AKB-6548
A New Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor, Increases Hemoglobin in Chronic Kidney Disease Patients Without Increasing Basal Erythropoietin Levels

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AKB-6548 Background and Safety Overview

- Akebia Therapeutics is a venture-backed biotechnology company started in 2007
  - AKB-6548 was in-licensed from Proctor & Gamble Pharmaceuticals
- AKB-6548 is a hypoxia-inducible factor (HIF) stabilizer
  - Mechanism: inhibition of the prolyl-hydroxylase enzymes (PHD) which target HIF for degradation
  - Initial indication: anemia associated with chronic kidney disease (CKD) (pre-dialysis)
- AKB-6548 stabilizes HIF2 > HIF1
  - HIF2 is less widely expressed, but is critical for production of erythropoietin (EPO)
  - HIF1 is found in almost all cell types
- AKB-6548 has been generally very well tolerated in initial studies:
  - Phase 1a: up to 1200 mg as a single dose in healthy male volunteers
  - Phase 1b: up to 900 mg/day for 10 days in healthy male volunteers
  - Phase 2a: single dose PK study at 500 mg in subjects with CKD
  - Phase 2a pilot: open label, dose escalation up to 700 mg/day for 28 days in 10 subjects with anemia secondary to CKD

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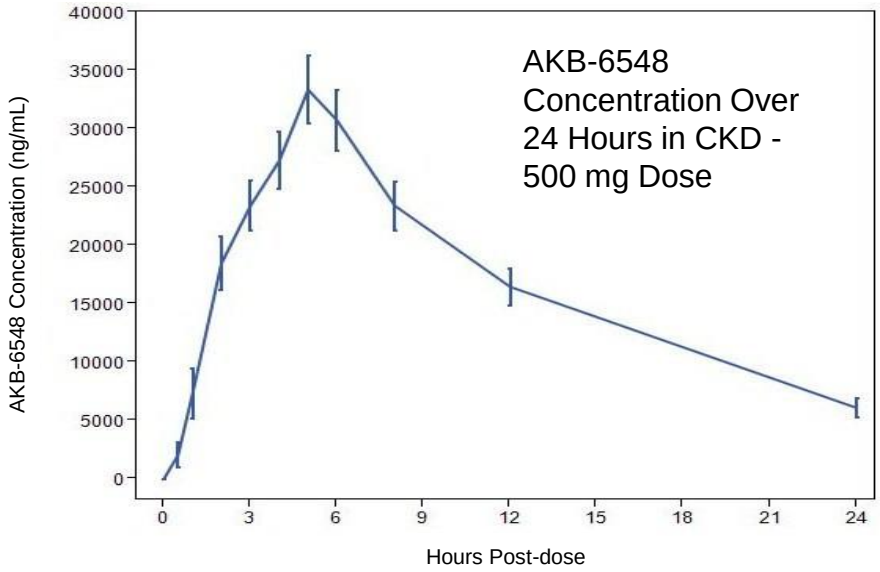
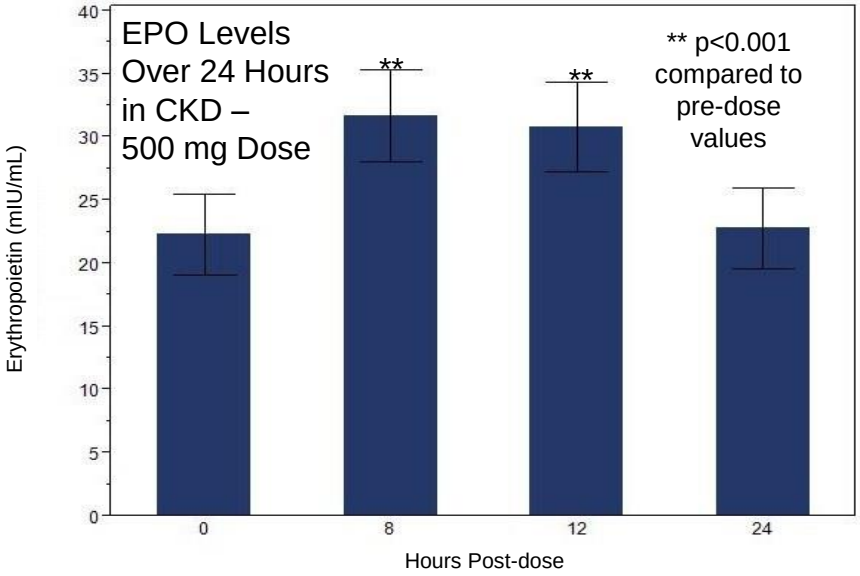
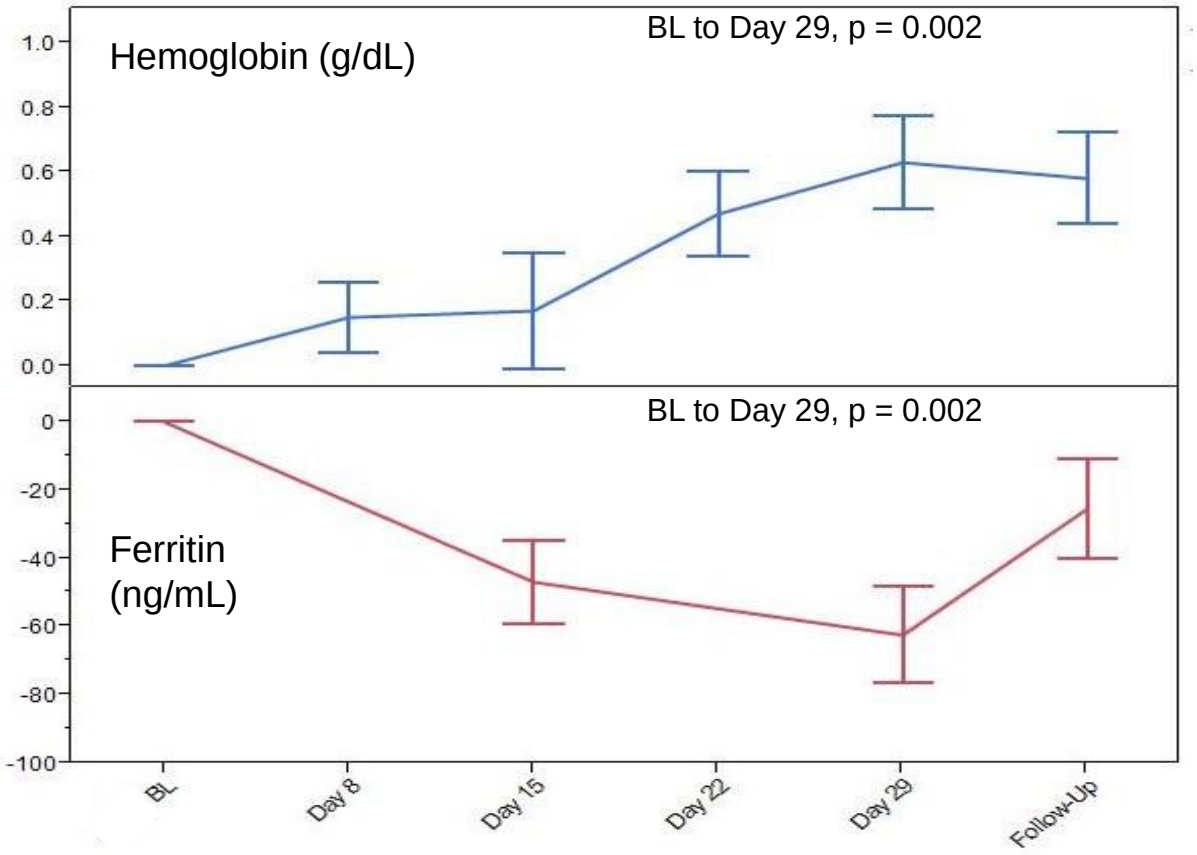
Single Dose Study: PK and EPO





