Controlled Hemoglobin Response in a Double-Blind, Placebo-Controlled Trial of AKB-6548 in Subjects with Chronic Kidney Disease

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AKB-6548 Background

- Akebia Therapeutics is a public biopharmaceutical company focused on the development and commercialization of novel proprietary therapeutics based on hypoxia inducible factor (HIF) biology
- 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 HIF2α > HIF1α
  - HIF2α is less widely expressed, but is critical for production of erythropoietin (EPO)
  - HIF1α is found in almost all cell types
- AKB-6548 has been generally very well tolerated in four 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
- AKB-6548 is presently being evaluated in a 200 subject, randomized, placebo controlled, Phase 2b study in subjects with anemia secondary to CKD.

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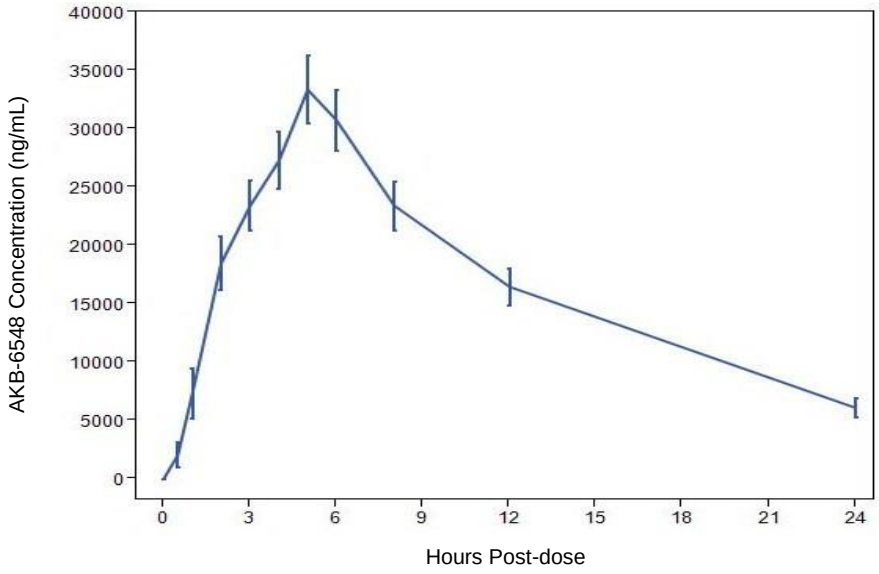
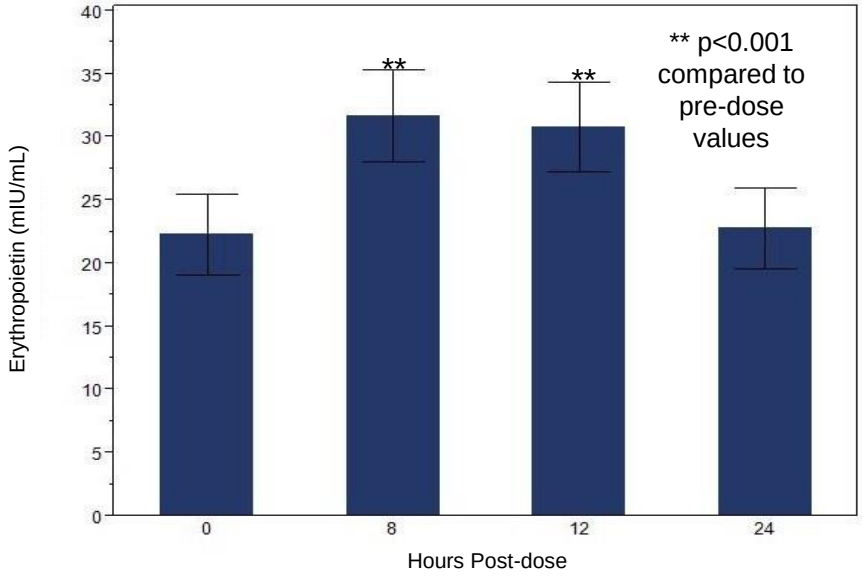
Single Dose Study in CKD: PK and EPO



