AKB-6548, A Novel Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Reduces Hepcidin and Ferritin while It Increases Reticulocyte Production and Total Iron Binding Capacity In Healthy Adults

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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 which sets up HIF for degradation
  - Initial indication: anemia associated with chronic kidney disease (CKD)
- AKB-6548 stabilizes HIF2 > HIF1
  - HIF2 is less commonly 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:
  - Phase 1a: up to 1200 mg as a single dose
  - Phase 1b: up to 900 mg for 10 days of dosing

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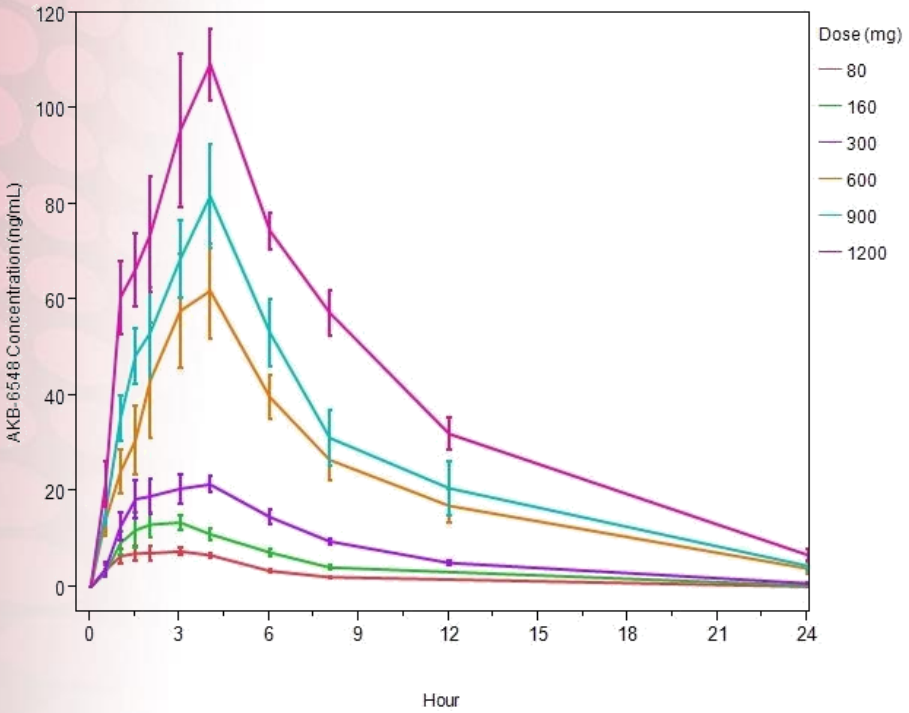
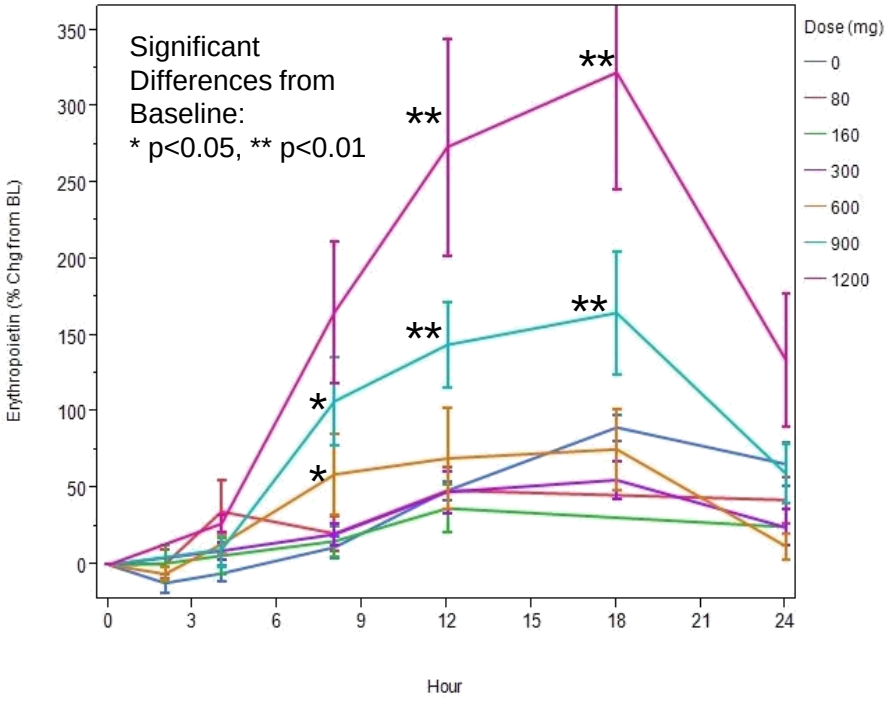
Study Background

