Akebia Therapeutics, Inc.
Form 10-K
March 04, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

OR

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

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. ¨

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

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer x (Do not check if a 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, 2014, was $546,323,693.

The number of shares of Registrant's Common Stock outstanding as of February 28, 2015 was 20,370,624.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement for our 2015 Annual Meeting of Stockholders scheduled to be held June 10, 2015 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 (the "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) data from our recently completed Phase 2b study of AKB-6548 in non-dialysis patients with anemia related to chronic kidney disease (CKD), (2) commencement of a Phase 3 development program of AKB-6548, (3) submission of an NDA for AKB-6548 and (4) data from our Phase 2 clinical study of AKB-6548 in CKD patients undergoing dialysis;
- our plans to commercialize AKB-6548, if it is approved;
- our development plans with respect to AKB-6899;
- the timing or likelihood of regulatory filings and approvals, including any required post-marketing testing or any labeling and other restrictions;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expense, future revenue, capital requirements and needs for additional financing; and
- other risks and uncertainties, including those listed under Part II, 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.

NOTE REGARDING STOCK SPLIT

Unless otherwise indicated, all information in these 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, as well as any other stock-splits in historical periods.

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PART I

Item 1. Business

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 kidney disease. HIF is the primary regulator of the production of red blood cells, or RBCs, in the body and a potentially novel mechanism of treating anemia. We were incorporated in Delaware in 2007.

Our lead product candidate, AKB-6548, is being developed as a once-daily, oral therapy. We have successfully completed a Phase 2b study demonstrating that AKB-6548 can safely and predictably raise hemoglobin levels in non-dialysis patients with anemia related to chronic kidney disease, or CKD.

On October 27, 2014, we announced positive top-line results from our Phase 2b study of AKB-6548 in non-dialysis patients with anemia related to CKD, and we expect complete efficacy and safety data to be presented in the first half of 2015. We expect to initiate Phase 3 studies for anemia secondary to CKD in 2015 and anticipate submitting an NDA for AKB-6548 in the United States by 2019, if the Phase 3 data are favorable. We have also initiated Phase 2 clinical development for AKB-6548 for the treatment of anemia in patients undergoing dialysis, the second indication we will pursue. The results from that study are expected in the third quarter of 2015. We have also commenced discussions with European regulatory authorities in the first quarter of 2015, with the goal of potentially also submitting European marketing application(s). Also in the third quarter of 2014, we completed a thorough QT (TQT) study, demonstrating that AKB-6548 does not have an adverse effect on cardiac repolarization or conduction (i.e., negative TQT study).

Our preclinical candidate, AKB-6899, is a small molecule with minor structural differences from our lead compound AKB-6548. However, AKB-6899 has distinctive biochemical and physiological properties that may be beneficial for treatment of certain cancers. In several preclinical mouse models, AKB-6899 has been active in reducing tumor growth and development of metastases. Therefore, Investigational New Drug, or IND, enabling studies are being performed with the goal of opening an IND with the U.S. Food and Drug Administration (FDA) in 2015.

We own worldwide rights to our HIF-based product candidates, including AKB-6548. If approved by regulatory authorities, we plan to commercialize AKB-6548 in the United States ourselves and intend to seek one or more collaborators to commercialize the product candidate in additional markets.

Anemia is a serious medical condition in which blood is deficient in RBCs and hemoglobin, both of which are 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 protein erythropoiesis stimulating agents, or rESAs—including Epogen, Aranesp and Procrit—with iron supplementation or an RBC transfusion. Based on the reported revenues of companies that market and sell rESAs, we estimate that global sales of injectable rESAs were $6.3 billion in 2012, 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 also need to be delivered subcutaneously or intravenously. In particular, injectable rESAs may lead to thrombosis, stroke, myocardial infarction and death, and 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 CKD patients, and we believe that a safe, effective, oral therapeutic option will take significant market share and meaningfully grow the market in patients not requiring dialysis.

AKB-6548 works by a differentiated mechanism of action that we believe has the potential to be safer than that of injectable rESAs. 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, AKB-6548 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.

To date, AKB-6548 has been studied in ten clinical trials across three separate patient populations: healthy volunteers, patients with CKD stages 3, 4 and 5 (non-dialysis), and patients with end-stage renal disease (ESRD) on hemodialysis. Our Phase 2a trial enrolled 91 patients with anemia secondary to CKD, which showed significantly increased hemoglobin levels among subjects taking AKB-6548 compared to baseline in a dose-dependent manner across all treatment arms ($p < 0.0001$). No drug-related serious adverse events were reported, and dosing was well-tolerated. In addition, AKB-6548 was also shown to stabilize the iron supply to the bone marrow while improving hemoglobin production.