AKB-6548 Concentration Over 24 Hours in CKD - 500 mg Dose

T_{max} (h)	Half-life (h)
4.8 ± 1.6	7.9 ± 2.1



EPO Levels Over 24 Hours in CKD – 500 mg Dose

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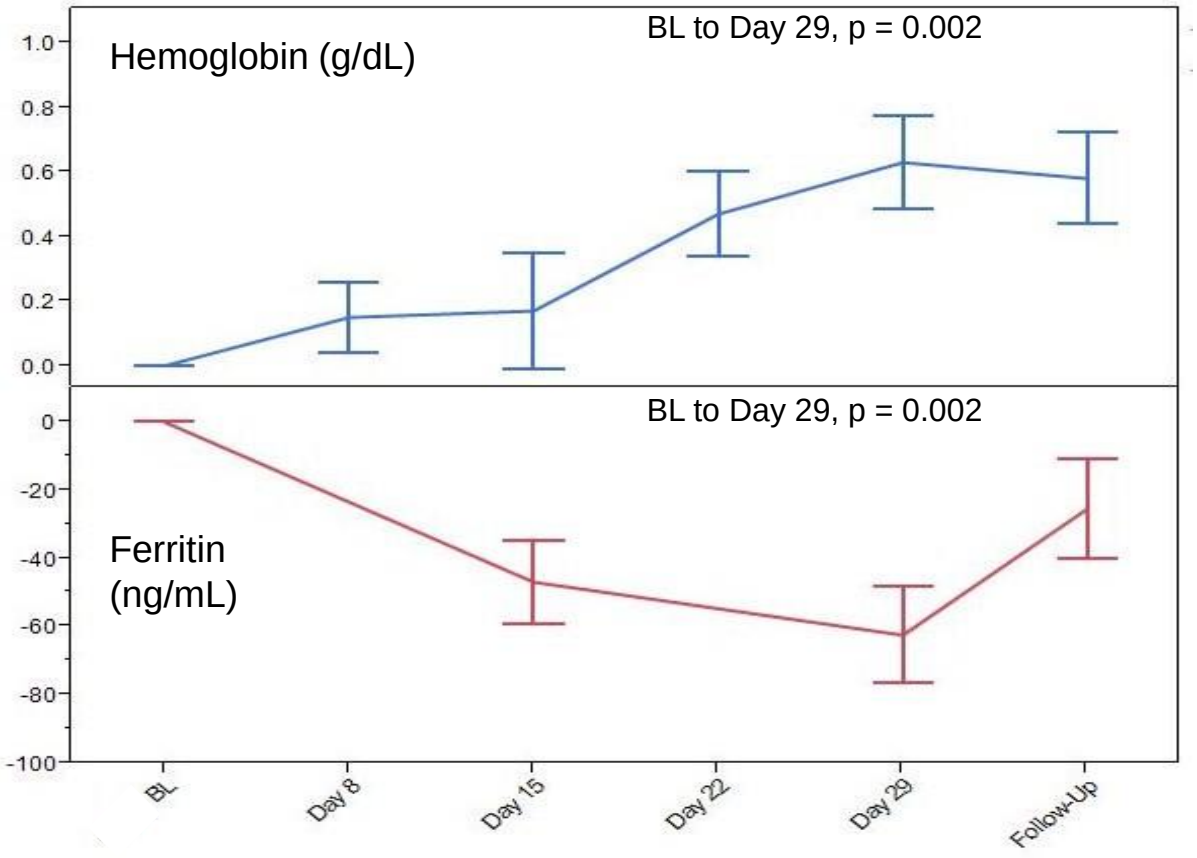
Pilot, 28 Day, Dose Escalation Study in CKD: HGB and Ferritin



