AKB-6548, A New Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Increases Hemoglobin While Decreasing Ferritin in a 28-day, Phase 2a Dose Escalation Study in Stage 3 and 4 Chronic Kidney Disease Patients With Anemia

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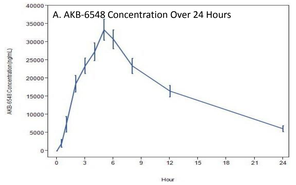
ABSTRACT

Current treatment of anemia associated with chronic kidney disease (CKD) with erythropoiesis-stimulating agents (ESAs) can lead to supraphysiological levels of circulating erythropoietin (EPO) that persist for days, a profile that may be associated with increased cardiovascular side effects. Therefore, a drug that provides moderate increases and reestablishes the diurnal variation in EPO may be a better treatment for patients with CKD. AKB-6548, a new short-acting hypoxia-inducible factor prolyl hydroxylase inhibitor, was selected to induce controlled daily rises in EPO that closely simulate physiologic responses to changes in altitude. In a Phase 2a dose escalation study, 10 CKD patients received AKB-6548 once daily for 28 days. Dosing began at 400 mg in CKD Stage 3 patients and 300mg in CKD Stage 4 patients. It increased by 100 mg for each week that absolute reticulocyte count (ARC) did not increase by 18,000 above the baseline (BL) average. Dosing was generally well tolerated. Results, including both Stage 3 and 4 CKD patients, demonstrated that hemoglobin (Hgb) rose from 9.91 g/dL at BL to 10.54 g/dL by Day 29. Ferritin decreased from 324.0 ng/mL at BL to 271.7 ng/mL by Day 29.

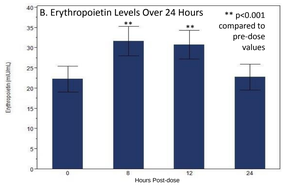
BACKGROUND

Single Dose Pharmacokinetic Study in CKD Subjects

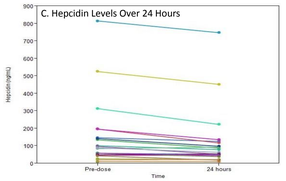
Figure 1: In a previous single dose Phase 2a study in Stage 3 and 4 CKD subjects, 500 mg of AKB-6548 demonstrated the following:



Panel A: AKB-6548 half-life of approximately 7.9 hours



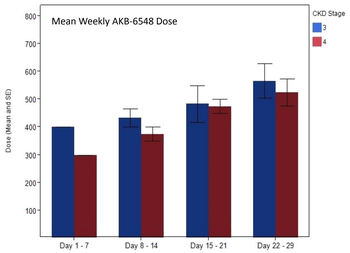
Panel B: Paired t-tests showed a significant increase of mean EPO at 8 and 12 hours



Panel C: Significant decrease of mean hepcidin at 24 hours, paired t-test: p = 0.0002

STUDY DESIGN

- Phase 2a non-placebo controlled dose escalation pilot study to assist in study design for subsequent full Phase 2a study
- 10 CKD patients received AKB-6548 once daily for 28 days
  - Dosing began at 400 mg in CKD Stage 3 and 300 mg in CKD Stage 4 patients
  - Dosing increased by 100 mg for each week that absolute reticulocyte count (ARC) was not increased by 18,000 cells/µL above the BL average
  - Dosing decreased by 100 mg for each week that Hgb increased by ≥1.5 g/dL from BL or increased above 12 g/dL
  - Possible dose range included 200-700 mg
- All patients received minimum iron supplementation of 50 mg/day
- Clinical and safety assessments were performed at Screening, Pre-baseline, BL (Day 1), Weekly (Days 8, 15, 22, and 29), and Follow-up 2 weeks after last dose



Key Inclusion Criteria
- 18 to 79 years of age, inclusive
- CKD Stage 3 or Stage 4
- Hgb <10.5 g/dL
- TSAT >20%

Key Exclusion Criteria
- ESA within 10 weeks prior to screening visit
- Met criteria of ESA resistance within the previous 4 months
- Doses of IV iron of 250 mg or larger within the past 21 days
- Red blood cell transfusion within 12 weeks
- Androgen therapy within the previous 21 days
- BMI >40
- Active bleeding or recent blood loss of >240 mL
- AST or ALT >1.8x ULN, Alkaline phosphatase >2x ULN
- Total bilirubin >1.5x ULN