We recently completed a Phase 2b study demonstrating that AKB-6548 can safely and predictably raise hemoglobin levels in non-dialysis patients with anemia secondary to CKD. The results of this Phase 2b study support advancement into Phase 3 to further evaluate the efficacy and safety of AKB-6548 for the treatment of anemia in CKD patients not on dialysis. We plan to initiate Phase 3 global registration studies for AKB-6548 in patients with anemia secondary to CKD in 2015, positioning us to file for approval in the United States by 2019.

Given the burdens of the current standard of care and costs associated with administering an injectable rESA, we believe AKB-6548 is a promising alternative for the overall cost-effective treatment of anemia. We intend to commercialize AKB-6548 ourselves 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. We intend to seek one or more commercial collaborators for the development and commercialization of AKB 6548 outside the United States. We may also explore opportunities to expand AKB-6548 into additional markets not adequately addressed by injectable rESAs because of safety or dosing delivery issues.

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 former President of Genzyme Corporation’s renal division which grew to over $1 billion in annual revenue under his leadership, and is currently the 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 novel therapeutics for patients based on HIF biology and to commercialize products for patients with kidney disease, beginning with AKB-6548 for patients with anemia secondary to CKD. The key elements of our strategy are to:

- Complete the development of AKB-6548 for anemia secondary to CKD. We intend to initiate a Phase 3 development program in 2015 following our end of Phase 2 meeting with the United States Food and Drug Administration, or FDA.

- Obtain regulatory approval of AKB-6548 for anemia secondary to CKD in the United States, Europe and other markets. We plan to complete an end of Phase 2 meeting with the FDA and seek scientific advice from the European Medicines Agency, or EMA, to define the Phase 3 development program necessary to secure regulatory approval to market AKB-6548. We would expect to initiate Phase 3 trials for anemia secondary to CKD in 2015, and anticipate submitting an NDA for AKB-6548 in the United States by 2019 if the Phase 3 data are favorable.

- Commercialize AKB-6548 in the United States and other territories. We will establish a specialty sales and marketing organization to commercialize AKB-6548 in the United States. Outside of the United States, we intend to seek one or more commercial collaborators.

- Advance AKB-6899 into clinical development. We plan to advance AKB-6899, a second HIF-PH inhibitor product candidate, which we believe, based on preclinical testing, has the ability to increase EPO levels while reducing vascular endothelial growth factor, or VEGF, levels. We intend to file an Investigational New Drug, or IND, application and begin a Phase 1 trial to determine its potential use in oncology.

- Acquire or in-license additional nephrology products. We will look to diversity our pipeline with additional products that would be prescribed by nephrologists.

We may enter into strategic collaborations to fully realize elements of our strategy.

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, and carbon dioxide from, 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 has a number of potential causes, including nutritional deficiencies, iron deficiency, bone marrow disease, medications, and abnormalities in EPO production or sensitivity. Common causes of anemia due to inadequate EPO production include CKD, age, heart failure, inflammatory diseases, cancer and other critical illnesses.

Untreated anemia is associated with chronic fatigue, increased risk of progression of multiple diseases, and death. This morbidity and mortality risk has been clearly shown in the CKD population, where in patients age 66 and older, anemic patients with mid-stage CKD (Stage 3) have a 149% increase in cardiovascular events and patients with severe CKD (Stage 4 and 5) have a 24% increase in cardiovascular events versus non-anemic patients in the same group, according to a paper published in 2006 in the peer-reviewed journal Blood. Similarly, compared to non-anemic patients, anemia increases the mortality rate by 199% in mid-stage CKD, and 59% in severe CKD. Successful treatment of anemia significantly improves patients' quality of life, especially with respect to vitality, fatigue and physical function. In addition, patients whose anemia has been successfully treated have demonstrated lower mortality rates, less frequent hospitalization, and decreases in cardiovascular morbidity.

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 can cause waste products to build up in the patient's blood and can lead to other health problems, including cardiovascular disease, anemia, 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 protein levels in urine. As seen 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, as shown below. Risk factors for the development of CKD include underlying disease (hypertension, diabetes 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 from May 2013, projected worldwide population changes suggest that the potential number of cases of kidney disease, specifically end-stage, will increase disproportionately in developing countries, such as 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 improves.

The prevalence and severity of anemia in CKD increases as renal function deteriorates. Three variables which may combine to accentuate and accelerate anemia as CKD progresses include:

- 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 in the transport of oxygen.