AKB-6548: Phase 2a 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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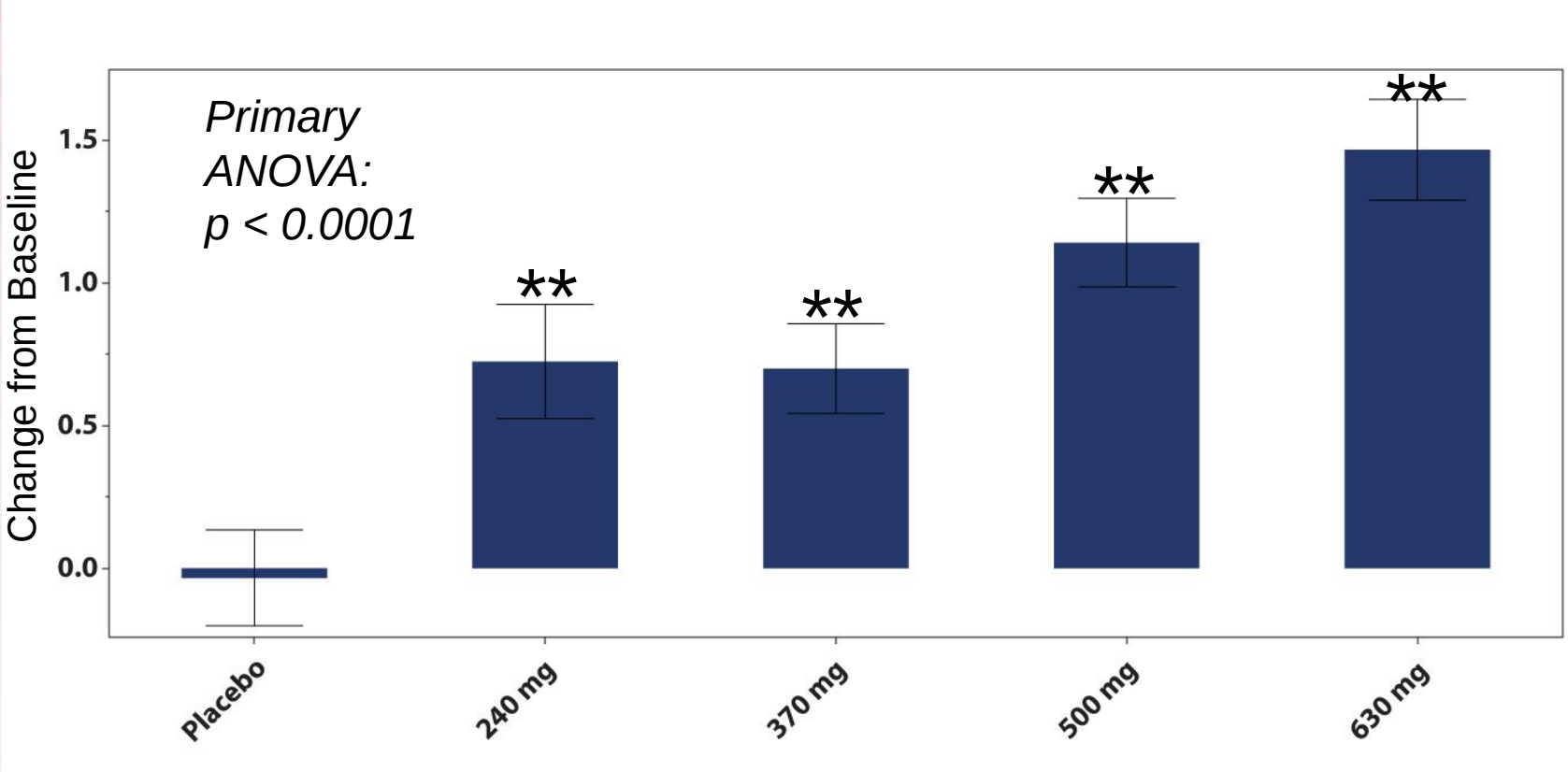
Hemoglobin: Change from Baseline to Week 6



