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PRODUCT DEVELOPMENT

FULL STEAM AHEAD

BY SUSAN SCHAEFFER, EDITOR

Akebia Therapeutics Inc. is moving ahead with plans to begin a Phase III trial of anemia candidate AKB-6548 in the second half of next year, despite investors' swift and negative reaction to deaths reported in a Phase IIb study. The company says the deaths are not a safety signal, and it will have plenty of positive catalysts before it needs to raise money for the next study.

Top-line data from the company's first Phase IIb trial, reported on Monday, Oct. 27, showed AKB-6548 met the primary endpoint of increasing hemoglobin levels vs. placebo in patients with anemia secondary to chronic kidney disease (CKD). But there was a higher proportion of serious adverse events in the treatment arms, including three deaths, one of which was ruled to be possibly related to treatment.

The company said two to four deaths in the treatment arms were expected based on the number of patients enrolled and their high disease burden. Moreover, one of the deaths was ruled possibly related to treatment because information about the cause of death could not be obtained, not because there was evidence suggesting that AKB-6548 played a role.

The absence of deaths in the placebo arm was unexpected, and likely a random occurrence, management said on a conference call. One to two deaths would have been expected.

The study enrolled 209 CKD patients who were not on dialysis and were randomized 2:1 to AKB-6548 or placebo.

Investors clearly were not assuaged, as they sent Akebia's shares tumbling $5.75 (29%) to $13.97 on Monday, and the decline continued throughout the week. By Friday's close, the company had lost $6.76 (34%) to $12.96.

Akebia, which raised $115 million in an IPO in March, has said all along it will need to raise more money for Phase III. However, the company reported $95.4 million of cash at June 30 and President and CEO John Butler told BioCentury it will last through mid-2016.

"We're not in a rush to raise money," he said. "Regulatory interactions will begin next year, and we expect to present full data at the **International Society of Nephrology** meeting in mid-March. So there are multiple events, and lots of opportunities to talk to investors about the data."

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>
> JOHN BUTLER, AKEBIA

GETTING TO GOAL

AKB-6548 is an oral inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH; EGLN), a class of compounds designed to work by mimicking the body's natural response to hypoxic conditions.

In response to a reduction in oxygen, reduced HIF-PH activity leads to stabilization of the transcription factors hypoxia-inducible factor 1a (HIF1A) and HIF2A, which in turn leads to increased EPO secretion and red blood cell production. HIF1A helps cells survive under very low oxygen conditions, while HIF2A helps cells survive modest reductions in oxygen such as those that occur with a modest increase in altitude.

At least five other HIF-PH inhibitors are in the clinic, including one from **FibroGen Inc.**, **Astellas Pharma Inc.** and **AstraZeneca plc**, which is in Phase III.

Akebia believes its HIF-PH inhibitor is different from others in the class in that it is specific for the HIF2A response, leading to improved production of hemoglobin and RBCs while maintaining normal levels of EPO that are more consistent with normal diurnal variation in the hormone.

The Phase IIb study was designed to show that the dosing algorithm Akebia has developed for AKB-6548 could provide sustained control of anemia over 20 weeks of treatment without hemoglobin excursions above 13 g/dL. Hemoglobin levels above that threshold have been associated with higher rates of stroke in studies of erythropoiesis-stimulating agents (ESAs).

On the primary endpoint, 54.9% of the treatment group vs. 10.3% of the placebo group achieved hemoglobin levels of at least 11 g/dL or gained at least 1.2 g/dL from baseline to weeks 19 and 20 ($p<0.0001$).

Six patients (4.4%) experienced excursions above 13 g/dL. Five of the six had only one value that was above 13 g/dL.

"The dosing algorithm says that you basically withhold dose when you get to 13, and then you resume it depending on the level it drops down to after that. So those five patients had a single excursion and then continued on with the trial and did well," SVP and CMO Brad Maroni said on Monday's conference call.