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, including epoetin alfa, epoetin beta, and darbepoetin alfa, 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 $6.3 billion in 2012, as compared to an estimated $12 billion in 2006. Of these 2012

revenues, an estimated $3.4 billion were generated in the United States, 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. The percentage of dialysis patients in the United States receiving IV iron has increased from 50% in 1999 to 71% during in 2011. Among U.S. patients receiving IV iron, the mean monthly dose has also increased by 21%. Despite the increased use of IV iron and the rate of RBC transfusions, patients are still 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, transmission of blood-borne pathogens, impairment of venous access in CKD patients (not on dialysis) and iron overload with chronic transfusions. The risks of IV iron include hypersensitivity reactions, such as 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 role of normalized hemoglobin levels. The strongest correlation of adverse outcomes in the post-hoc analyses has been to the level of the injectable rESA dose, not the hemoglobin level achieved. All of the studies analyzed to date demonstrate that both non-dialysis and dialysis-dependent CKD subjects who achieved normal hemoglobin levels had better clinical outcomes than subjects assigned to higher hemoglobin targets who failed to reach the assigned level despite increasing doses of injectable rESAs. In addition, CKD patients who were able to achieve and maintain normal hemoglobin levels through means other than the use of injectable rESAs (such as hypoxia or iron supplementation) experienced fewer cardiovascular events and reduced morbidity and mortality. Recent studies of injectable rESA use in various preclinical models (including non-human primates) also showed that the frequency of mortality and thrombotic events cannot be explained solely by the achieved higher hemoglobin levels, rather, they are related to the dose, dose frequency, and dose duration of injectable rESAs.

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 high injectable rESA dose in an effort to reach the target level.

This chart is consistent with the previous chart as it shows that patients with high hemoglobin levels on low injectable rESA doses have better outcomes than patients with high injectable rESA doses and low hemoglobin levels. Therefore, high injectable rESA doses, not high hemoglobin levels, appear to be correlated most strongly 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 responses 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. 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 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 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 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. The collective preclinical and clinical data support a critical re-thinking on the best approach to treating anemia, the appropriate and safe hemoglobin target, and the right time to initiate treatment for these patients.

AKB-6548 as a potential solution

We are developing our lead product candidate, AKB-6548, to be a best-in-class HIF-PH inhibitor for the treatment of anemia secondary to CKD. AKB-6548 may potentially offer:

- Predictable, meaningful and sustained improvements in hemoglobin levels;

- 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; 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

AKB-6548 is designed to work by a mechanism of action that differs from injectable rESAs. This novel mechanism of action is referred to as a HIF-PH inhibitor. 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. In this way, AKB-6548 achieves a controlled, adaptive stimulation of the erythropoietic system in the body. This activation of the whole system results in both increased RBC production and improved stabilization of the bone marrow's iron supply, which ensures the proper incorporation of iron into hemoglobin necessary for RBC production. This adaptive simulation is very similar to the natural response that is induced when a person ascends in altitude. At higher altitudes, low levels of oxygen circulating in the blood stream lead to reduced HIF-PH activity in relevant cells in the kidney and liver. The reduced HIF-PH activity stabilizes and increases levels of HIFa proteins (HIF1a and HIF2a) in these cells. For most cells, the stabilization of HIF2a is greater than that of HIF1a, ultimately leading to an increase in EPO secretion and a subsequent increase in RBC production.

HIF-PH inhibitors work by blocking the effect of the prolyl-hydroxylase enzymes, which promote the breakdown of HIFa proteins. As the breakdown is inhibited, the level of these HIFa proteins increases in cells. These HIFs are the primary protein mediators that enable the body and all of its individual cells to adapt to changes in levels of oxygen. Both HIF1a and HIF2a proteins are consistently produced and their 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 and the body 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 genetic signal for the production of EPO and several other proteins. The HIF-PH inhibitors increase HIFa levels in much the same way that a reduction in oxygen increases HIFa levels by inhibiting the HIF-PH enzymes in the body. With continued stabilization of HIFa (either by staying at higher altitude or by daily dosing of the HIF-PH inhibitor), the level of hemoglobin and RBCs will rise in order to increase the amount of oxygen circulating in the blood. In this way, once-daily dosing of AKB-6548 may have the potential to restore the normal level of EPO for a patient with anemia.

AKB-6548, our lead compound in development, works by inhibiting HIF-PH, leading to stabilization and increased levels of HIFa, and improved production of hemoglobin and RBCs, while maintaining normal levels of EPO in patients. In addition, we believe that AKB-6548'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 an enhancement in the normal diurnal variation 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 AKB-6548 has compelling clinical data demonstrating a best-in-class profile with several potential safety and efficacy advantages over current injectable rESA therapy for the treatment of anemia secondary to CKD.