Multidose Pilot Study: HGB and Ferritin



AKB-6548: Multidose Study Design

- Randomized, double-blind, placebo-controlled
- Primary objective to assess HGB response with 42 days of dosing
- Dosing groups: AKB-6548 240, 370, 500, or 630 mg or placebo
- 93 subjects:
  - CKD stage 3, 4, or 5 (not on dialysis)
  - HGB ≤ 10.5 g/dL
  - TSAT ≥ 20%
  - Ferritin ≥ 50 ng/mL
  - Age 18 – 79 y.o.
  - Either ESA naïve, or off ESA for > 11 weeks prior to screening
- All patients received minimum 50 mg, oral, elemental iron per day
- AKB-6548 dose could be reduced 50% for excess rise in HGB
- Clinical and safety assessments performed at Screening, Baseline, Weeks 2 & 4, End of Treatment (Week 6), and Follow-Up
- Erythropoietin measured at Baseline, Week 2, End of Treatment, and Follow-Up
- Oversight of safety by Study Monitoring Team (met at 25%, 50%, and 75% of total planned enrollment)

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Demographic and Baseline Characteristics

Characteristic	AKB-6548 240 mg N=18	AKB-6548 370 mg N=18	AKB-6548 500 mg N=17	AKB-6548 630 mg N=19	Placebo N=19
Gender, n (%)					
Male	9 (50.0)	11 (61.1)	4 (23.5)	12 (63.2)	7 (36.8)
Female	9 (50.0)	7 (38.9)	13 (76.5)	7 (36.8)	12 (63.2)
Age, years, Mean (SD)	64.2 (12.17)	68.9 (7.84)	64.7 (9.47)	64.9 (8.79)	64.9 (9.97)
BMI, Mean (SD)	30.6 (4.23)	29.8 (5.64)	32.1 (6.79)	29.1 (6.45)	29.8 (6.59)
eGFR, Mean (SD)	22.3 (12.10)	25.0 (11.22)	25.3 (9.18)	24.9 (12.28)	25.2 (11.05)
Kidney disease stage, n (%)					
Stage 3	5 (27.8)	4 (22.2)	4 (23.5)	5 (26.3)	5 (26.3)
Stage 4 & 5 (not on dialysis)	13 (72.2)	14 (77.8)	13 (76.5)	14 (73.7)	14 (73.7)
Diabetic, n (%)	14 (77.8)	12 (66.7)	12 (70.6)	13 (68.4)	13 (68.4)

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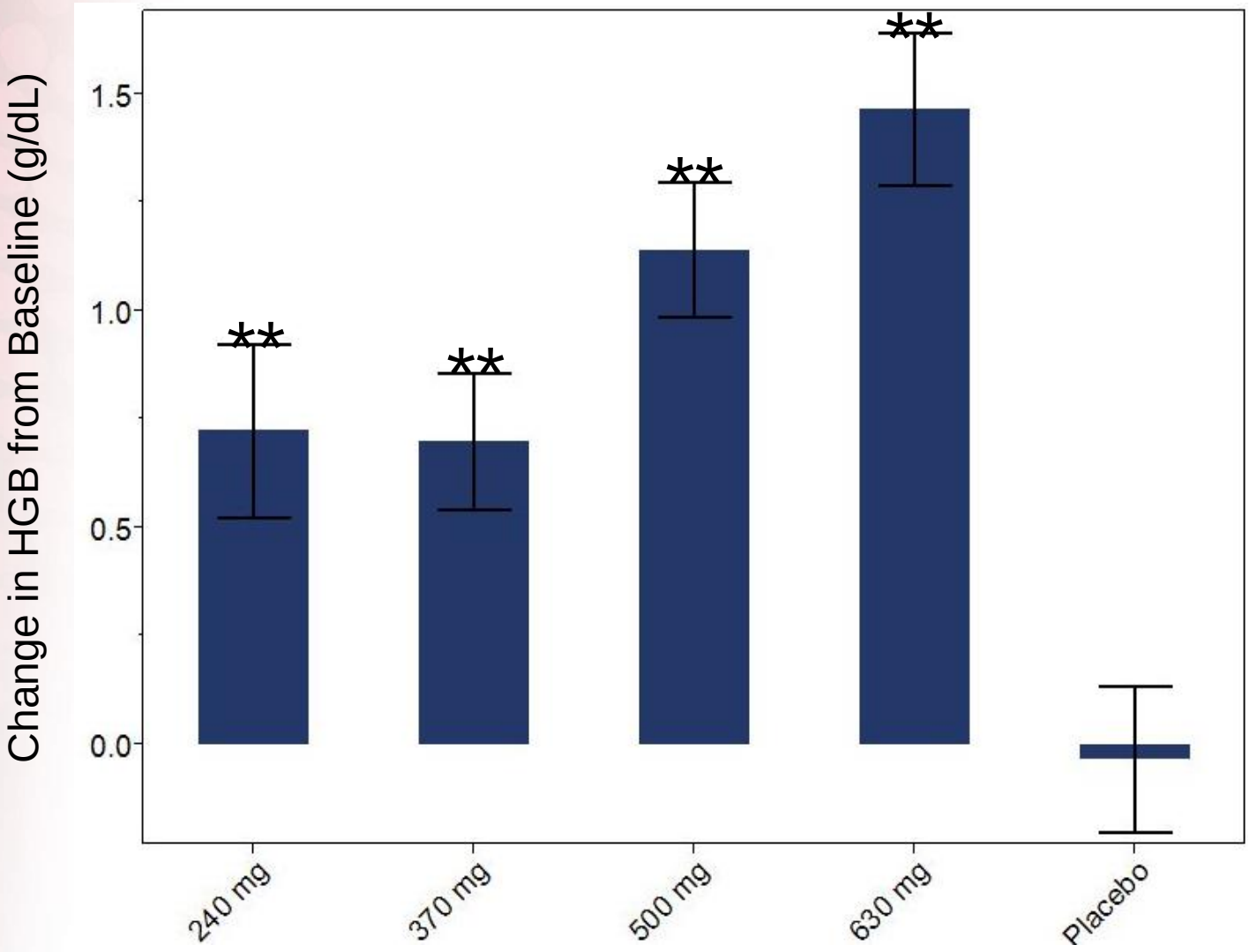
Hemoglobin: Change from Baseline to Week 6