Pharmacokinetics



EPO Response



In a Phase 1a, single dose study, AKB-6548 demonstrated the following in healthy male subjects (6 cohorts of 8 males: 6 receiving AKB-6548 and 2 receiving placebo per cohort):

1. Dose proportionate increases in C_{max} and AUC, with a half-life of approximately 4.5 hours
2. Dose-responsive increases in diurnal EPO production, with peak rises in EPO at around 18 hours, and then a return to near basal levels at 24 hours; Significant increases from baseline were observed at 8 hours, starting at 600 mg ($p<0.05$)

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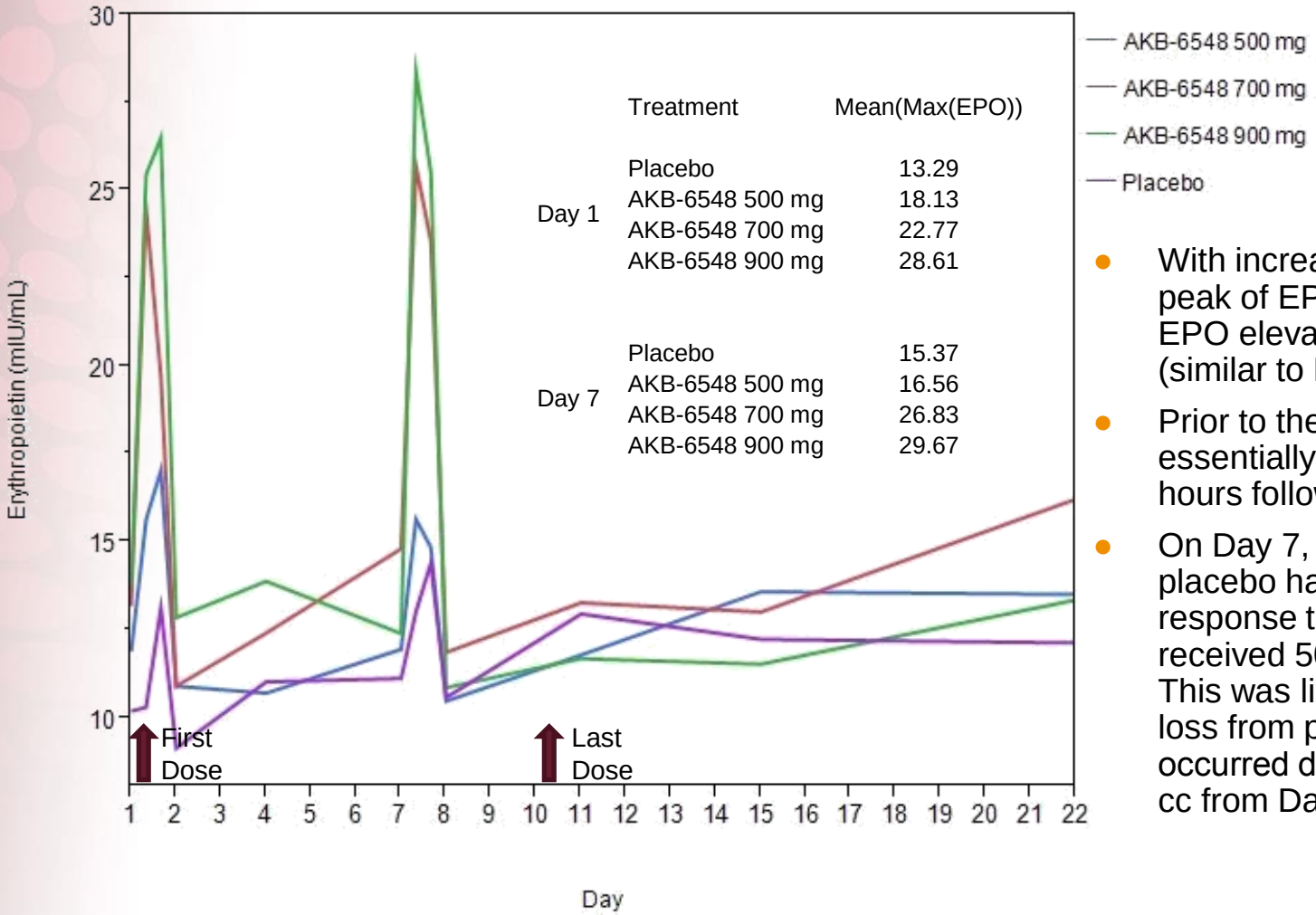
Study Design

