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Phase 2b study of AKB-6548, a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor for the treatment of anemia in patients with chronic kidney disease not on dialysis (ND-CKD)

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ABSTRACT

INTRODUCTION: AKB-6548 is a novel, once-daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) that preferentially stabilizes HIF-2α. Earlier studies in ND-CKD patients have shown AKB-6548 produces physiologic increases in erythropoietin levels, enhances iron mobilization, and produces a dose-dependent increase in hemoglobin (HGB). We now report the results of a Phase 2b trial of AKB-6548 as a novel treatment for anemia of CKD.

METHODS: A randomized, double-blind, multicenter, placebo-controlled study was conducted at 60 sites across the United States to assess the HGB response and safety of AKB-6548 over 20 weeks of dosing in CKD subjects (stages 3–5) with anemia. Subjects were randomized (2:1) to once daily AKB-6548 (450 mg) or placebo and stratified by CKD stage and diabetic status. Three groups of subjects were enrolled and randomized to AKB-6548 or placebo: (1) erythropoiesis-stimulating agent (ESA) naïve with HGB ≤10.5 g/dL, (2) previously treated with ESA with HGB ≤10.5 g/dL, or (3) actively treated with ESA with a HGB ≥9.5 and ≤12.0 g/dL. The primary endpoint was the percent of subjects with either a mean HGB of ≥11.0 g/dL or an increase in HGB by ≥1.2 g/dL from baseline at weeks 19–20. A protocol-defined dose adjustment algorithm was used to achieve the primary endpoint by raising and maintaining HGB and to minimize excursions ≥13 g/dL. Subjects could receive ESA or red blood cell transfusion rescue for worsening anemia.

RESULTS: 210 subjects (138 AKB-6548 and 72 placebo) were in the intent-to-treat population, and 160 (Per Protocol) were used for the primary efficacy analysis. The mean age was 66 years, ~75% of subjects had diabetes and the mean estimated glomerular filtration rate (eGFR) was 25 mL/min/1.73m². The primary endpoint was met in 54.9% of AKB-6548-treated subjects compared to 10.3% of placebo-treated subjects (p<0.0001). 4.4% of subjects in the AKB-6548 group had a HGB excursion ≥13.0 g/dL vs. zero in the placebo group. Increases in HGB in the AKB-6548 group were associated with an increase in reticulocytes and total iron-binding capacity, and a decrease in serum hepcidin and ferritin relative to placebo. AKB-6548 was generally well tolerated and adverse events were well balanced between treatment groups (74.6% vs. 73.6%). Serious adverse events occurred in 23.9% and 15.3% of the AKB-6548 and placebo treated subjects, respectively, with the most common being renal-related. The initiation of dialysis was similar between treatment groups (AKB-6548 8.0% vs. placebo 9.7%). Three vs. zero deaths occurred in AKB-6548 and placebo treated subjects, respectively.

CONCLUSIONS: AKB-6548, a novel HIF-PHI being developed for the treatment of anemia of CKD, raised and maintained HGB while minimizing HGB excursions ≥13.0 g/dL. This study forms the basis for the conduct of future Phase 3 studies.

AKB-6548 BACKGROUND

- Once-daily, oral inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIF-PHs)
- In development for treatment of anemia related to chronic kidney disease (CKD) in patients not on dialysis and those requiring dialysis
- Well tolerated in studies of healthy volunteers and patients with CKD
  - Direct dose-response relationship observed between drug dose and erythropoietin (EPO) or hemoglobin (HGB) levels
- Facilitates iron homeostasis by decreasing hepcidin and increasing transferrin levels
  - Facilitates iron transport mechanisms that should enhance terminal steps of erythropoiesis

STUDY DESIGN

- Double-blind, randomized, parallel-group, placebo-controlled study
- Primary objective: to assess HGB response (compared with baseline and placebo) to orally administered AKB-6548 in patients with CKD glomerular filtration rate (GFR) categories G3a-G5 (pre-dialysis)
- Patients assigned to a study group based on ESA status at screening:
  - ESA naïve: never received treatment with an ESA; screening HGB level of ≤10.5 g/dL
  - Previously treated: previously received ≥1 dose of an ESA and had been off ESA therapy for ≥11 weeks at the time of screening; screening HGB level of ≤10.5 g/dL
  - Actively treated: actively treated with an ESA for minimum 4 months before screening; screening HGB level ≥9.5 g/dL and ≤12.0 g/dL
- Patients assigned in a 2:1 ratio within each study group to once-daily AKB-6548 (initial dose 450 mg) or placebo
- Randomization stratified to maintain balance between the AKB-6548 and placebo groups with respect to CKD status (GFR categories G3a/b, G4, or G5) and presence/absence of diabetes mellitus
- Study medication doses adjusted in accordance with protocol-defined dose adjustment guidelines and algorithm