Two tailed paired t-test of HGB: Baseline vs. Week 6

**p<0.01

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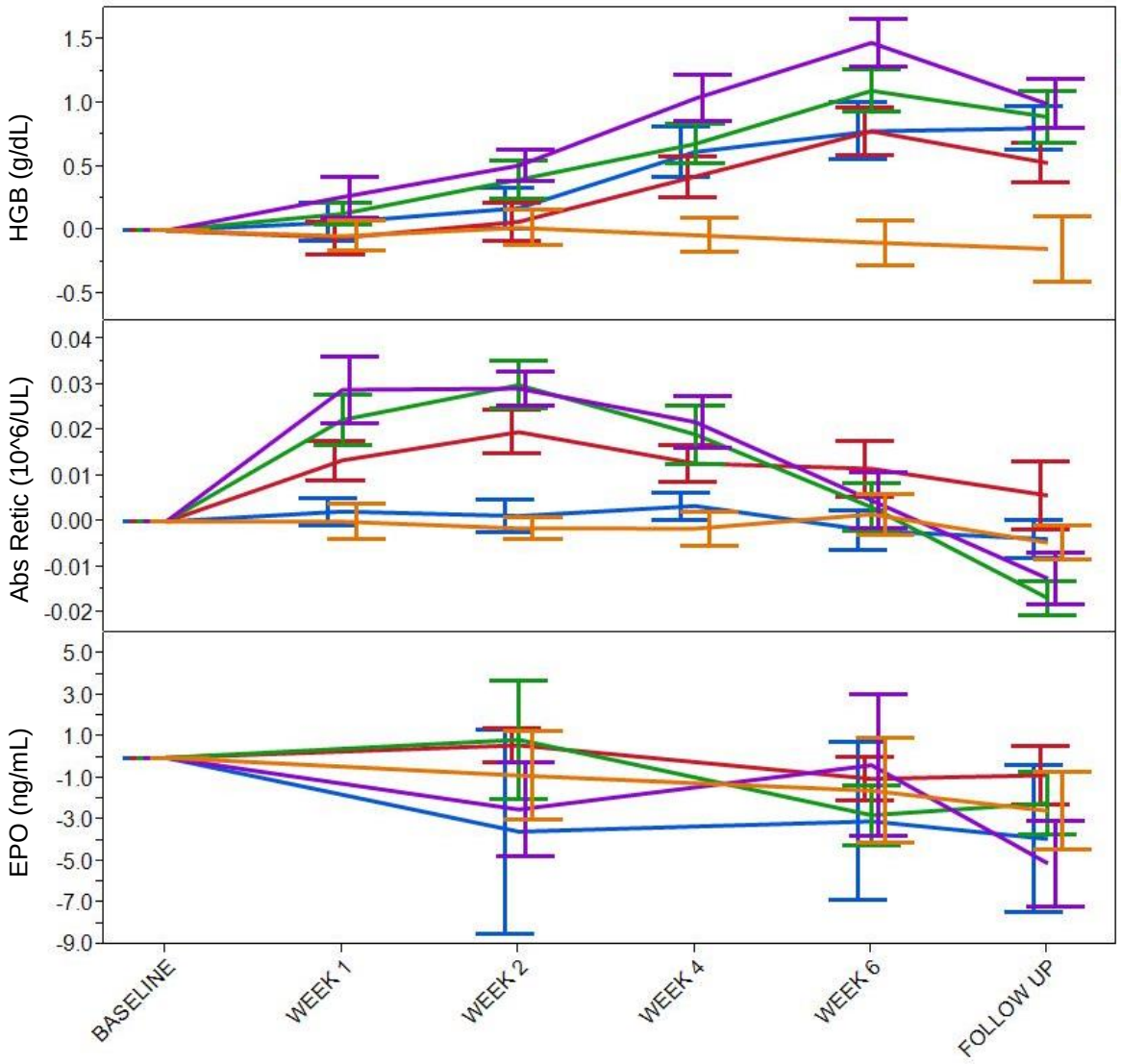
HGB, Absolute Reticulocyte Count, Erythropoietin: Time Course of Change from Baseline