Primary ANOVA:
p < 0.0001

Two tailed paired t-test of HGB: Baseline vs. Week 6
**p<0.01

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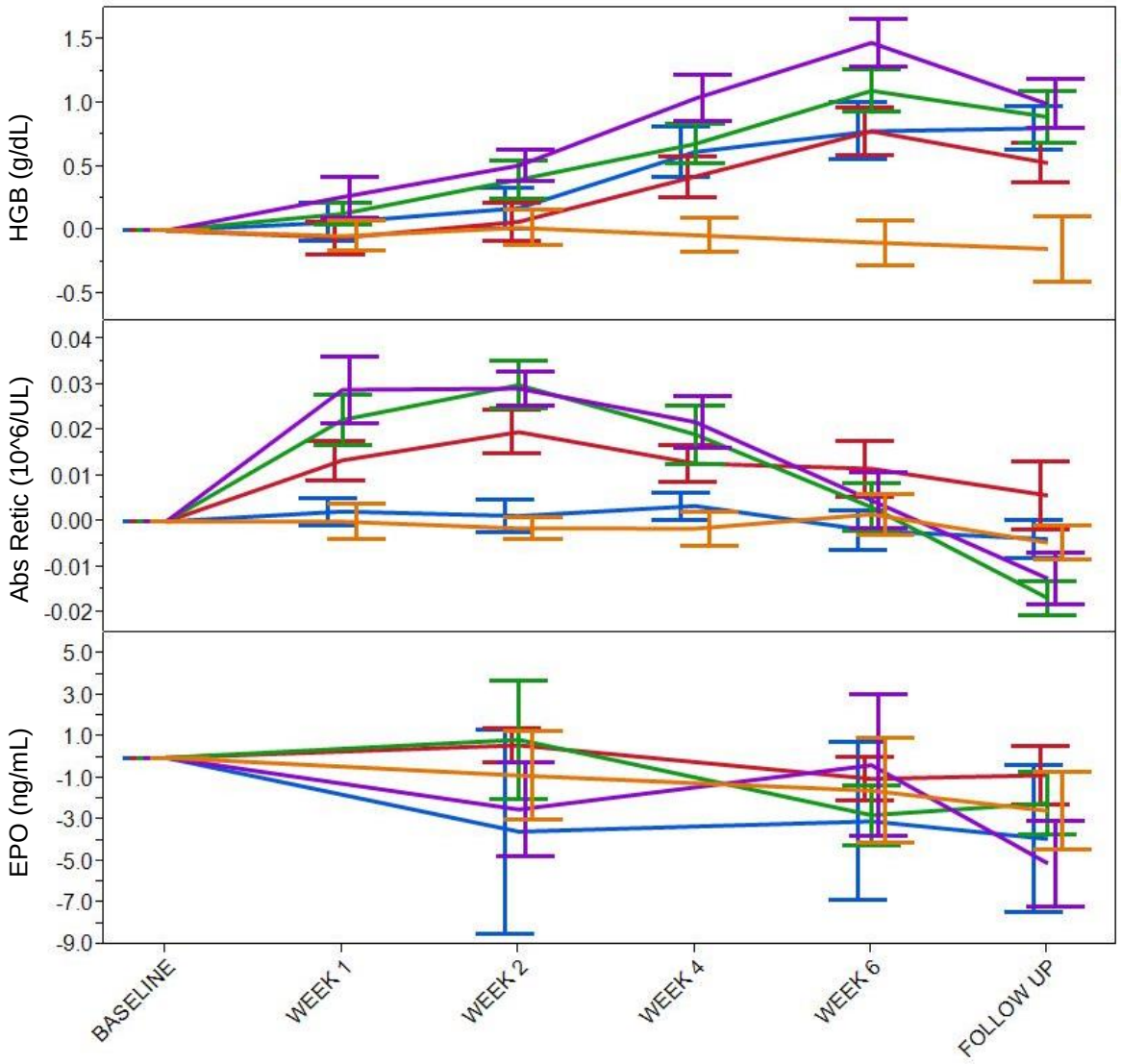
HGB, Absolute Reticulocyte Count, Erythropoietin: Time Course of Change from Baseline



