment in the PRO_2TECT and $INNO_2$VATE clinical programs;
- our development program for vadadustat in Japan;
- our anticipated funding from our collaborations;
- our plans to seek another geographic collaboration for the development and commercialization of vadadustat;
- our development plans with respect to vadadustat and our other product candidates;
- the timing or likelihood of regulatory filings and approvals, including any required post-marketing testing or any labeling and other restrictions;
- 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;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses (including those associated with the PRO_2TECT and $INNO_2$VATE clinical programs), 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.

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 uncertainty and may prove inaccurate. 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.

PART I

Item 1. Business

Overview

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

HIF, a pathway involving hundreds of genes, is responsible for orchestrating 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 red blood cell production, a normal biological process known as erythropoiesis, and enhancement of the delivery of iron to the bone marrow to support erythropoiesis. The significance of the HIF pathway was recognized by the 2016 Albert Lasker Basic Medical Research Award, which honored the three physician-scientists who discovered the HIF pathway and elucidated this primary oxygen sensing mechanism that is essential for survival. HIF protein is constantly being produced under normal oxygen conditions, but is quickly degraded by prolyl hydroxylases, or PH. Under hypoxic conditions, HIF-PH's are inhibited, allowing HIF to stimulate erythropoiesis. These findings have opened up new possibilities for developing therapeutics, such as HIF-PHI, which have the potential to treat many diseases.

Our lead product candidate, vadadustat, a HIF-PH inhibitor in Phase 3 development for the treatment of anemia of CKD. Anemia is a serious medical condition in which blood is deficient in hemoglobin, which is critical for delivering oxygen to organs and tissue. 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.

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 CKD is currently treated by injectable recombinant erythropoiesis-stimulating agents, or rESAs, such as EPOGEN® and Aranesp®, as well as with iron supplementation or red blood cell transfusion. Based on the reported revenues of companies that market and sell rESAs, global sales of injectable rESAs were estimated to be between $6.5 and $7.0 billion in 2015. The vast majority of these sales were for the treatment of anemia associated with renal disease.

rESAs deliver supra-physiological levels of exogenous erythropoietin, or EPO, to stimulate production of RBCs. While injectable rESAs may be effective in raising hemoglobin levels, they carry significant potential side effects, and need to be injected under the skin (subcutaneously) or into a vein (intravenously). In particular, injectable rESAs may lead to thrombosis, stroke, myocardial infarction and death. These safety concerns, which became evident starting in 2006, have led to a significant reduction in the use of injectable rESAs. Today, anemia is either not treated or inadequately treated in the majority of non-dialysis dependent (NDD) CKD patients. We believe that novel treatment options that address these concerns are needed and would have significant market potential. Because it mimics the body's natural adaptive response to hypoxia, vadadustat's HIF-PH inhibition may raise hemoglobin levels without

causing supra-physiological levels of EPO.

Vadadustat has the potential to set a new standard of care for the treatment of anemia in CKD. Early clinical studies of vadadustat demonstrated that diurnal variation of EPO was maintained resulting in predictable increases in hemoglobin in normal human volunteers and similar results were seen in NDD-CKD. These data led us to the design of our Phase 3 clinical program. The vadadustat Phase 3 program in NDD-CKD patients with anemia, called PRO_2TECT, and in dialysis dependent (DD) CKD patients with anemia, called $INNO_2VATE$, is designed to enroll approximately 5,700 patients evaluating once daily oral dosing of vadadustat against an rESA active comparator, darbepoetin alfa. The enrollment numbers and the completion of the Phase 3 program will be driven by the rate of major adverse cardiovascular events, or MACE. In December 2015 the first patient was dosed in PRO_2TECT, and the first patient was dosed in $INNO_2VATE$ in August 2016. We plan to initiate a Phase 3 study in the second half of 2017 to evaluate three-times weekly dosing of vadadustat in approximately 300 DD-CKD patients receiving hemodialysis using the same active comparator, darbepoetin alfa. We currently anticipate submitting marketing applications for the treatment of anemia associated with CKD in the United States and Europe in 2019.

If vadadustat is approved by the United States Food and Drug Administration, or FDA, we plan to establish our own commercial organization in the United States while leveraging our collaboration with Otsuka Pharmaceutical Co. Ltd., or Otsuka, and its well-established commercial organization. In Japan and other countries in Asia, we plan to commercialize vadadustat through our

collaboration with Mitsubishi Tanabe Pharma Corporation, or MTPC, and intend to seek one or more collaborators to commercialize vadadustat in Europe and other markets.