- AKB-6548 significantly increases hemoglobin in anemic CKD patients. We have successfully completed two Phase 2 trials, in which AKB-6548 significantly increased hemoglobin levels. In the first study (CI-0005), AKB-6548 was demonstrated to raise hemoglobin in a dose-dependent manner compared to baseline and across all treatment arms ($p < 0.0001$). In the second Phase 2 study (CI-0007), AKB-6548 effectively increased hemoglobin while the dose was adjusted in accordance with a dosing algorithm ($p = 0.0001$ compared to placebo). The purpose of the algorithm was

to minimize the frequency of increases in hemoglobin ³ 13.0 g/dL. Only 4.3% of subjects on AKB-6548 had single excursions ³ 13.0 g/dL. Further, AKB-6548 provides a physiologic reticulocyte, or newly formed RBC, response, which leads to a more gradual and consistent increase in hemoglobin levels than what is

seen with injectable rESA therapies, reducing the likelihood of a patient's hemoglobin to rising to levels that cause concern.

- AKB-6548 may have the potential to restore the normal diurnal variation of EPO for a patient with anemia in a way that an injectable rESA cannot. Instead of binding directly to and saturating the EPO receptor for prolonged periods of time as is the case with current injectable rESA treatments, AKB-6548 acts by simulating the body's natural response to hypoxia that is carried out by stabilization of HIFa. We believe the manner in which AKB-6548 works permits a more prominent HIF2a response (as naturally occurs with a moderate increase in altitude) and there is an enhancement in the normal diurnal variation in EPO, which is the normal rise and fall of EPO during the each day, without continuous elevation of EPO levels. The graph below illustrates the EPO levels that are obtained with AKB-6548 compared with doses of Aranesp and Epogen.

- Oral, once-daily dosing. Once daily, oral dosing of AKB-6548 offers improved convenience for patients as compared to injectable rESAs. This convenience may increase access to anemia therapy for the largely underserved population of patients with anemia secondary to CKD who are not yet on dialysis and for patients with other forms of anemia. AKB-6548 offers the potential of flexible oral dosing that provides a more gradual and reliable means of titration than that of injectable rESAs.

- Ability to stabilize the iron supply to the bone marrow while improving hemoglobin production. In clinical trials, AKB-6548 has demonstrated dose-related increases in iron mobilization and total iron binding capacity. These results indicate that AKB-6548 will stabilize the iron supply to the bone marrow while improving hemoglobin production and should improve EPO responsiveness. As a result, unlike injectable rESAs which have no effect on iron mobilization, AKB-6548 offers the added potential benefit of reducing the amount of supplemental iron required by anemia patients.

- Differentiated safety profile. AKB-6548's novel mechanism of action and dosing profile offer the opportunity to potentially avoid the black box label ascribed to injectable rESAs. In our recently completed Phase 2b study, AKBA-6548 was generally well tolerated with no safety concern identified.

AKB-6548 Clinical Development Overview

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

An IND was filed for AKB-6548 for the treatment of anemia associated with CKD and chronic renal failure on July 17, 2009. Under the IND, we may investigate AKB-6548 in subjects who are not on dialysis and in subjects who are on dialysis. To date, AKB-6548 has been studied in ten clinical trials across three separate patient populations: healthy volunteers, patients with CKD stages 3, 4, and 5 (non-dialysis), and patients with end-stage renal disease (ESRD) on hemodialysis. These clinical trials consisted of one Phase 2b clinical trial, four Phase 2a clinical trials and five Phase 1 clinical trials. The early clinical studies (CI-0001 through CI-0004) for AKB-6548 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 AKB-6548 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, AKB-6548 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 adverse events, or AEs, in our eight clinical trials were gastro-intestinal disorders, including diarrhea, nausea and constipation. In our CI-0001 trial, there was one subject who had diarrhea that was considered potentially related to the study drug. In our CI-0002 trial, the potentially drug-related TEAEs were gastroesophageal reflux and dyspepsia, each reported in separate subjects. In our CI-0006 trial, three of the eight subjects in the capsule group reported potentially drug-related AEs (nausea in two subjects and headache and dizziness in one subject each), and one of the eight subjects in the tablet group reported potentially drug-related headache and dizziness. In our CI-0003 trial, five subjects experienced AEs that were considered potentially drug-related. Two subjects had nausea. Other potentially drug-related AEs that were noted once included tachycardia, vomiting, pyrexia, upper respiratory tract infection, hypomagnesemia, myalgia, headache, somnolence, tremor, oropharyngeal pain, cold sweat and hypotension. In our CI-0004 trial, three subjects had potentially drug-related TEAEs, including nausea, chills, peripheral neuropathy, peripheral sensory neuropathy and muscle spasms. In our CI-0005 trial, the most frequently reported TEAEs considered to be potentially drug-related were gastrointestinal disorders, including one subject with abdominal discomfort, three subjects with constipation, one subject with diarrhea

and two subjects with nausea. Other one-time events in the CI-0005 trial that were considered to be potentially drug-related included neutropenia, cardiac palpitations, decreased transferrin saturation, muscle spasms, dizziness, pollakiuria, hypertension and abnormal hair texture.