The sixth patient remained at 13 g/dL for three months after AKB-6548 was withdrawn, he said.

FibroGen has reported that 71% of patients in a Chinese Phase IIb trial who received a low or high dose of roxadustat reached hemoglobin levels of at least 11 g/dL — a secondary endpoint — compared with 3% of patients on placebo.

Low and high doses of roxadustat met the primary endpoint of a mean maximum increase in hemoglobin by week 9 from baseline (1.6 and 2.4 g/dL vs. 0.4 g/dL; $p<0.0001$ for both doses).

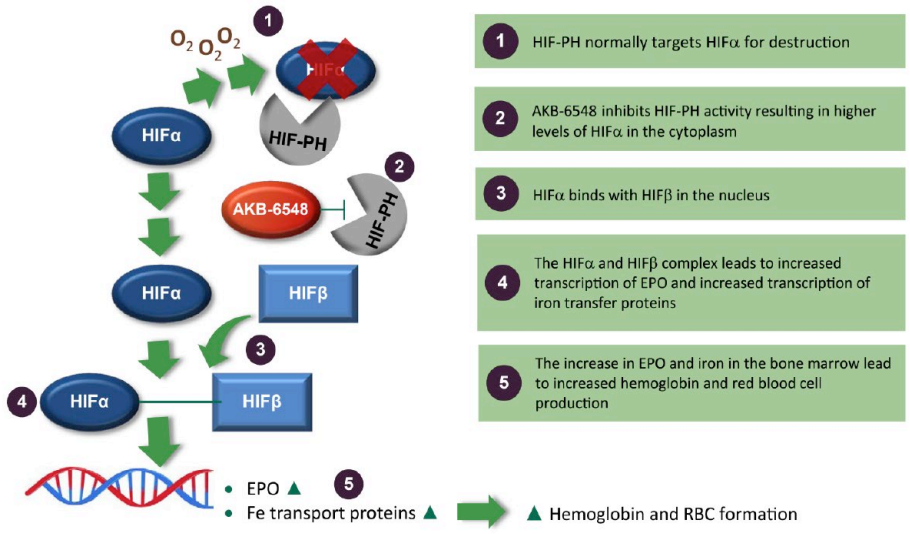
The trial randomized 91 patients 1:1:1 to low- or high-dose roxadustat or placebo dosed three times per week. The duration of treatment was eight weeks.

FibroGen, which has filed for an IPO and is in a quiet period, has not reported data on excursions above 13 g/dL.

Neither has the company reported enough detail on the study population to determine how comparable it might be to the patients in Akebia's trial. The Chinese patients had hemoglobin levels <10 g/dL, were not taking ESAs and were not allowed to have IV iron supplements.

Patients in Akebia's study had CKD stages 3-5, with three-quarters in stage 4 or 5. Three-quarters also had diabetes, and 95% had a medical history of hypertension.

AKB-6548'S MECHANISM OF ACTION



SOURCE: AKEBIA THERAPEUTICS INC.

The study enrolled patients who were receiving recombinant ESAs and switched to AKB-6548 in the study (20%), as well as patients who had discontinued rESA treatment more than 11 weeks before the study (30%) and patients who were rESA-naïve (50%). Data on these subgroups were not reported. IV iron was permitted only for patients who could not tolerate oral iron.

Butler could not comment on how similar or different the populations might have been in the two companies' trials, or what factors might have contributed to the differences in reported efficacy for both the treatment and the placebo groups in each case. But he noted Akebia's goal was not to maximize responses, but rather to demonstrate consistent and predictable control over the treatment period.

"You want to show a clinically meaningful increase in hemoglobin but avoid breakthrough to 13," Butler told BioCentury. "If a patient got to 10.7 in the study, the idea was not to increase the dose to get them higher and improve the success rate, but to maintain them. What we wanted to demonstrate was real control."

SAFETY FINDINGS

Including the three deaths in Akebia's Phase IIb, 23.9% of patients given AKB-6548 experienced SAEs vs. 15.3% of patients given placebo. SAEs were mainly renal related.

