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MCRI Updates

Akebia's AKB-6548 for Anemia

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Summary

We recently hosted a conference call to discuss Akebia Therapeutics' (AKBA) AKB-6548 for treating anemia. The product is a small molecule that inhibits hypoxia-inducible factor prolyl hydroxylase (HIF-PH), leading to increased red blood cell formation. It is designed to be an oral alternative to the blockbuster class of injectable erythropoietin analogs. AKB-6548 successfully completed a 42-day phase II dosing study. The drug is now in a 20-week, 200-patient phase II trial of patients with chronic kidney disease who are not on dialysis. We believe the current phase II trial is likely to be successful based on the effect seen with the previous phase II trial. However, we doubt the product will be without safety concerns and believe it will not have a clear safety superiority to erythropoietin analogs. Its biggest advantage may be that it can be produced at a much lower cost than erythropoietin; however, the sales price has not been disclosed.

Stocks Impacted

- **Akebia Therapeutics (AKBA-$25.80-NR)**

Background

- ***AKB-6548 is in a phase II trial in patients with chronic kidney disease who have not received dialysis.*** Results are expected in 4Q14.

Reasons for Research

- ***Investors are waiting to learn the results of the phase II trial.***

The Impact

- ***The first phase II trial demonstrated biological activity.*** Patients receiving treatment had a dose-dependent increase in hemoglobin levels.
- ***Safety could be an issue with AKB-6548.*** Erythropoietin analogs received black box warnings for causing increased deaths and cancer progression. These effects could be due to normalizing hemoglobin levels in a patient with chronic disease. Anemia could actually be an adaptive response to cancers and kidney disease. Improving hemoglobin levels with any agent could be risky.
- ***The ongoing current phase II trial uses biologically active doses that would be expected to improve hemoglobin levels.*** The current trial administers to patients oral doses of AKB-6548 that were effective in the prior phase II trial. Furthermore, the dose can be adjusted in the trial if the hemoglobin levels become too high or are not therapeutic.
- ***Pricing may eventually be the biggest factor determining whether AKB-6548 will be a commercial success.*** Competition is expected to strengthen as new products, including biosimilars, enter the market and have to compete in an environment where drugs for dialysis patients are bundled. Oral small molecules tend to be less expensive to manufacture than biologicals, giving AKB-6548 a potential advantage.

MCRI Insights

- ***We believe the current phase II trial is likely to be successful based on the effect seen in the previous phase II trial.*** However, we doubt the product will be without safety concerns and believe it will not have a clear safety superiority to erythropoietin analogs. Its biggest advantage may be that it can be produced at a much lower cost than erythropoietin analogs; however, the sales price has not been disclosed.

Tech Assessment: Akebia Therapeutics' (AKBA) AKB-6548 for Anemia

I. AKB-6548
- Oral, small molecule
- Hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) inhibitor

II. Proposed Mechanism of Action
- Hypoxia-inducible factor (HIF): Natural promoter of RBC production
- HIF: Acts intracellularly to increase erythropoietin production
- HIF: Is naturally degraded in the cells by prolyl hydroxylase
- AKB-6548: Inhibits prolyl-hydroxylase, leading to increased intracellular HIF

III. Anemia Associated with Kidney Disease
- Interstitial fibroblasts of the kidney produce erythropoietin
- Chronic kidney disease leads to decreased erythropoietin
- Decreased erythropoietin leads to anemia

IV. Epidemiology of Anemia of Kidney Disease in US
- 14.0% of the US adult population had CKD in 2007-2010
- Anemia occurred in 15.4% of US adults with CKD versus 7.6% in the general population
- The prevalence of anemia increased with stage of CKD
- 8.4% at stage 1 to 53.4% at stage 5
- A total of 22.8% of CKD patients with anemia are on treatment for anemia
- Anemia treatment: 14.6% of patients at CKD stages 1-2 and 26.4% of patients at stages 3-4
- Total US adults with CKD on anemia treatment: .14 * .228 * 243 million = 7.75 million

V. Erythropoietin Market
- Chronic kidney disease
- Anemia of cancer
- Products approved for US market: Epogen, Procrit, Aranesp, (Omontys — removed)
- Biosimilars common throughout the world
- Cost of erythropoietin in US: Some estimate $6,000 a year
- Toxicity issues caused decreased use
- Bundling in chronic kidney disease, further decreasing use in the US
- AstraZeneca-Fibrogen: Phase III, FG-4592, oral HIF-PH inhibitor
- Palkion Inc. is also working on HIF-PH inhibitors
- Bayer: Molidustat (BAY 85-3934) HIF-PH inhibitor
- GlaxoSmithKline is developing GSK-1278863, a HIF-PH inhibitor

VI. Existing Phase IIa Data
- Randomized, double blind
- n=93 patients with chronic kidney disease (eGFR <60 mL/min), not on dialysis
- Patients enrolled in study had hemoglobin ≤ 10.5 g/dL
- Randomized into five different groups — four different doses and a placebo group
- Once-daily dosing: 240 mg, 370 mg, 500 mg, 630 mg
- 42-day endpoint
- Primary endpoint: Mean absolute change in hemoglobin
- Results: Dose-dependent increase in hemoglobin ($p<0.0001$)
- Placebo group had an average decline of 0.1 g/dL in hemoglobin
- Treatment patients had an increase in hemoglobin between 0.7 to 1.4 g/dL
- Reticulocyte count also increased

VII. Ongoing Phase IIb Trial
- Randomized, double blind
- n=200 patients with chronic kidney disease and not yet on dialysis
- eGFR ≥ 10 and ≤ 65 mL/minute/1.73 m2
- Randomized to AKB-6548 or placebo
- Administered once daily
- Dose adjustment based on hemoglobin
- Duration: 20 weeks
- Primary endpoint: Percent achieving or maintaining a hemoglobin response
- Secondary endpoint: Need for transfusion and/or ESA rescue

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