HGB Statistics vs. Placebo

Dose	Wk 1	Wk 2	Wk 4	Wk 6
240			*	**
370				**
500			*	**
630			**	**

* $p < 0.05$; ** $p < 0.01$

Abs. Retic. Statistics. Vs. Placebo

Dose	Wk 1	Wk 2	Wk 4	Wk 6
240				
370		**		
500	*	**	**	
630	**	**	**	

* $p < 0.05$; ** $p < 0.01$

Treatment
- AKB-6548 240 mg
- AKB-6548 370 mg
- AKB-6548 500 mg
- AKB-6548 630 mg
- Placebo

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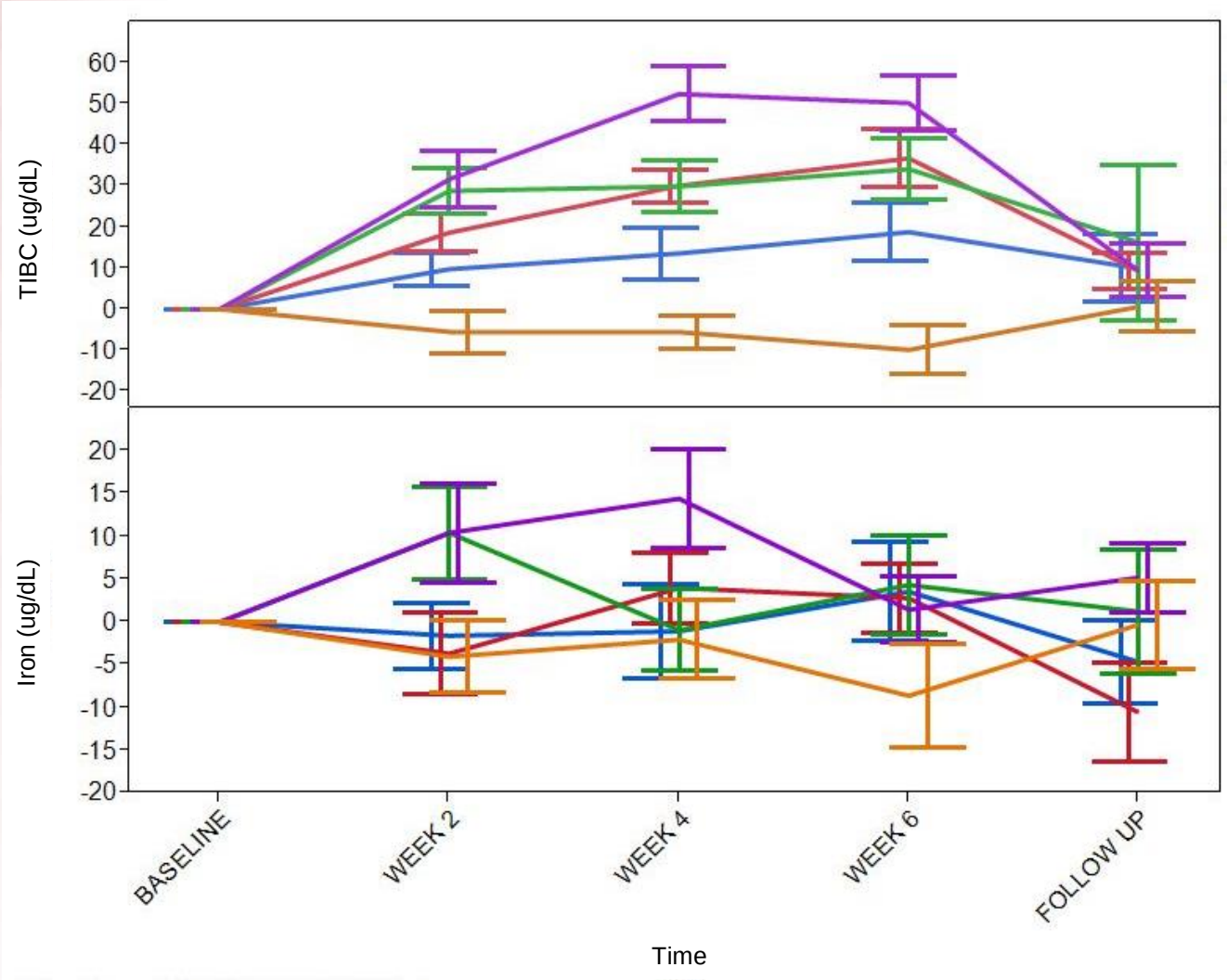
Total Iron Binding Capacity (TIBC) and Iron: Time Course of Change from Baseline