- Three cohorts, with each cohort consisting of 11 healthy males
  - 8 received AKB-6548 and 3 receive placebo
  - AKB-6548 doses were: Cohort 1 – 500 mg; Cohort 2 – 700 mg; and Cohort 3 – 900 mg
  - Subjects received drug or placebo once daily (fasting) for 10 days (Days 1 – 10 on the graphs)
    - Subjects were allowed to eat 2 hours after dosing; Subjects received high fiber diet for first 2 days of dosing to facilitate stool collection
    - Subjects were discharged on Day 11, and followed up on Days 15 and 22.
  - Safety labs were drawn prior to dosing each morning; Additional labs were drawn on days 1 and 7 for EPO, PK, and exploratory biomarkers
- Pharmacodynamic effect was evaluated through Day 11 (24 hours following last dose)

Study Demographics

Category	Placebo N=9	AKB-6548 500 mg N=8	AKB-6548 700 mg N=9	AKB-6548 900 mg N=8	Total N=34
Age (SD)	35.2 (11.0)	28.8 (9.6)	30.9 (10.9)	35.6 (9.5)	32.6 (10.3)
White	5	2	5	4	16
African Am.	4	6	4	4	18
Weight, kg (SD)	83.1 (6.5)	78.0 (11.2)	84.4 (9.0)	82.9 (13.1)	82.2 (9.9)
BMI (SD)	26.2 (2.2)	24.9 (3.5)	26.3 (2.4)	26.1 (3.3)	25.9 (2.8)

EPO Response
(Peak Responses Only Measured on Days 1 and 7)



	Treatment	Mean(Max(EPO))
Day 1	Placebo	13.29
	AKB-6548 500 mg	18.13
	AKB-6548 700 mg	22.77
	AKB-6548 900 mg	28.61
Day 7	Placebo	15.37
	AKB-6548 500 mg	16.56
	AKB-6548 700 mg	26.83
	AKB-6548 900 mg	29.67

- With increased dose, both the peak of EPO and the duration of EPO elevation is increased (similar to Phase 1a)
- Prior to the morning dose, EPO essentially returns to baseline 24 hours following AKB-6548 dose
- On Day 7, subjects who received placebo had a similar EPO response to those subjects who received 500 mg of AKB-6548. This was likely driven by blood loss from phlebotomy that occurred during the study (≈ 230 cc from Day -1 through Day 8)

