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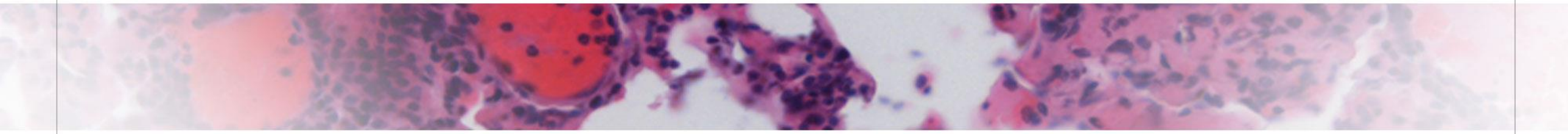

ADMINISTRATION OF KER-047, A NOVEL ALK2 INHIBITOR, ELICITED ROBUST AND SUSTAINED INCREASES IN SERUM IRON IN HEALTHY PARTICIPANTS

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Poster # 769

Session: 102. Regulation of Iron Metabolism: Poster I

Disclosures

Ordonez C, Lachey J, Barger R, Serino T, Tseng C, and Seehra J are employees of and security holders in Keros Therapeutics, Inc.

Rovaldi C is a paid consultant and security holder in Keros Therapeutics, Inc.

Snyder B has no disclosures

Iron Homeostasis is a Tightly Regulated Process

- Absorption, transport, storage and excretion of iron is maintained as a semi-closed system to avoid both iron deficiency and overload.
- Imbalance can produce systemwide and cellular-level defects
  - Low iron in circulation and bone marrow leads to reduction in erythropoiesis
  - Inadequate iron in cells can result in a variety of defects including reduced proliferation (Seligman et al. 1992) and disrupted enzymatic activity (Ilbert and Bonnefoy 2012)