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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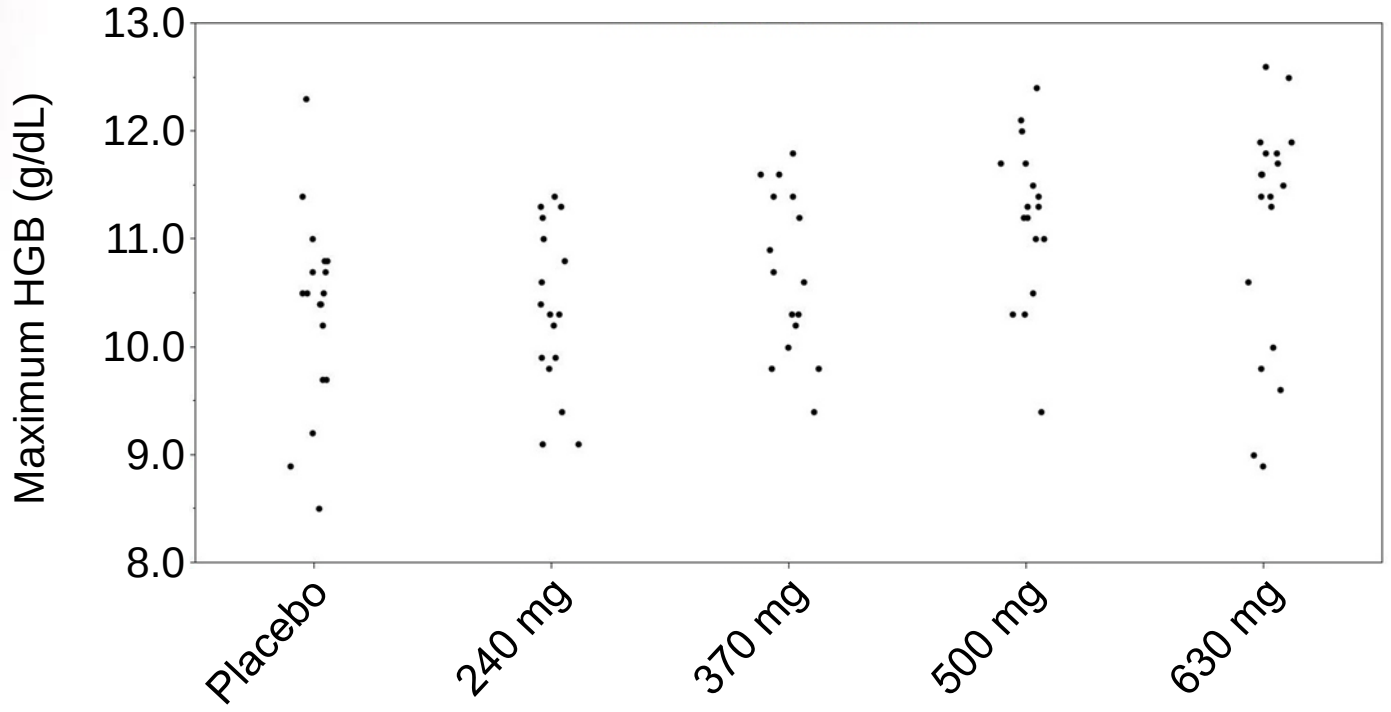
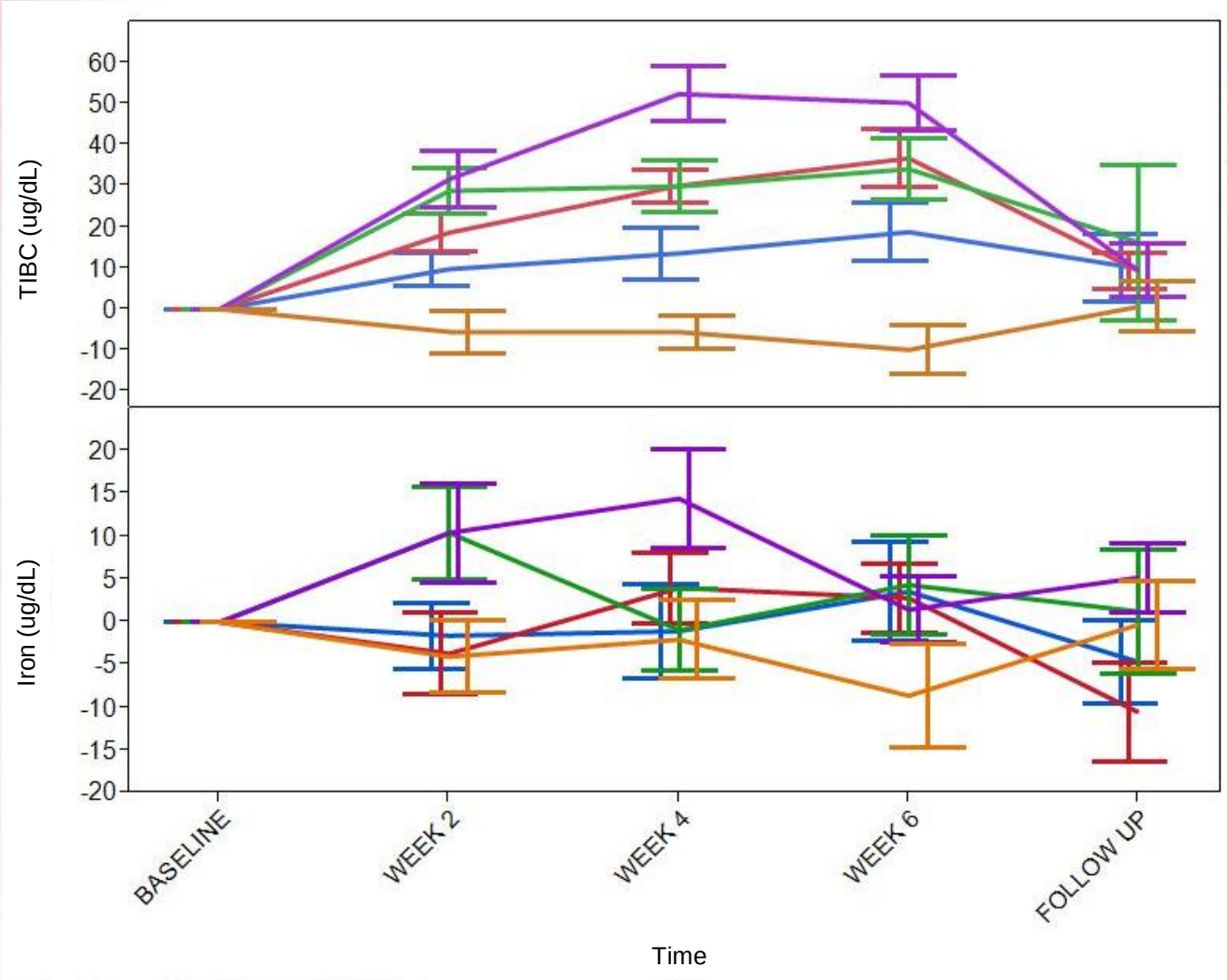
Maximum HGB throughout the dosing period remained <13.0 g/dL