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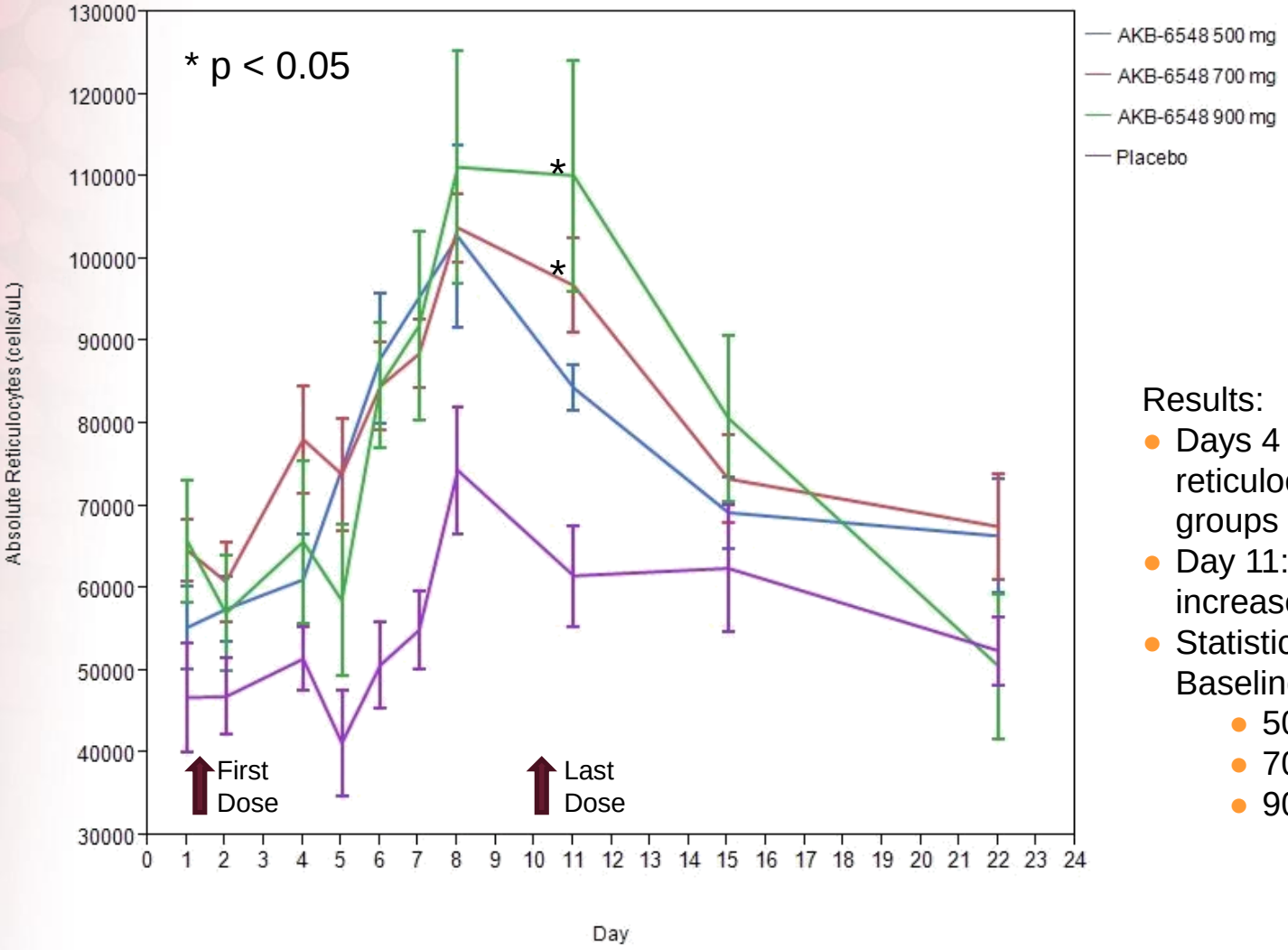
Absolute Reticulocyte Count



Results:

- Days 4 – 8: Earlier rise in reticulocytes in drug treated groups
- Day 11: Clear dose related increase in reticulocytes.
- Statistics (Day 11 vs. Baseline)
  - 500 mg, p = 0.08
  - 700 mg, p = 0.02
  - 900 mg, p < 0.01

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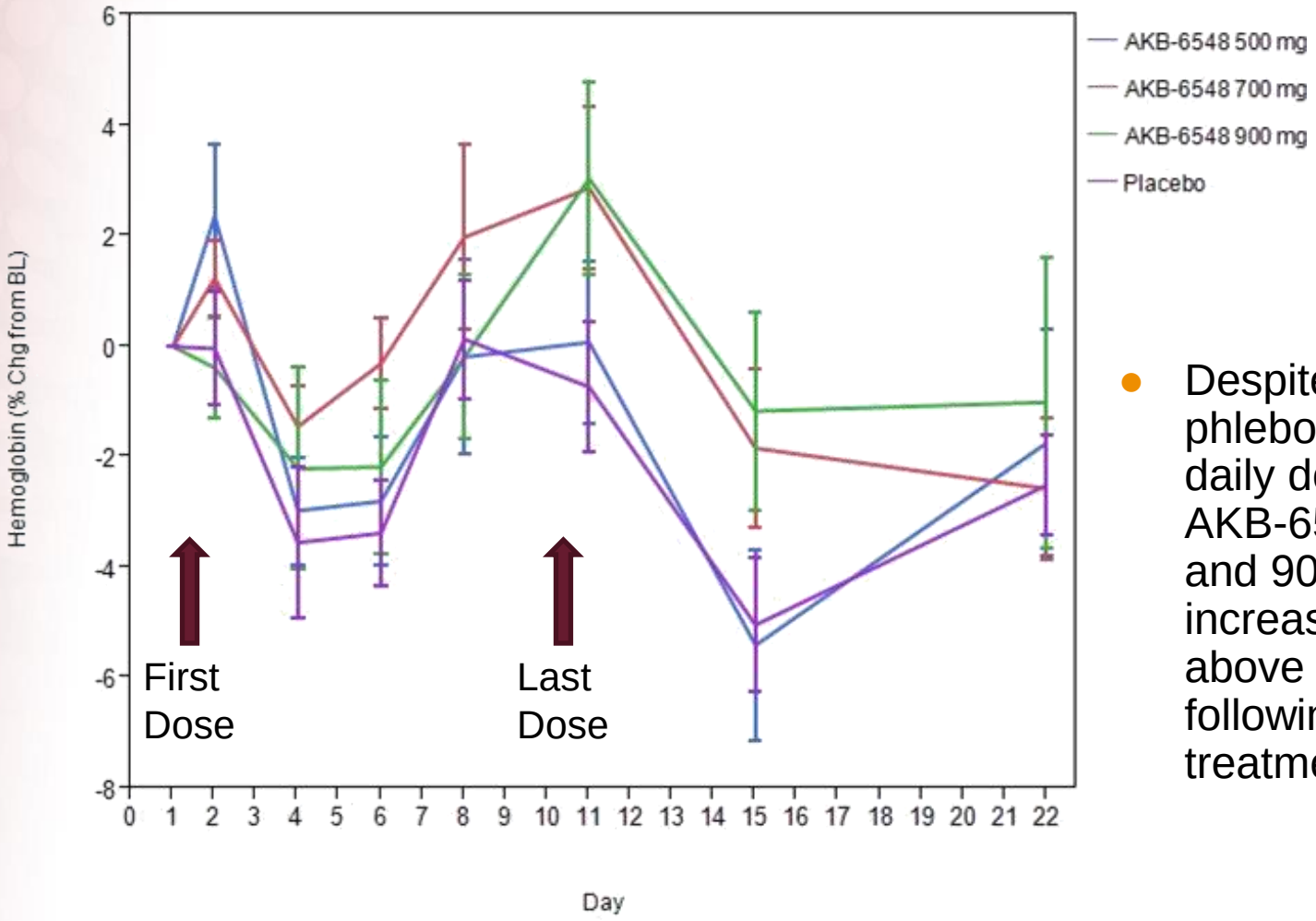
Rise in Hemoglobin