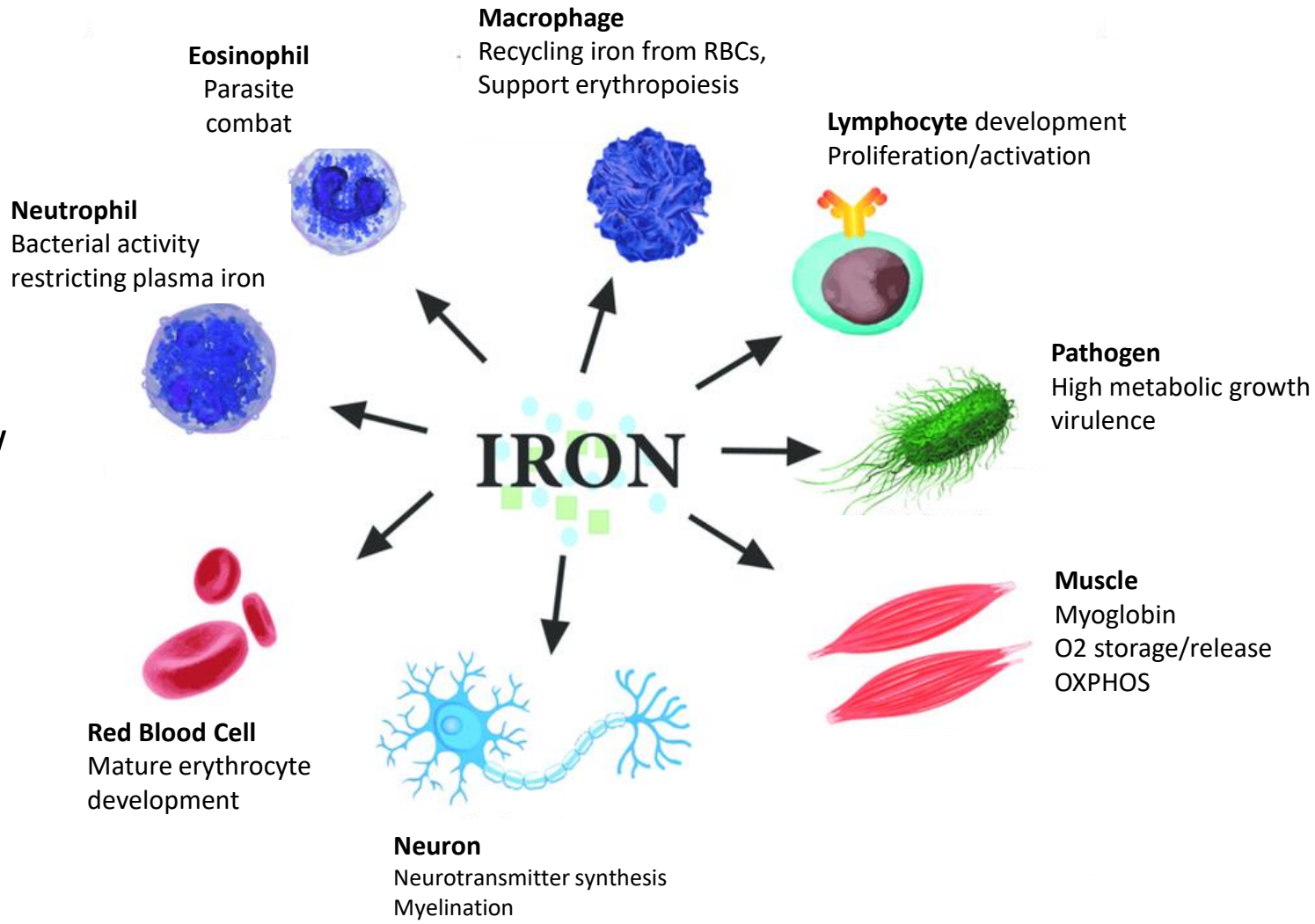
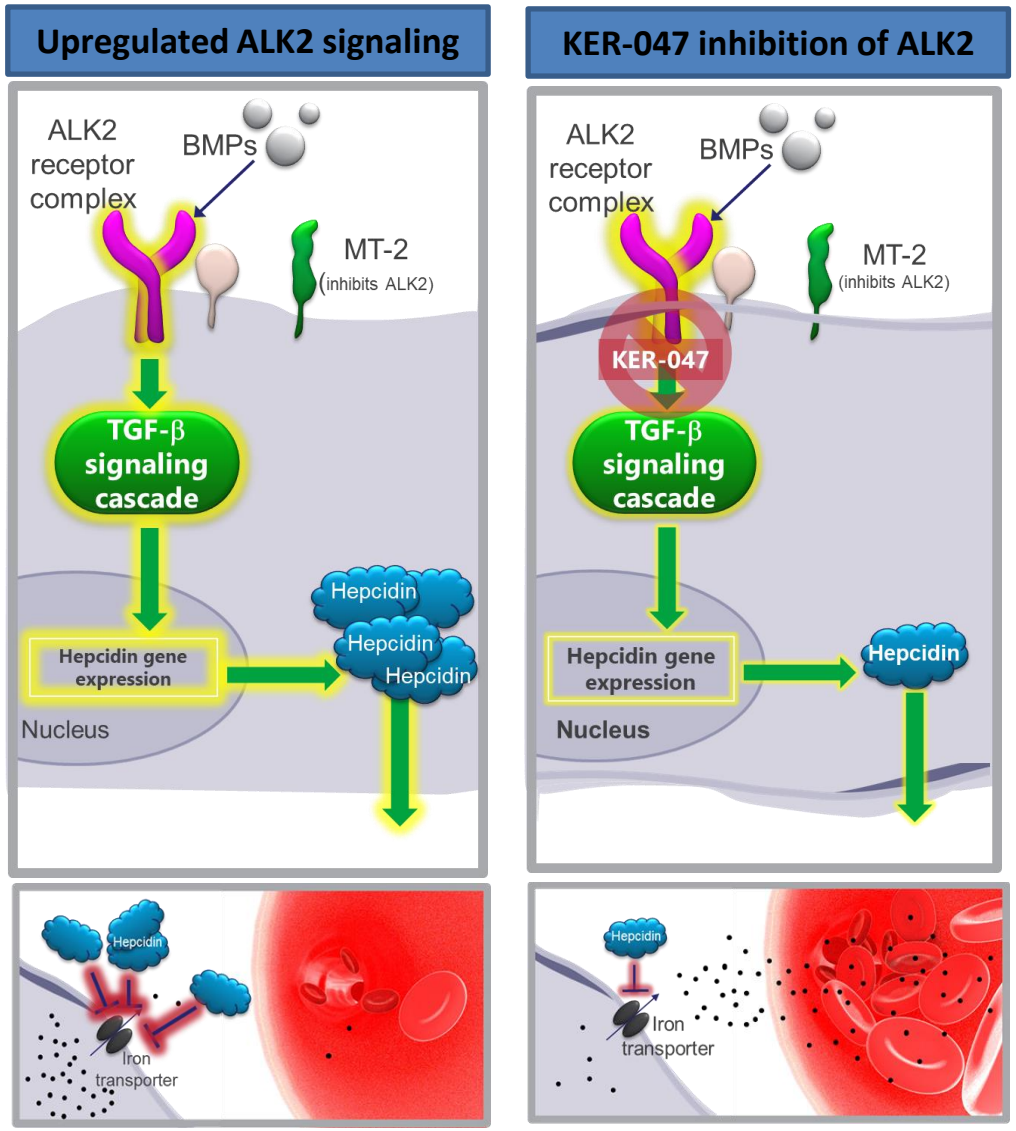