DEMOGRAPHICS

Patient disposition and demographics

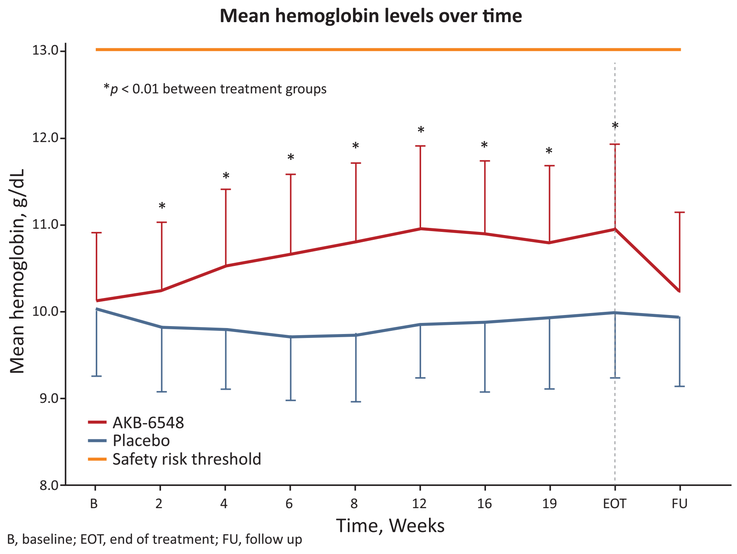
	AKB-6548 n (%)*	Placebo n (%)*
Patients dosed (intent-to-treat population)†	138 (100.0)	72 (100.0)
Per protocol population‡	102 (73.9)	58 (80.6)
Patients completing through Week 20	112 (81.2)	63 (87.5)
Sex – male	57 (41.3)	38 (52.8)
Age, mean (years)	66.6	65.9
Diabetes mellitus	106 (76.8)	57 (79.2)
Chronic kidney disease stage G3a/b G4 G5	 36 (26.1) 85 (61.6) 17 (12.3)	 18 (25.0) 42 (58.3) 12 (16.7)
eGFR, mean (mL/min/1.73m²)	25.2	25.0
Urine albumin-to-creatinine ratio, mean/median (mg/g)	1146/416	1455/487

*Number of patients unless otherwise stated; †Number of patients dosed was used to calculate percentages;
‡Completed through Week 20 with compliance ≥80%
eGFR, estimated glomerular filtration rate

RESULTS

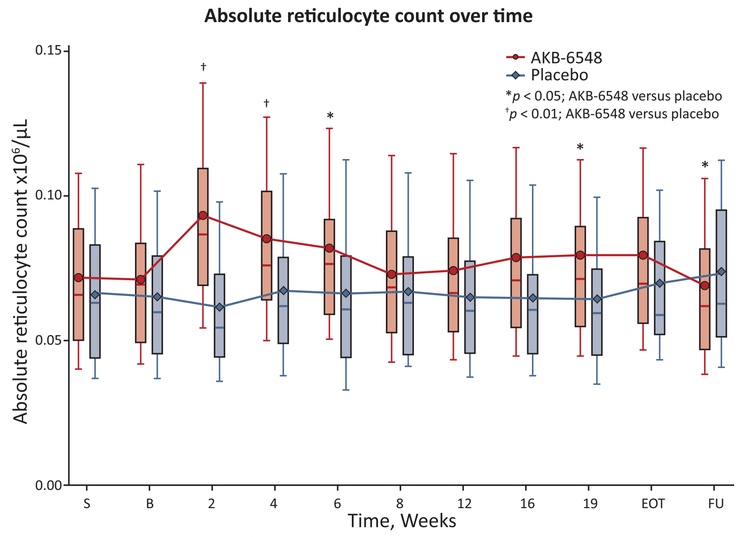
HEMATOPOIETIC RESPONSE

Mean hemoglobin levels over time



B, baseline; EOT, end of treatment; FU, follow up

Absolute reticulocyte count over time



B, baseline; EOT, end of treatment; FU, follow up; S, screening
Box and whiskers plot represents 10th, 25th, 75th, and 90th percentile; median is the line within the box, mean is symbol within the box

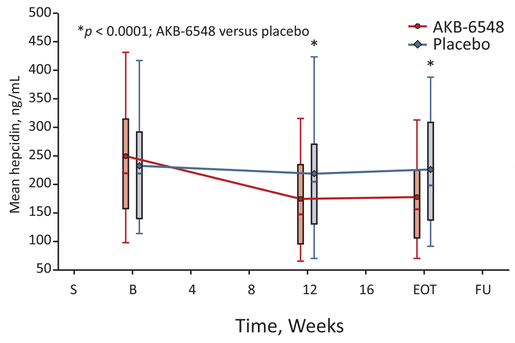
Met primary endpoint (54.9% versus 10.3%, $p < 0.0001$)
Only 4.4% of patients (n=6) experienced excursions beyond 13 g/dL

