Phase 2 Study of AKB-6548, a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) in patients with end stage renal disease (ESRD) undergoing hemodialysis (HD)

Charlotte S. Hartman, Tasha M. Farmer, Karen Annis, Farhad Kazazi, Paul Pollack and Robert Shalwitz

Akebia Therapeutics, Inc., Cambridge, MA, United States

ABSTRACT

Background: Anemia is a significant comorbidity in patients with chronic kidney disease (CKD) and worsens with severity of kidney disease. AKB-6548 is a novel once-daily, oral hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) inhibitor that has been shown to produce a coordinated erythropoietic response, with modest increases in erythropoietin as well as improvements in iron mobilization. Completed studies have demonstrated its effectiveness in increasing hemoglobin (HGB) in a dose-responsive manner in CKD patients not on hemodialysis (HD). An initial pharmacokinetic study in patients with end stage renal disease (ESRD) undergoing HD supports dosing of AKB-6548 without regard to the timing of the HD procedure, and demonstrated minimal impact on clearance of AKB-6548. AKB-6548 will now be studied to evaluate its efficacy and safety in a population of patients with ESRD undergoing HD.

Methods: AKB-6548-CI-0011 is a Phase 2, multi-center, open-label study to be conducted in 20 US centers to assess the HGB response, safety and tolerability of two different starting doses along with algorithm-guided dose adjustments of orally administered AKB-6548 dosed once daily for 16 weeks. The study will include male and female subjects, 18–79 years of age, with anemia secondary to ESRD, undergoing chronic HD, routinely receiving epoetin alfa (EA), and with HGB >9 g/dL and <12 g/dL. EA will be continued during the screening period, but will be discontinued prior to the start of AKB-6548. Treatment will be initiated with the first starting dose at the beginning of the study, and the second starting dose for subsequent subjects (to be implemented later in the study) will be determined by a study monitoring team (SMT). The SMT will also oversee safety during the study. Individual subject dosing will be adjusted in accordance with a protocol-defined algorithm. Intravenous iron therapy will be administered per the site's local guidelines and usual routine.

Conclusions: This Phase 2 study will provide important information regarding the efficacy, safety and dosing of AKB-6548, a novel oral HIF-PH inhibitor, in patients with ESRD undergoing HD.

BACKGROUND

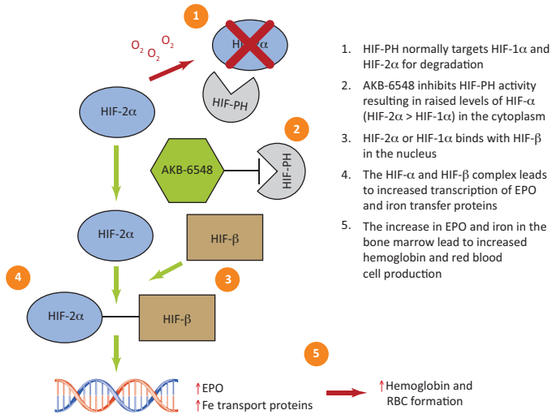
- Anemia is a significant comorbidity in patients with CKD and worsens with increasing CKD severity
- Although many factors contribute to anemia in CKD, the primary cause is inadequate production of erythropoietin (EPO) by injured or failing kidneys, which in turn results in hypoxic injury to or depletion of EPO-producing peritubular cells[1,2]

Current treatment

- Erythropoiesis-stimulating agents (ESAs) are the mainstay of treatment and include epoetin alfa, epoetin beta, and darbepoetin alfa (intravenous or subcutaneous administration)
- ESAs have been associated with an increased risk of cardiovascular events, possibly due to fluctuations in HGB concentrations, rapidly increasing HGB concentrations, and overshooting target HGB concentrations[3,4]
- An alternative pharmacologic agent that can provide a controlled, steady rise in HGB concentration would be of value
- A once-daily oral agent would also provide a simplified administration and dose titration

AKB-6548

- Once-daily, oral inhibitor of HIF-PHs (also referred to as the prolyl 4-hydroxylase domains)
- Inhibition of HIF-PH results in increased cytoplasmic levels of HIF-2α, which in turn binds to HIF-β, stimulating production of EPO (Figure 1)

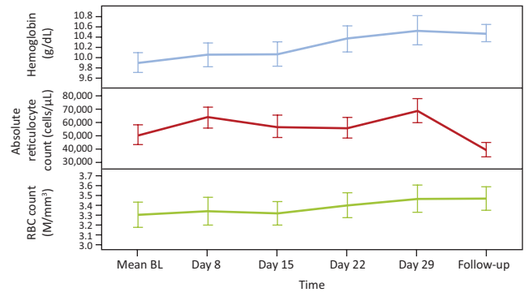


1. HIF-PH normally targets HIF-1α and HIF-2α for degradation
2. AKB-6548 inhibits HIF-PH activity resulting in raised levels of HIF-α (HIF-2α > HIF-1α) in the cytoplasm
3. HIF-2α or HIF-1α binds with HIF-β in the nucleus
4. The HIF-α and HIF-β complex leads to increased transcription of EPO and iron transfer proteins
5. The increase in EPO and iron in the bone marrow lead to increased hemoglobin and red blood cell production