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	**	**	**

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

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

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Adverse Events (AEs)

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 was generally well tolerated and no safety signals were observed
- AEs were evenly distributed across dosing groups with no apparent dose related effect
- None of the SAEs were considered to be drug related
  - The subject who died received only three or four doses of study drug. Subject was hospitalized for uremia. The subject's death occurred several days into her hospitalization following an in-hospital procedure when she developed sustained ventricular tachycardia and cardiac arrest. The initial SAE and her death were not considered to be related to AKB-6548.

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Summary and Conclusions

- 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)
  - Controlled increase in HGB, without increases above 13.0 g/dL
  - Daily dosing did not lead to an increase in predose EPO 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
  - Dose responsive increase in TIBC

Acknowledgements

- Pharm-Olam International, Ltd.
  - Dmitri Davydov, MD
  - Colleen Trosclair and the CI-0005 team
- LEAD Clinical Research
  - Lynne Welling
  - Lori Weaver
  - Keri Van Becelaere
- Akebia Scientific Advisory Board
  - Volker Haase, MD
  - H. Franklin Bunn, MD
  - John Adamson, MD
  - Peter Hutt, Esq.
  - Randall Johnson, PhD
- Participating CROs
  - Covance
  - Midwest Bio Research (WIL Research)
  - Intrinsic Life Sciences
  - Rules Based Medicine (Myriad RBM)
  - Xerimis, Inc.
- CI-0005 Investigative Team
  - Fahd Al-Saghir, MD
  - Marializa Bernardo, MD
  - Riad Darwish, MD
  - Brian Donner, DO
  - Mohamed El-Shahawy, MD
  - Michael Germain, MD
  - Timothy Hines, MD
  - Robert Hootkins, MD
  - Radu Jacob, MD
  - Aamir Jamal, MD
  - Samia A Khwaja, MD
  - Oleksandr Kovalchuk, MD
  - Jian Li, MD
  - Edouard Martin, MD
- CI-0005 Investigative Team
  - Carlos Martinez, MD
  - Reza Mizani, MD
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  - Peter Nguyen, MD
  - Robert Provenzano, MD
  - Peter Ramirez, MD
  - John Robertson, MD
  - Dennis Ross, MD
  - Shayan Shirazian, MD
  - Chris Sholer, MD
  - Mark Smith, MD
  - Fernanco Trespalacios, MD
  - Raja Zabaneh, MD

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