In addition to vadadustat, we are developing a HIF-based portfolio of product candidates that target serious diseases of high unmet need. Our portfolio includes product candidates developed internally, such as AKB-6899, as well as in-licensed product candidates, such as AKB-5169. AKB-6899 has demonstrated a robust hemoglobin response in early preclinical studies, and we plan to further investigate its potential in multiple preclinical models of anemia and assess next steps based on these data. In February 2017, we signed an agreement with Janssen Pharmaceutica NV, or Janssen, for access to an extensive library of well-characterized HIF pathway compounds with potential applications across multiple therapeutic areas. The lead compound, AKB-5169, is a differentiated preclinical compound in development as an oral treatment for inflammatory bowel disease (IBD) and we intend to complete further preclinical development with the goal of an Investigational New Drug application with the FDA in 2018.

Our Product Pipeline

Anemia Overview

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

Chronic Kidney Disease

CKD, a common cause of anemia, is a condition in which the kidneys are progressively damaged to the point that they cannot properly filter the blood circulating in the body. This damage causes waste products to build up in the patient's blood leading to other health problems, including anemia, cardiovascular disease and bone disease. CKD patients are classified by the degree of their loss of kidney function as measured by the glomerular filtration rate, or GFR, and the level of protein in the urine, referred to as albuminuria. As 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, including diabetes mellitus and hypertension. The prevalence and incidence of CKD is increasing in all segments of the United States 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 countries, such as Japan, China and India, where the numbers of elderly people are increasing. This effect will be enhanced further if the growth in the prevalence of hypertension and diabetes persists along with the associated increased risk of stroke and cardiovascular disease and access to treatment does not improve.

Current Treatments Leave a Substantial Unmet Need

Injectable 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. In 2006, data on the risks of rESA use among these patients became available, forcing physicians to balance serious safety concerns against the efficacy of rESAs. The well-documented safety concerns[1] associated with the

[1] Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339(9):584-590.

Pfeffer MA, Burdmann EA, Chen CY, Coopper ME, de Zeeuw D, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361(21):2019-2032.

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

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use of injectable rESAs include increased cardiovascular risk, and the potential for increased rate of tumor progression in patients with cancer.

As a result of the safety concerns related to rESA use, patients live with lower hemoglobin levels, higher rates of RBC transfusions, and receive more intravenous iron, or IV iron, to treat anemia associated with CKD. The increased use of IV iron and RBC transfusions, also subject patients 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, the potential transmission of blood-borne pathogens and iron overload with chronic transfusions. The risks of IV iron use include hypersensitivity reactions, including fatal anaphylactic-type reactions.

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

Vadadustat Has the Potential to Set a New Standard of Care

We believe that, based on the HIF-PH inhibition mechanism of action and clinical data to date, vadadustat has the potential to set a new standard of care for the treatment of anemia secondary to CKD. Below is a summary of the clinical findings and further details are included under the “Vadadustat Clinical Development Overview” section below.

- Vadadustat maintained a normal diurnal variation of EPO. In studies in healthy volunteers and CKD patients, vadadustat acted by simulating the body’s natural response to hypoxia and maintained a normal diurnal variation in EPO without causing supra-physiological levels of EPO.
- Vadadustat significantly increased and maintained hemoglobin levels. Our Phase 2 studies in CKD patients with anemia demonstrated that vadadustat significantly increased and/or maintained hemoglobin levels.

- Vadadustat has been studied as a once-daily or three times weekly oral dose. Phase 2 studies have shown that vadadustat can be orally dosed once daily in NDD-CKD patients over 20 weeks of dosing. In addition, a Phase 2 clinical study in DD-CKD patients demonstrated once daily or three times weekly oral dosing of vadadustat maintained stable hemoglobin levels in patients converting from ESA therapy over 16 weeks.
- Vadadustat improved mobilization of iron supply to the bone marrow for RBC production. In Phase 2 clinical studies, vadadustat demonstrated favorable changes in iron parameters (e.g. decrease in hepcidin and ferritin and increase in total iron binding capacity and transferrin saturation) consistent with improved iron mobilization to the bone marrow to support erythropoiesis in NDD-CKD and DD-CKD patients.

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

HIF-PH Inhibition: A Different Mechanism of Action That Mimics the Body's Natural Physiologic Response to Hypoxia

Vadadustat is designed to work by a mechanism of action that differs from injectable rESAs. This mechanism of action is referred to as HIF-PH inhibition. 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 body's 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.

When stabilized, HIFa 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.

Vadadustat Clinical Development Overview

In the 15 studies of vadadustat completed to date, the safety, tolerability, pharmacokinetic and pharmacodynamic properties of vadadustat have been demonstrated:

- nine completed Phase 1 studies in healthy volunteers (CI 0001, CI 0002, CI 0006, CI 0008, CI 0010, CI 0012, CI 0013, CI-0019, and CI-0020);
- one completed Phase 1 study in DD-CKD patients with anemia (CI 0009);
- three completed Phase 2a studies in NDD-CKD patients with anemia (CI 0003, CI 0004, and CI 0005);
-