DEMOGRAPHICS

	Age	Weight	eGFR	HGB (Mean BL)*	Race	# of Patients	Sex	# of Patients
CKD 3								
Mean	58.33	198.7	43.97	10.09	Caucasian White	2	Male	3
St. Dev	14.24	74.12	7.64	0.61	African-American	3	Female	3
					Other	1		
CKD 4								
Mean	63.75	173	19.73	9.64	Caucasian White	2	Male	2
St. Dev	8.02	62.46	5.34	0.64	African-American	2	Female	2
					Other	0		
Combined								
Mean	60.5	188.4	34.27	9.91	Caucasian White	4	Male	5
St. Dev	11.91	67.28	14.09	0.63	African-American	5	Female	5
					Other	1		

RESULTS

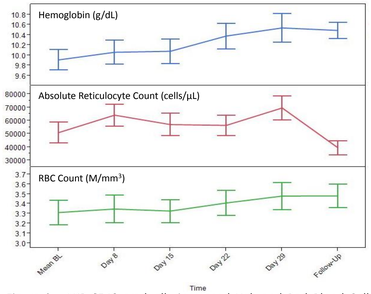


Figure 2: AKB-6548 gradually increased Hgb and Red Blood Cells (RBCs) over time.

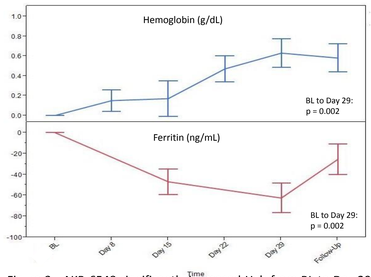


Figure 3: AKB-6548 significantly increased Hgb from BL to Day 29 while significantly decreasing ferritin from BL to Day 29.

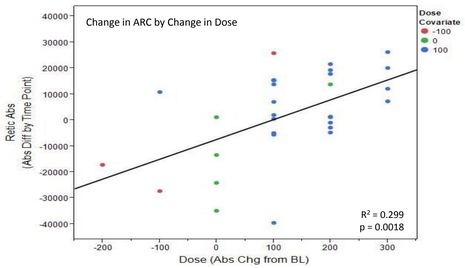


Figure 4: Change in dose was significantly related to change in ARCs when looking at intervals: Day 8-15, Day 15-22, and Day 22-29. (Dose Covariate refers to change in dose from time point to next time point as opposed to BL).

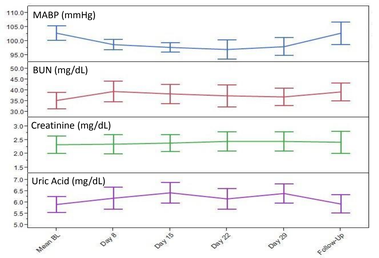
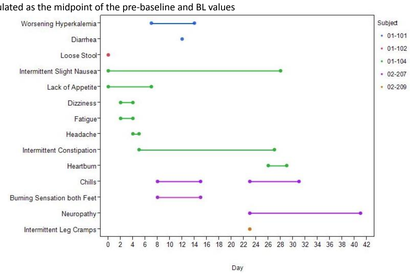


Figure 5: A slight decrease in blood pressure was observed with AKB-6548. It did not effect biochemical measures of renal function.

ADVERSE EVENTS

*Mean BL of Hgb calculated as the midpoint of the pre-baseline and BL values



SUMMARY

	Baseline	Day 29	Paired t-test
Hemoglobin (g/dL)	9.91±0.63	10.54±0.89	p=0.002
Ferritin (ng/mL)	324.0±199.2	271.7±181.3	p=0.002

CONCLUSIONS

We conclude that AKB-6548 is well-tolerated and increases hemoglobin while decreasing ferritin in a dose-dependent manner in patients with Stage 3 or 4 CKD. The consistent rise in hemoglobin and the concurrent fall in ferritin over the course of the study suggest an efficacious daily dose of AKB-6548 begins between 300 and 400 mg.