All three patients who died had multiple co-morbidities and risk factors. One was an obese 71-year-old man who had stage 4 CKD, heart failure, diabetes, atrial fibrillation, high blood pressure and chronic obstructive pulmonary disease (COPD) with pulmonary hypertension, who was on continuous oxygen. His death was ruled as unrelated to study drug, with the cause listed as chronic heart failure and atrial fibrillation.

The other death unrelated to treatment was a 54-year-old woman who had Type II diabetes and hypertension and had smoked a pack a day for 40 years, among other health problems. This patient presented to the ER with presumed sepsis and an ischemic foot due to peripheral vascular disease, and underwent an above-the-knee amputation. She died after supportive care was withdrawn following complications including *Klebsiella* infection, sepsis, respiratory failure and two cardiac arrests.

The one death that was ruled possibly related to treatment was a patient who was found dead at home due to sudden cardiac death. The patient had atherosclerotic vascular disease, and multiple risk factors for heart disease.

The family declined an autopsy, so the precise cause of death could not be determined.

"The PI basically felt that since they didn't have an autopsy where they could find and attribute [the death] to an alternative cause, he took a conservative stance and basically said it was possibly related to study drug, although the patient had many other risk factors," Maroni said on the conference call.

According to FibroGen's amended S-1, as of Oct. 22, the company had seen only three SAEs possibly attributed to roxadustat in its clinical program, which included a total of 1,503 treated patients. One was a stroke in a patient with a prior history of multiple strokes, one was an incident of vomiting, and one was an incident of deep venous thrombosis.

The company has not reported how many deaths have been seen. A poster presented at the 2011 **American Society of Nephrology** meeting reported two deaths in an open-label Phase IIb study in 96 patients with CKD stage 3 or 4 who were not receiving dialysis. Patients were treated with one of four roxadustat dosing regimens for 16-24 weeks. Neither death was attributed to roxadustat.

In one Phase II study in 161 patients on dialysis, FibroGen did report one cardiovascular SAE (1.5%) and eight SAEs (12.1%) for the composite safety endpoint in the roxadustat group, compared with two cardiovascular SAEs (8.7%) and four SAEs (17.4%) for the composite safety endpoint in a control group receiving ESAs. The composite safety endpoint included death, myocardial infarction, congestive heart failure, subendocardial ischemia, cerebrovascular accident, thrombosis (fistula), arteriovenous fistula occlusion, angina pectoris and vascular graft thrombosis.

Those SAEs were not among the three SAEs that have been possibly attributed to roxadustat. Indeed, on FibroGen's road show posted online on Oct. 30, Chairman and CEO Thomas Neff said, "No SAEs were attributed to roxadustat in any completed trials in the Phase II program."

Again, a lack of detailed information about the study populations makes comparisons difficult.

NEXT STEPS

Butler told BioCentury the SAEs in Akebia's study do not suggest a safety signal but rather are a reflection of the grave illness of patients with advanced CKD.

"We are as focused as anyone on safety, and there is no suggestion of a safety signal," he said.

The Phase III study will enroll 2,000-2,500 non-dialysis patients and, as is required for new anemia candidates, will include a non-inferiority CV safety analysis. The 2,500 figure assumes the upper bound of the 95% confidence interval (CI) for estimated CV risk is 1.5.

Akebia started a Phase II study in September in CKD patients undergoing dialysis. Data are expected in 3Q15.

"These are our patients," said Butler. "The ability to let them get their life back from chronic fatigue — we need to do this, it's full steam ahead." bc

COMPANIES AND INSTITUTIONS MENTIONED

Akebia Therapeutics Inc. (NASDAQ:AKBA), Cambridge, Mass.
American Society of Nephrology (ASN), Washington, D.C.
Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
FibroGen Inc., San Francisco, Calif.
International Society of Nephrology, Brussels, Belgium

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