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

Study	Study Design Subject	Design (Endpoint)	Dose, Duration [1]	Subjects Treated AKB-6548	Placebo	Key Findings
Phase 1						
CI-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)	AKB 6548 was well tolerated, and dose responsive increases in EPO levels were demonstrated following a single dose. Half-life of the compound was measured at approximately 4.8 hours. Ten subjects had an adverse event (AE) (seven in the AKB 6548 group and three in the placebo group). No serious adverse events (SAEs) were reported.
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)	AKB 6548 was well tolerated, and dose responsive increases in reticulocytes and hemoglobin levels were demonstrated. It was also shown that EPO levels returned to baseline by 24 hours following each dose. 26 subjects reported a treatment-emergent adverse event (TEAE). These were evenly distributed across dosing groups. No SAEs were reported.
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	Both capsules and tablets were well tolerated following a single dose, and shown to be bioequivalent. Six subjects had AEs considered related to study drug. No SAEs were reported.
CI-0008	Healthy volunteers	Mass Balance (Radioactivity/ PK)	650 mg; single dose (100 mCi ^{14}C-AKB-6548)	6	0	The drug was generally well tolerated during this study. There were no SAEs and no subjects dropped out of the study. 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 AKB 6548, followed by the AKB 6548-O-Glucuronide (~15%) and a very low contribution (<1%) coming

from the AKB 6548-Acyl-Glucuronide.

Study Design				Subjects Treated		
Study	Subject	Design (Endpoint)	Dose, Duration [1]	AKB-6548	Placebo	Key Findings
CI-0009	End-stage renal disease (ESRD)	Randomized, crossover, pharmacokinetic study with 72 hour wash-out between successive dosing (PK/Safety and tolerability of subjects on chronic hemodialysis)	450 mg dose four hours prior to start of a hemodialysis session; 450 mg dose 2 hours after completion of a different dialysis session	12	0	During the study, dosing of the drug was well tolerated. No SAEs were reported during dosing and over the 48-hr in-house observation period after each of the pre-dialysis and post-dialysis dose administrations, although one subject experienced an exacerbation of a concurrent diabetic foot ulcer resulting in 2 reported SAEs during the follow-up period, 7 days after the last sample collection. These 2 events were considered unrelated to the study drug. The timing of administration of AKB-6548 doses (pre- or post-hemodialysis) did not markedly affect pharmacokinetics of AKB 6548 and two measured glucuronide metabolites. The hemodialysis procedure had minimal impact on the clearance of AKB 6548.
CI-0010	Healthy volunteers	Randomized, partially double-blind, single-dose, 4 treatment, 4 period, 4 sequence crossover study to evaluate the effect of AKB 6548 on cardiac repolarization intervals (Thorough QTc Study)	600 mg AKB-6548 tablet; 1200 mg AKB-6548 tablet; placebo tablets, 400 mg moxifloxacin tablet	49	48	In general, study drug was well tolerated with no SAEs reported. AKB 6548 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.
Phase 2						
CI-0003	CKD, Stages 3 & 4	Open-label, fed (Safety/PK/PD)	500 mg; single dose	22	0	Following a single dose of 500 mg of AKB 6548, the changes in EPO levels followed a 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 half-life was modestly longer at 7.9 hours. Dosing was well

tolerated. Five subjects had AEs considered related to study drug. No SAEs were reported.

Study	Study Design Subject	Design (Endpoint)	Dose, Duration [1]	Subjects Treated AKB-6548	Placebo	Key Findings
CI-0004	CKD, Stages 3 & 4	Open-label (Safety/Change in Hgb, hematocrit, reticulocytes)	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	In this study, subjects started at 300 mg (CKD 4) or 400 mg (CKD 3). Dose adjustments could be made weekly based on reticulocyte count and hemoglobin data. Dosing was well tolerated. Average hemoglobin levels rose from 9.91 g/dL at baseline to 10.54 g/dL by Day 29. Three subjects had AEs considered related to study drug. No SAEs were reported.
CI-0005	CKD, Stages 3, 4 & 5, not on dialysis	Double-blind, placebo-controlled (Mean absolute change in Hgb between the pre-dose 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	Dosing was well tolerated. AKB 6548 significantly increased hemoglobin levels in subjects compared to baseline in all dose groups and compared to placebo. The hemoglobin increase occurred without increasing pre-dose EPO levels (prior to daily AKB-6548 dose). Ten subjects had AEs considered related to study drug. There were eight reported SAEs in separated subjects which were all considered unrelated to study drug.
CI-0007	CKD, Stages 3, 4 & 5, 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 and AKB 6548 was generally well tolerated, confirming that the once-daily, oral therapy can successfully increase and maintain hemoglobin (Hgb) levels. 54.9% of patients who received AKB 6548 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). TEAEs with AKB 6548 were consistent with those reported in