Fig. modified from Cronin et al. 2019, Front. Mol. Biosci

Iron Levels are Regulated via ALK2 Signaling and Hepcidin

- Hepcidin is the master regulator of iron homeostasis.
- Expression of hepcidin is controlled, in part, by signaling through transforming growth factor-beta (TGF-β) receptors including activin receptor-like kinase-2 (ALK2).
- Dysregulation of ALK2 signaling results in inappropriately high hepcidin and leads to insufficient iron for red blood cell production in the bone marrow, resulting in anemia.
- KER-047 is a selective ALK2 inhibitor that has the potential to normalize ALK2 signaling and the downstream sequelae that results in anemia as a result of elevated hepcidin.

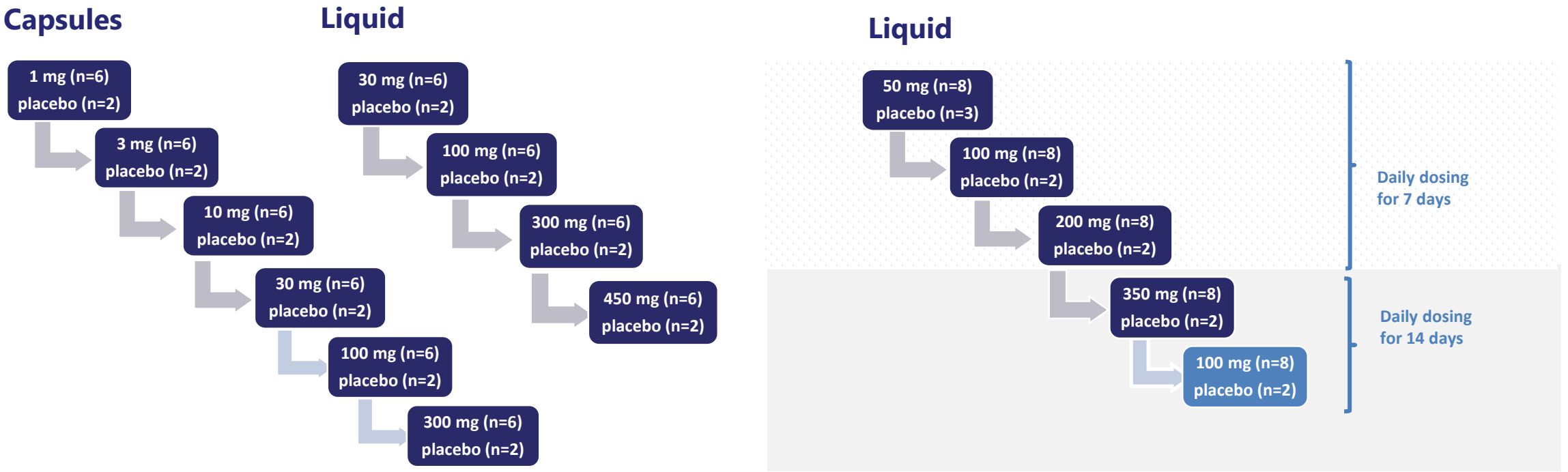


KER-047 First-in-Human Study in Healthy Participants

- **Primary Objectives: safety, tolerability and PK**
- **Secondary Objectives: PD (hematology, iron indices)**

Part 1: Single Ascending Doses (SAD)
- 60 participants received KER-047
- 20 participants received placebo