Abbreviations: EPO, erythropoietin; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; RBC, red blood cells

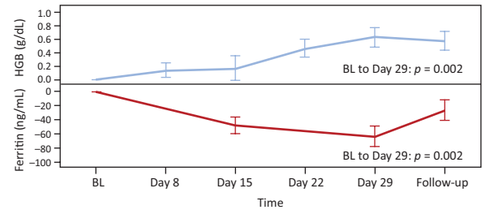
Figure 1. Mechanism of action of AKB-6548

- AKB-6548 may provide a more physiologic therapeutic approach to treating anemia compared with the currently available treatment of injectable ESAs, with the potential to maintain EPO within physiologic range and to enhance iron mobilization
- Flexible oral dosing with AKB-6548 may provide a gradual and reliable means of titration
- The safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of AKB-6548 have been characterized in three completed Phase 1 studies and three completed Phase 2 studies in patients with CKD not on dialysis:[5]
  - well tolerated overall with limited adverse events (AEs) and serious AEs
  - consistent, dose-proportional PK and PD
  - dose-dependent increase in EPO concentration accompanied by dose-responsive increases in iron mobilization, which stimulated an increase in reticulocytes and HGB (Figures 2 and 3)



Abbreviations: BL, baseline; RBC, red blood cells

Figure 2. AKB-6548 gradually increased HGB and red blood cells over time[5]



Abbreviations: BL, baseline; HGB, hemoglobin

Figure 3. AKB-6548 significantly increased HGB from baseline to Day 29 while significantly decreasing ferritin from baseline to Day 29[5]

- A PK study in patients with ESRD undergoing HD supports dosing of AKB-6548 irrespective of the timing of the HD procedure and with minimal impact of HD on its clearance [see Buch A, *et al*. Poster FR-PO952 in Pharmacokinetics/ Pharmacodynamics/Pharmacogenomics poster session on Friday 14 November 2014][6]
- The efficacy and safety of AKB-6548 is now under investigation in ESRD patients with anemia secondary to ESRD who are undergoing HD; the protocol for this study is presented here

STUDY DESIGN

- ClinicalTrials.gov identifier: NCT02260193 (see Figure 4 for study design)
- Phase 2, multi-center, open-label study to be conducted in approximately 20 US centers
- AKB-6548 to be administered once daily for 16 weeks
  - Treatment will be initiated using the first starting dose at the beginning of the study, with a second starting dose (determined by a study monitoring team) implemented later in the study for subsequent patients
  - Individual patient dosing will be adjusted in accordance with a protocol-defined algorithm
- Key inclusion criteria:
  - men and women aged 18–79 years, inclusive, and undergoing chronic HD for ≥3 months
  - anemia secondary to CKD treated with ESA and intravenous iron
    - ESA to continue during the screening period but discontinued prior to start of AKB-6548
    - intravenous iron to continue per the site's local guidelines and usual routine
  - HGB >9 g/dL and <12 g/dL

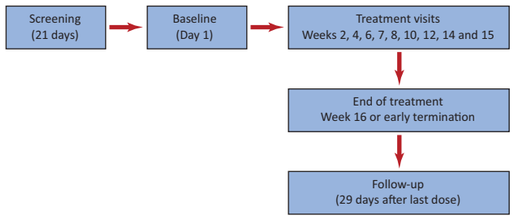


Figure 4. Study design

- Key exclusion criteria:
  - body mass index >44.0 kg/m^2
  - alanine transaminase or total bilirubin >1.25x upper limit of normal
  - uncontrolled hypertension; class III or IV congestive heart failure; myocardial infarction, acute coronary syndrome, stroke or transient ischemic attack within 6 months prior to screening

OUTCOME MEASURES

Primary outcome measures

- HGB response to two different starting doses

Secondary outcome measures

- PD response, measured by actual values and change from baseline in HGB, hematocrit, red blood cell count and reticulocyte count over the duration of study treatment
- Number of patients that require transfusion and/or ESA rescue over the duration of study treatment
- Safety and tolerability measures to include assessments of AEs, vital signs, electrocardiograms and laboratory assay results
- Concentration measurements of investigational product and its metabolites pre- and post-dialysis at 2 and 16 weeks

Other pre-specified outcome measures

- Change in iron metabolism (actual values and change from baseline in iron indices) over the duration of study treatment
- Intravenous iron utilization over the duration of study treatment

CURRENT STATUS

- The first patient was screened on September 10, 2014, and the first patient was dosed on September 24, 2014
- Enrollment is expected to be completed in January 2015, and the study is due to report in the third quarter of 2015

CONCLUSIONS

- This Phase 2 study will provide important information regarding the efficacy, safety and dosing of AKB-6548, a novel oral HIF-PH inhibitor, in patients with ESRD undergoing HD
- This information will be used for Phase 3 study design

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