past studies and were well balanced overall between the active and placebo treatment groups (74.6% and 73.6%, respectively). There was a higher incidence of SAEs reported in the active treatment group versus the placebo group (23.9% and 15.3%, respectively), the most common being renal-related. Of the 49 SAEs reported in the active treatment group, one was considered probably related to active treatment and two were considered possibly related, including one death. There were two additional deaths in the treatment group, neither of which was considered drug-related.

[1] All doses were administered orally, once-daily.

CI-0005: Positive Phase 2a Proof of Concept Trial

CI-0005 was designed to confirm the findings of the early clinical studies and to demonstrate efficacy in CKD patients. In November 2012, we presented at the American Society of Nephrology the results of a randomized, double-blind, placebo controlled trial of AKB-6548 in patients with CKD stages 3, 4 and 5 (not on dialysis) to evaluate the change in hemoglobin levels over 42 days at multiple dose levels. The study enrolled 93 patients with CKD stages 3, 4, or 5 (not on dialysis) who initiated treatment with either placebo or AKB-6548 in the following dose groups: 240 mg, 370 mg, 500 mg, or 630 mg once-daily for 42 days. Depending upon hemoglobin response, patients may have had their initial dose titrated to avoid too rapid of a rise in hemoglobin levels.

The primary endpoint for the trial was the mean absolute change in hemoglobin from baseline. As shown in the first graphic below, the study results show all doses of AKB-6548 increased hemoglobin significantly compared with placebo. A one-way analysis of variance, or ANOVA, test showed a statistically significant increase in mean absolute hemoglobin from baseline to week 6 for treatment compared with placebo ($p<0.0001$). The 95% simultaneous confidence limits for the four AKB-6548 treatment groups all showed significant increases in mean absolute hemoglobin from baseline to week 6.

At Day 42, AKB-6548 significantly increased hemoglobin levels in a dose-dependent manner compared to baseline in all dose groups. Important findings included:

1. AKB-6548 treated patients experienced a statistically significant mean increase in hemoglobin, ranging from 0.7 to 1.4 g/dL by Day 42, while placebo-treated patients experienced a small mean decrease in hemoglobin of 0.1 g/dL. The average baseline hemoglobin level was 9.8 g/dL.

2. No patient's measured hemoglobin level exceeded 13 g/dL throughout the study period.

3. The dose-dependent increases in hemoglobin occurred even though 26% of patients in the 630 mg dose and 11% of patients in the 500 mg dose decreased their dose, per protocol, as a result of a hemoglobin increase of greater than 1.5 g/dL or more by Day 28.

4. The increase in hemoglobin levels occurred without increasing pre-dose EPO levels (prior to daily AKB-6548 dose), demonstrating that AKB-6548 is able to improve RBC production without chronically elevating the body's EPO levels.

5. The increase in hemoglobin levels was preceded by an increase in reticulocytes showing that an increase in hemoglobin levels is a result of a physiologic increase in RBC production.

6. A dose-related increase in TIBC indicated enhanced ability to stabilize the iron supply to the bone marrow while improving hemoglobin production, as shown below with the dose-dependent increase in TIBC.

AKB-6548 was generally well tolerated in the 91 subjects who received study drug. In total, 45 subjects had an AE: 34 (47.2%) in the AKB-6548 groups and 11 (57.9%) in the placebo group. AEs were evenly distributed across the dosing groups with no apparent dose related effect. Ten subjects (13.9%) treated with AKB-6548 and one placebo subject (5.3%) had AEs that were considered study drug related.

There were eight SAEs in separate subjects which were all considered unrelated to the study drug by the study investigators; seven in the AKB-6548 groups (9.7%) and one in the placebo group (5.3%). 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, who we believe received only three or four doses of study drug, died after being hospitalized for uremia. The subject’s death occurred several days into her hospitalization following an in-hospital procedure when she developed sustained ventricular tachycardia and cardiac arrest. The subject’s death was not considered to be related to AKB-6548. All other subjects recovered.

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. AKB-6548 provides for the ability to induce a more prominent HIF2a response, and consistent with this mechanism, no statistically significant change in VEGF levels were observed from baseline for any of the AKB-6548 dose groups.

