**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-6548-015 is a 2, phase 2, multi-center, open-label study to be conducted in ≥20 U.S. centers to assess the HGB response, safety and tolerability of the different starting doses along with algorithm-guided dose adjustments of orally administered AKB-6548 dose for a 16-week study period. The study will include male and female subjects, ≥18–79-years of age, with anemia secondary to CKD, undergoing HD, receiving signout episodes (F5), and with HGB-<9.5 and ≤12 g/dL. EA will be continued during the screening period, but will be discontinued prior to the start of the study. Treatment will be initiated with the first starting dose at the beginning of the study, and the second starting dose for subsequent doses (to be implemented later in the study) will be determined by a study monitoring team (SMT). The SMT will also overview safety during the study. Individual patient 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.

**OUTCOME MEASURES**

- Primary outcome measures:
  - HGB response to two different starting doses
- Secondary outcome measures:
  - PO 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-doses at 2 and 16 weeks

**REFERENCES**

5. 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 30 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

**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

**ACKNOWLEDGEMENTS**

Thank you to all site coordinators, investigators and patients (current and future) involved in this study.