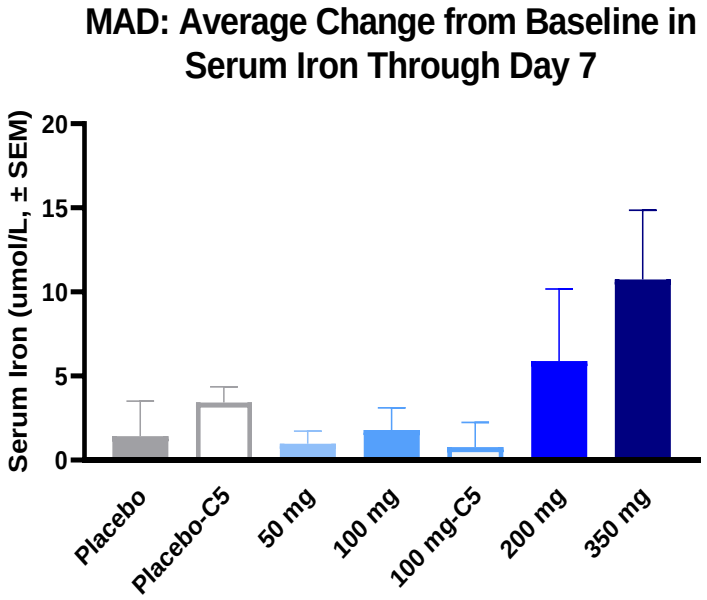
Part 2: Multiple Ascending Doses (MAD)
- 40 participants received KER-047
- 11 participants received placebo