We also found no statistically significant change in inflammation (C-reactive protein), renal function (Cystatin-C), heart rate, blood pressure and EKG values (including QT assessments).

Phase 2b Study (CI-0007)

We have completed a Phase 2b study of AKB-6548 in subjects with anemia (hemoglobin £ 10.5 g/dL) secondary to CKD not requiring dialysis. This double-blind, randomized, placebo controlled study evaluated the efficacy and safety of AKB-6548 in 210 subjects across 62 U.S. sites. The study enrolled patients based on their prior treatment with rESAs: naïve (never received rESA therapy), previously treated with rESAs, and actively treated with rESAs (previous history of hemoglobin £ 10.5 g/dL). Patients initiated treatment with either 450mg of AKB-6548 or placebo once-daily for 20 weeks. The dose of AKB-6548 was adjusted in accordance with the patient's hemoglobin response. The primary purpose of this study was to demonstrate an adaptive approach to dosing AKB-6548 that would enable subjects to appropriately raise their hemoglobin from baseline without excessive excursions to ³ 13.0 g/dL. Subjects were extensively evaluated for clinical and laboratory safety, changes in specific biomarkers, and changes in quality of life and neuro-cognitive outcomes.

Patients were assigned in a double-blind fashion in a 2:1 ratio to either AKB-6548 or placebo. After initiating treatment at 450 mg, the dose was adjusted in accordance with the protocol defined "Dose Adjustment Guidelines and Algorithm."

The primary endpoint (determined from values at Weeks 19 and 20) of this study was the percent of subjects who either (i) achieve a mean hemoglobin of ³ 11.0 g/dL, or (ii) increase their hemoglobin by ³ 1.2 g/dL over their pre-dose average hemoglobin between screening and baseline. Subjects who received injectable rESA or transfusion rescue were counted as treatment failures and subjects receiving transfusion for a non-rescue reason were removed from the primary analysis. Treatment with AKB-6548 was very effective, compared to placebo, in achieving the primary endpoint ($p<0.0001$).

The results from this study will enable Akebia to determine the optimal dosage, including tablet size and number of tablets per dose, and dose adjustment for the Phase 3 studies. Preliminary analysis indicates that the range of doses will not be significantly changed, and the algorithm was effective at achieving and maintaining the desired response in

hemoglobin as designed in the primary outcome (the algorithm will be subject to review and acceptance by FDA and other regulatory authorities). The algorithm was also designed to help minimize hemoglobin fluctuation and reduce the frequency of excessive excursions in hemoglobin. Only 4.3% of subjects receiving AKB-6548 had a hemoglobin excursion ³ 13.0 g/dL.

Patients were also analyzed for safety, including AEs, vital signs, electrocardiograms, and laboratory assay results. AKB-6548 was generally well tolerated with similar percentages of subjects experiencing adverse events in AKB-6548 treated and placebo groups. There was an increase in renal (kidney) related serious adverse events reported in the AKB-6548 treated subjects (AKB-6548 9.4% vs. placebo 2.8%), however, the number of subjects requiring dialysis, an objective measure of the severity of renal disease, was somewhat less in the AKB-6548 treated subjects (AKB-6548 8.0% vs. placebo 9.7%). Overall adverse events for renal and urinary disorders was balanced (AKB-6548 14.5% vs. placebo 13.9%). The disparity in renal serious adverse events was likely related to differences in reporting between investigators (reasons included proceeding to dialysis in association with a serious adverse event that was not reported in the renal category, or proceeding to dialysis without being considered a serious adverse event). Other differences, favoring either AKB-6548 or placebo, in adverse events were as follows: nausea and diarrhea (AKB-6548 10.1% vs. placebo 4.2%); gastrointestinal hemorrhage (AKB-6548 0.0% vs. placebo 5.6%); upper respiratory tract infection (AKB-6548 1.4% vs. placebo 6.9%); hyperkalemia (AKB-6548 5.1% vs. placebo 0.0%); and hypertension (AKB-6548 8.0% vs. placebo 2.8%). There were three deaths in AKB-6548 treated subjects. This was the expected number of subject deaths based on previous studies in similar populations.

Additional assessments conducted during our Phase 2b study include: iron metabolism (changes from baseline in iron, transferrin saturation (TSAT), TIBC, and ferritin); the dose of iron replacement needed to maintain iron levels; actual values and change from baseline in reticulocyte hemoglobin content, HbA1c, and lipids; functional biomarkers; concentration measurements of AKB-6548 and its glucuronide metabolite; and measures of patient reported outcomes. These will be reported in various scientific sessions in 2015, including the World Congress of Nephrology meeting in March 2015.