TIBC Statistics vs. Placebo

Dose	Wk 2	Wk 4	Wk 6
240			*
370	**	**	**
500	**	**	**
630	**	**	**

* $p < 0.05$; ** $p < 0.01$

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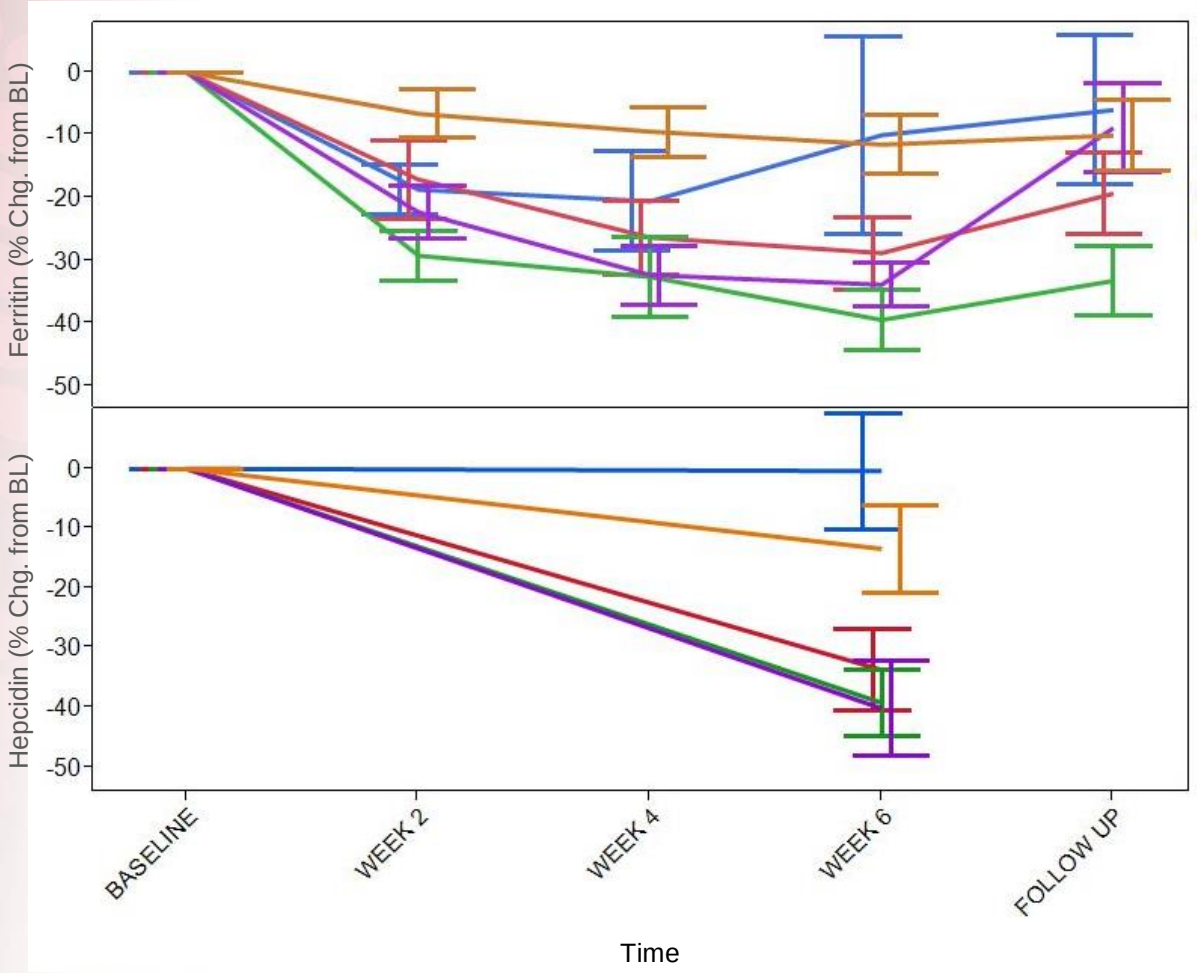
Ferritin and Hepcidin: Time Course of % Change from Baseline



Ferritin % Stats. Vs. Plac.

Dose	Wk 2	Wk 4	Wk 6
240			
370			
500	*	*	*
630	**	*	

* $p < 0.05$; ** $p < 0.01$

Hepcidin % Stats. vs. Plac.

Dose	Wk 6
240	
370	
500	0.06
630	*

* $p < 0.05$

Treatment
- AKB-6548 240 mg
- AKB-6548 370 mg
- AKB-6548 500 mg
- AKB-6548 630 mg
- Placebo

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Adverse Events

Category	AKB-6548 240 mg N=18	AKB-6548 370 mg N=18	AKB-6548 500 mg N=17	AKB-6548 630 mg N=19	Placebo N=19
Any TEAE	9 (50.0)	6 (33.3)	8 (47.1)	11 (57.9)	11 (57.9)
Drug-related TEAE	3 (16.7)	2 (11.1)	2 (11.8)	3 (15.8)	1 (5.3)
Serious TEAE	2 (11.1)	3 (16.7)	1 (5.9)	1 (5.3)	1 (5.3)
Deaths	0	1 (5.6)	0	0	0

- AKB-6548 appeared safe and was generally well tolerated
- Adverse events were evenly distributed across the dosing groups with no apparent dose related effect
  - None of the SAEs were considered to be drug related.

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Summary and Conclusions

- Generally well tolerated up to 630 mg for 42 days
- Treatment resulted in a dose responsive increase in HGB (Hct, RBC count, and absolute reticulocyte count)
  - Daily dosing did not lead to an increase in baseline (predose) erythropoietin levels
  - Reticulocyte response peaked in 1 to 2 weeks
- A parallel dose responsive increase occurred in iron mobilization (and likely absorption)
  - Stable iron levels with concurrent increase in HGB
  - Increase in TIBC
  - Decrease in Hepcidin and Ferritin
- Phase 2b study planned for 2013

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