- Despite substantial phlebotomy, once daily dosing with AKB-6548 at 700 and 900 mg increased Hgb above baseline following 10 days of treatment.

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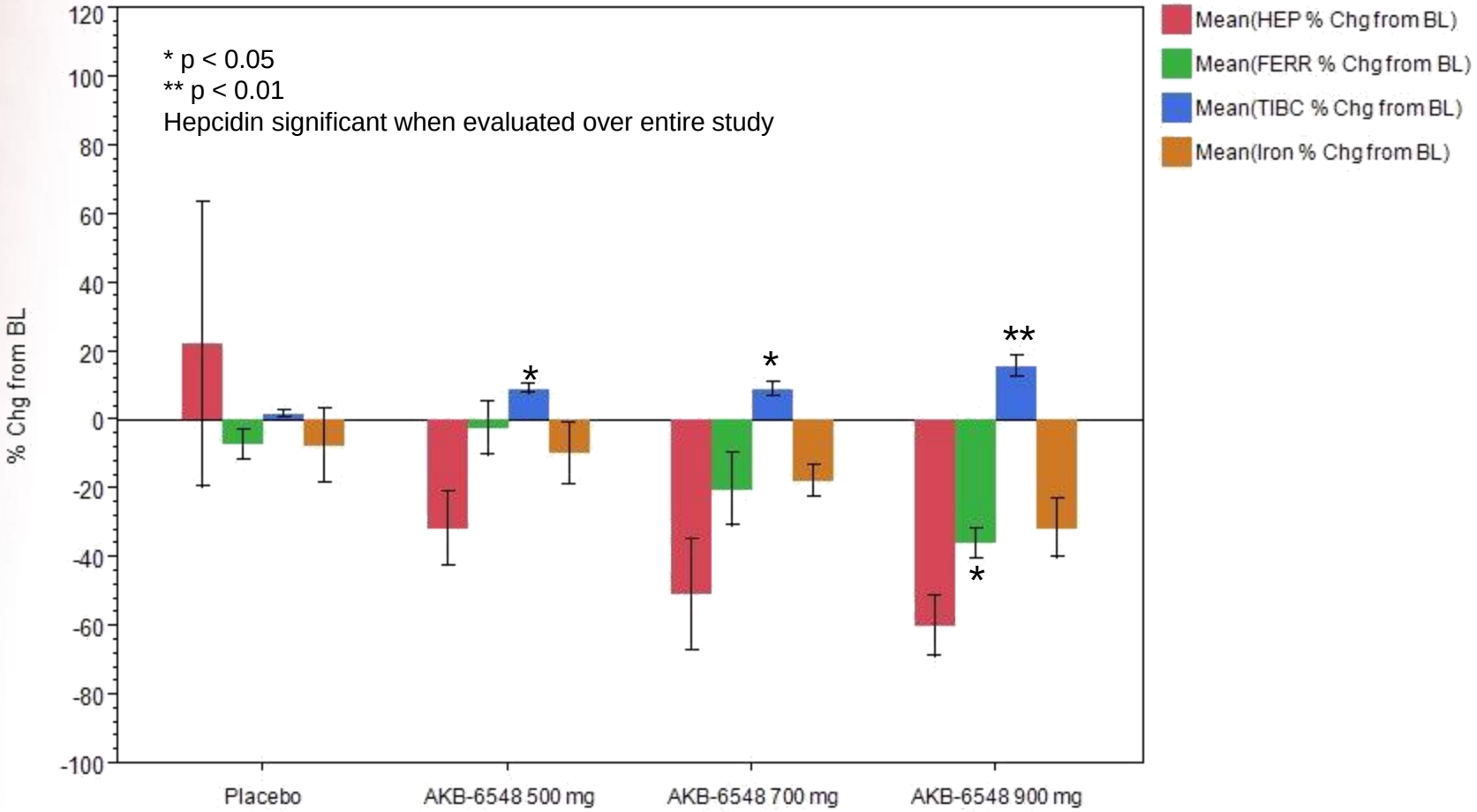
Significant Effect on Iron Metabolism