Ongoing and Planned Clinical Trials

Study of AKB-6548 in Dialysis Patients (CI-0011)

We are currently enrolling patients in a multiple dose, open label Phase 2 study in approximately 90 subjects (30 per cohort) on dialysis with anemia secondary to CKD. The primary endpoint will compare the change in hemoglobin from baseline for three different dosing regimens of AKB-6548: 1) 300 mg per dose administered once daily; 2) 450 mg administered once daily; and, 3) 450 mg administered three times per week. The first analysis of change in hemoglobin will be conducted at Week 8, and the second analysis at Week 16 will assess the change in hemoglobin with dose adjustment starting at Week 8. Key secondary endpoints will include (i) the safety of AKB-6548 in ESRD subjects on dialysis; (ii) the total dose of IV iron therapy for the eight weeks prior to baseline to the first (Weeks 1-8) and second (Weeks 9-16) eight weeks of treatment; and (iii) the effect of dialysis on the pharmacokinetics of AKB-6548. The first two cohorts (300 mg and 450 mg dose administered once daily, respectively) have been fully enrolled, and we have initiated enrollment in the third cohort. Thus far, dosing with AKB-6548 has been well tolerated. We plan to report the final results from this study in the third quarter of 2015 and to initiate Phase 3 studies for this indication in 2016.

Projected Phase 3 Clinical Trials

In the fourth quarter of 2014, we reported positive top-line results from a Phase 2b placebo-controlled study of AKB-6548 in non-dialysis patients with anemia related to chronic kidney disease (CKD). As a result, the company is planning meetings to discuss the Phase 2b study results with U.S. and European regulatory agencies in preparation for initiating global Phase 3 registration studies in 2015.

We are designing the Phase 3 program to be applicable for global development with limited protocol differences between geographic regions. We expect that two adequate and well controlled Phase 3 trials will be required to support the marketing application. The total number of patients to be enrolled in the Phase 3 studies will be determined upon agreement with FDA, EMA and other regulatory authorities.

We anticipate that one of the Phase 3 studies will be randomized, double-blind, and placebo-controlled enrolling CKD patients with anemia (hemoglobin < 10.5 g/dL). The primary endpoint would be to demonstrate non-inferiority for cardiovascular safety for AKB-6548 compared to the standard of care provided to the placebo group. The efficacy endpoint for this study will be to compare the ability to raise hemoglobin levels between AKB-6548 and placebo treatment groups. The study will include a rescue component for subjects with declining hemoglobin levels using injectable rESAs and/or transfusions in accordance with existing treatment guidelines (i.e. standard of care).

We expect that the second study will be a randomized, controlled, open-label study where subjects currently receiving treatment with rESAs are randomized 1:1 to receive AKB-6548 or to remain on their current rESA therapy. The primary efficacy endpoint would be to demonstrate non-inferiority for the mean change from the baseline hemoglobin level to the mean level during the evaluation period.

Although the exact size and timing cannot be known until final agreement is reached with the FDA, EMA and other regulatory authorities, we estimate that the two Phase 3 studies in non-dialysis patients with anemia related to CKD will include a total of approximately 3,000 - 3,500 subjects. We estimate that the cardiovascular safety study will be approximately 3 years in duration, with an average of 1.5 years on study drug.

Additional Studies

We have completed a thorough QT, or TQT, study in accordance with FDA guidance to ensure that AKB-6548 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. To date, AKB-6548 has not shown any tendency to affect the QT interval either in humans or animals. This study was a partially blinded, four way crossover study in 50 healthy volunteers, men and women. Each subject received the four different treatments (AKB-6548 600 mg, AKB-6548 1200 mg, Placebo, and Moxifloxacin 400 mg – each treatment taken at separate visits). The results from this study confirm that AKB-6548 does not alter cardiac repolarization intervals in healthy volunteers following a single dose of up to 1200 mg.

To test AKB-6548 in a chronic dosing setting, carcinogenicity assessments in two rodent species (rat and mouse) will be pursued. AKB-6548 has been shown to be orally bioavailable and pharmacologically active in both species. The results of a standard battery of tests that evaluate for mutations in cells or animals have indicated that AKB-6548 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 6 months of dosing in a transgenic mouse model) in each of the two rodent species will be conducted. Completion of three-month (mouse; ongoing) and six-month (rat; completed) oral toxicity evaluations will support dose selection for the respective carcinogenicity assessment.

Finally, in order to complete the registration package for drug approval, we are exploring the need to evaluate specific drug interactions with patients taking AKB-6548, as patients with CKD take multiple medications. It is likely we will conduct at least one of these additional clinical studies.

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