Physiologic response consistent with previous studies:
Reticulocytes rise initially, then decrease and stabilize to maintain HGB

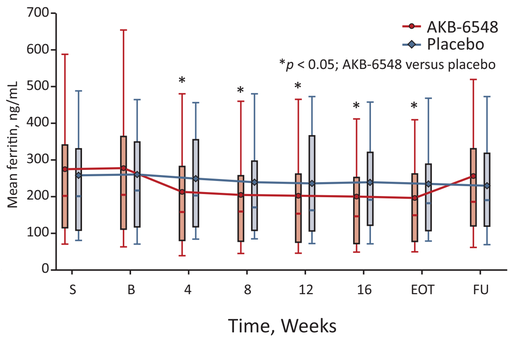
- Between Weeks 8–20, ~75% of all HGB values were 10–12 g/dL, indicating that the dosing algorithm resulted in predictable and controlled HGB response
- Mean number of tablets/day at Week 19 was 3.0, suggesting that 450 mg (3 tablets) once daily is an appropriate starting dose for patients with ND-CKD

IRON MOBILIZATION

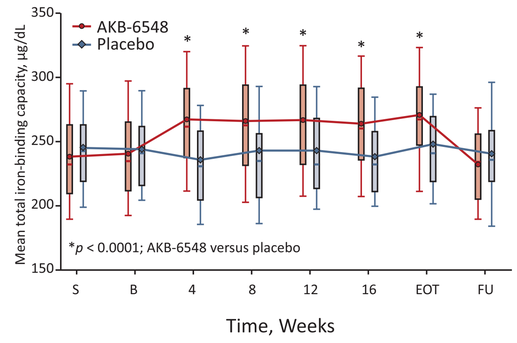
Hepcidin



Ferritin



Total iron-binding capacity



B, baseline; EOT, end of treatment; FU, follow up; S, screening
Box and whiskers plot represents 10th, 25th, 75th, and 90th percentile; median is the line within the box, mean is symbol within the box

Sustained improvement in iron mobilization, consistent with previous studies

SAFETY

Summary of treatment-emergent adverse events (intent-to-treat population)

	AKB-6548 (N=138) n (%)*	Placebo (N=72) n (%)*
At least one AE	103 (74.6)	53 (73.6)
SAEs	33 (23.9)	11 (15.3)
Drug-related SAEs	3 (2.2)	0 (0.0)
Died	3 (2.2)	0 (0.0)

*Number of patients
AE, adverse event; SAE, serious adverse event

- Overall, adverse events (AEs) were evenly distributed across treatment groups
- With the exception of renal and urinary disorders, the distribution of serious adverse events (SAEs) was similar between groups
- Three drug-related SAEs were abnormal liver function test, myocardial ischemia, and angioedema
- No change from baseline observed in vascular endothelial growth factor (VEGF) or cystatin-C

Summary of renal failure cases

	AKB-6548 (N=138) n (%)*	Placebo (N=72) n (%)*
Renal failure AEs	16 (11.6)	8 (11.1)
Renal failure SAEs	13 (9.4)	2 (2.8)
Initiation of dialysis	11 (8.0)	7 (9.7)
Serum creatinine (mg/dL), mean change from baseline to EOT	0.17	0.28

*Number of patients unless otherwise stated
AE, adverse event; EOT, end of treatment; SAE, serious adverse event

- Overall, renal and urinary AEs were well balanced between groups
- Need for dialysis, an objective measure of the severity of renal SAEs, was similar between groups
- Three SAEs in the AKB-6548 group occurred >3 weeks after completing 20 weeks' treatment
- Two patients receiving placebo progressed to end-stage renal disease and initiated hemodialysis, although these events were categorized as AEs
- No renal AE or SAE was considered related to study drug by the investigator

CONCLUSIONS

- Treatment with AKB-6548 using the prescribed dosing algorithm resulted in:
  - Increases in HGB that were maintained at the desired range while minimizing excursions ≥13.0 g/dL
  - A reticulocyte profile that closely mimicked the predicted response to altitude-associated hypoxia
  - Improvements in iron mobilization consistent with previous studies
- Overall safety profile consistent with previous studies
  - Treatment-emergent AEs were generally well balanced between AKB-6548 and placebo and were those expected in a trial conducted in this patient population
  - Imbalance in SAEs primarily related to renal events, which appears to be due to variability in AE reporting