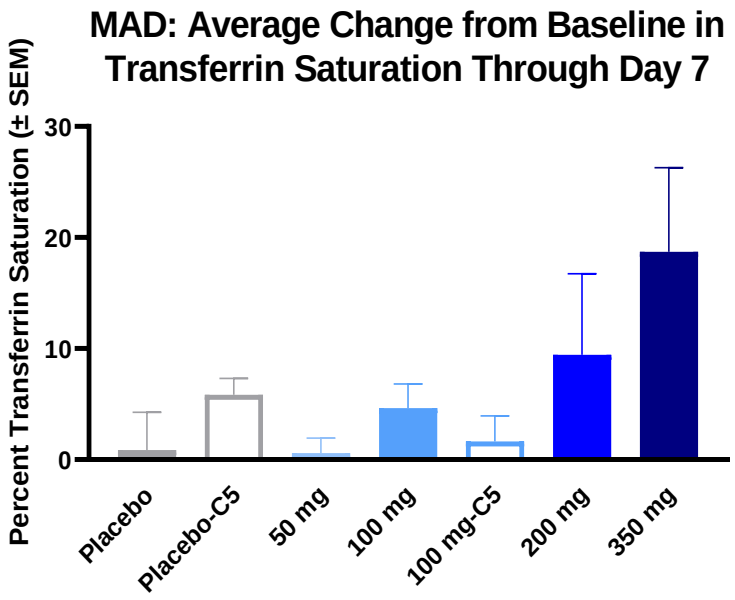


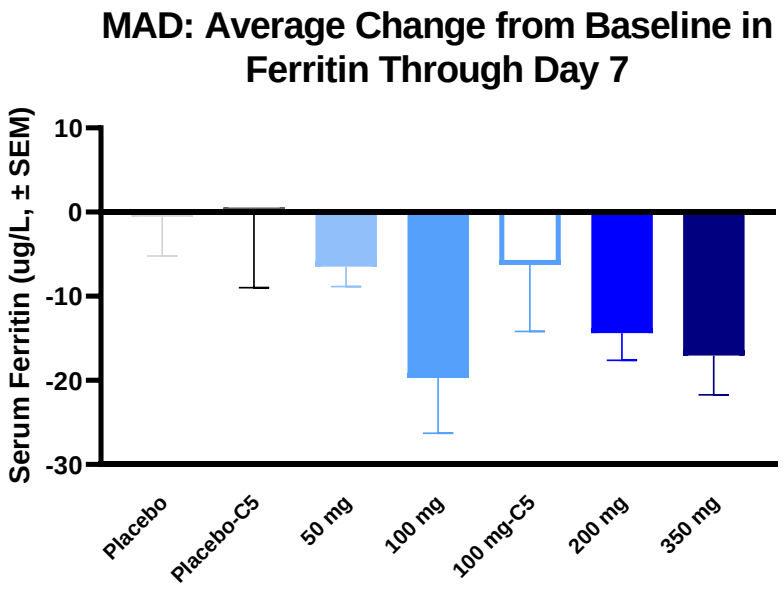
Safety Summary

- The tolerability profile of KER-047 in healthy participants has been characterized in this Phase 1 study.
- There were no serious adverse events (AEs) in either part of the study.
- In Part 2, 10 of 40 (25%) administered KER-047 and 1 of 11 (9.1%) administered placebo discontinued study drug due to AEs. AEs that led to study drug discontinuation in 3 or more participants in the KER-047 groups included lymphopenia and chills
- The majority of AEs observed were mild or moderate in severity; severe AEs were reported in 1 of 8 (12.5%) participants in the 350 mg and 100 mg (Cohort 5) dose groups.
- Adverse events reported in 2 or more participants and more common in the KER-047 groups than placebo were: abdominal discomfort, abdominal pain (upper), chills, decreased appetite, diarrhea, dizziness, fatigue, gastroenteritis, headache, lymphopenia, myalgia, nausea, neutropenia, pyrexia, rhinorrhea, tonsilitis, vomiting
  - Lymphopenia was observed after multiple doses; reversible after discontinuation of study drug.
    - Preclinical studies demonstrate that ALK2 inhibition results in redistribution of iron out of tissues into serum [Poster 771]
    - Exaggerated pharmacology could result in transiently low tissue iron and impact lymphocyte proliferation.
    - Consistent with literature, iron deprivation induced by chelating agents actively inhibits cell proliferation, including that of lymphocytes (Golding and Young 1995).

Administration of KER-047 Elicited Rapid, Robust and Sustained Changes in Serum Iron, Transferrin Saturation and Ferritin



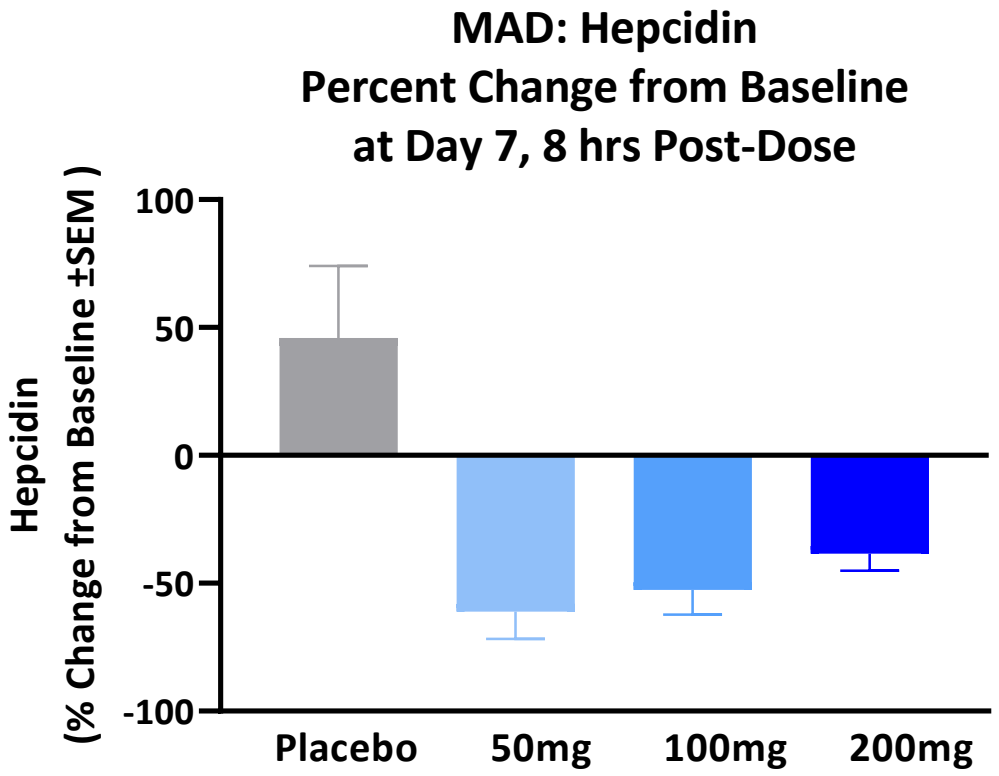




- In SAD and MAD (data shown for MAD) cohorts, we observed:
  - Dose-related increases in serum iron and transferrin saturation.
  - Reductions in ferritin, an effect which is consistent with mobilization of iron stores.