Day 11: Significant, dose related reductions in Hepcidin and Ferritin, associated with a significant increase in Transferrin (TIBC)

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Overview of Adverse Events

Category	Placebo N=9	AKB-6548 500 mg N=8	AKB-6548 700 mg N=9	AKB-6548 900 mg N=8	Total N=34
Any TEAE	7 (78%)	7 (88%)	6 (67%)	6 (75%)	26 (77%)
Drug Related TEAE	0 (0%)	0 (%)	1 (11%)	1 (13%)	2 (6%)
Serious TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

TEAE = Treatment Emergent Adverse Event

- Overall, AKB-6548 was very well tolerated
- Primary area of concern is GI tolerance
  - Subjects with various GI issues tended to improve during the course of the study
  - Manifestation of GI AEs may have been increased due to:
    - Use of high fiber diet during Days 1 and 2 to improve stool collection
    - Fasted dosing
- Two subjects had elevated LFTs (maximum ≤ 2x ULN)
  - 500 mg dose – LFT rise was diet related, with LFTs improving while still on dosing
  - 700 mg dose – LFT rise (Days 11 and 15) occurred following dose of Azithromycin (Day 8) for Chlamydia urethritis

Summary

	Dosing Groups			
	Placebo	**500 mg**	**700 mg**	**900 mg**
Average, Max EPO (mIU/mL)	15.50±2.87	18.01±5.15 p=0.8951	28.03±9.20 p=0.0207	32.44±15.29 p=0.0023
Abs Reticulocyte on Day 11 (thousands/µL)	61.59±18.31	84.41±7.91 p=0.1009	96.85±16.23 p=0.0067	110.21±37.15 p=0.0004
Mean TIBC % Change from BL	1.78±2.80	9.17±3.99 p=0.0176	8.94±5.37 p=0.0219	15.72±7.87 p<0.0001
Mean Hepcidin % Change from BL	22.12±124.49	-31.57±30.40 p=0.3215	-50.81±45.86 p=0.1226	-59.94±23.32 p=0.0862
Mean Ferritin % Change from BL	-7.16±12.55	-2.49±21.87 p=0.9381	-20.21±29.95 p=0.4338	-36.00±11.36 p=0.0246

BL: Baseline

- Double-blind, placebo-controlled study, 33 healthy males were randomized to three treatment groups of 500, 700, or 900mg AKB-6548
- Dosing was generally well tolerated, and the results show a dose-related increase in maximum EPO, reticulocytes, and total iron binding capacity (TIBC), as well as dose-related reductions in hepcidin and ferritin

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Conclusions

- AKB-6548 enhances erythropoiesis by inducing dose proportionate increases in diurnal EPO production in concert with enhanced iron mobilization (decreases in hepcidin and ferritin, and increased iron)
- Combined effects result in significant, dose proportionate increases in reticulocyte production starting by Day 6, following the start of dosing
- Hemoglobin is also increased by Day 11 at mid and high dose levels
- AKB-6548 was generally well tolerated
- AKB-6548 could represent a safer and more effective approach to treating anemia than currently available agents

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