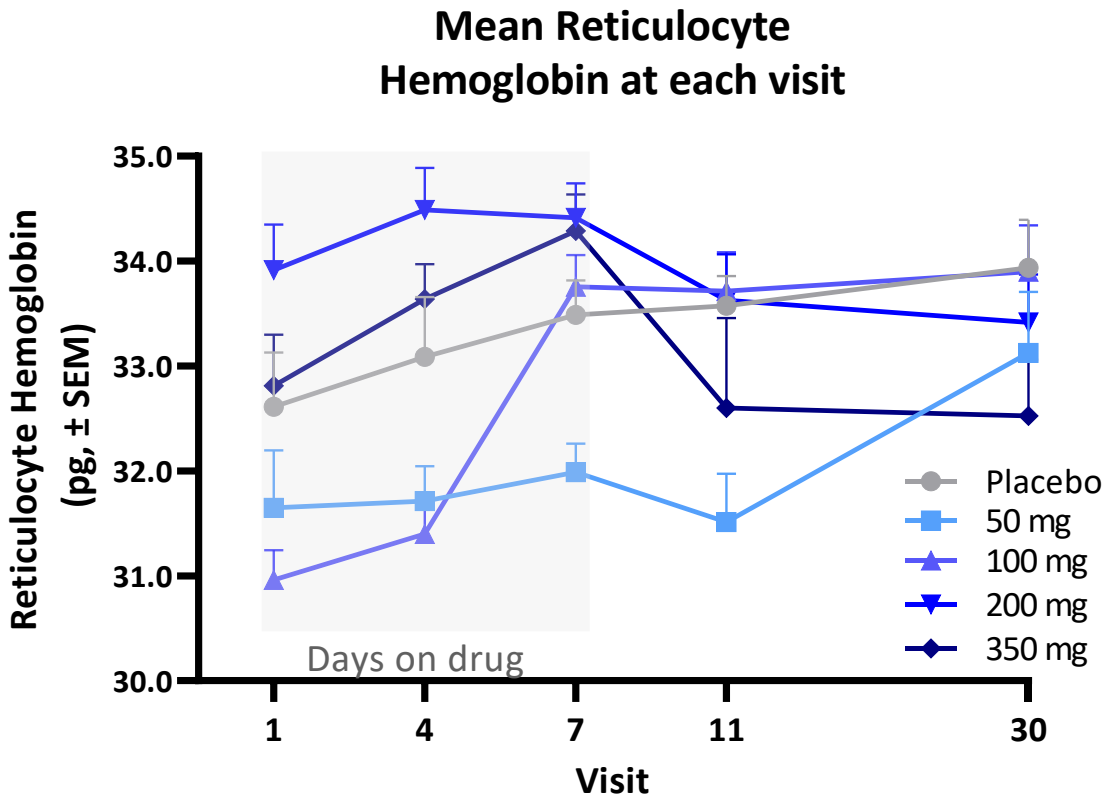
KER-047 Inhibition of the ALK2 Receptor Led to Reduced Hepcidin Levels

- Consistent with ALK2 Inhibition, decreases in serum hepcidin were observed in the 50, 100 and 200 mg multiple dose cohorts 1-3 (not collected in SAD or 350 mg MAD).
- Cohort 5 demonstrated decrease in hepcidin as early as 4-hours after administration of the first dose.
- Observed decreases in serum hepcidin were not dose dependent, which could be due to the low baseline hepcidin levels in healthy participants resulting in a narrow dynamic range in which to see an effect.



KER-047 Administration Increased Hemoglobin Content in Reticulocytes

- An increase in reticulocyte hemoglobin was observed in healthy participants in MAD cohorts 1-4 starting on Day 4 of treatment.
- The timing of the effect is consistent with the time needed for induction of erythropoiesis and iron incorporation into hemoglobin.
- The magnitude of reticulocyte hemoglobin increase appears to be more pronounced in the cohorts with less saturated reticulocyte hemoglobin content at baseline.



ALK2 inhibition increased iron availability at the erythroblastic island leading to changes in reticulocyte hemoglobin content

Summary

- The tolerability profile of KER-047 in healthy participants has been characterized in this Phase 1 study.
- There were no serious adverse events. Most common AEs in the KER-047 groups with higher incidence than placebo were: abdominal discomfort, abdominal pain (upper), chills, decreased appetite, diarrhea, dizziness, fatigue, gastroenteritis, headache, lymphopenia, myalgia, nausea, neutropenia, pyrexia, rhinorrhea, tonsilitis, vomiting.
- Lymphopenia, possibly related to reduced intracellular iron, was reversible following study drug discontinuation.
- Administration of KER-047 resulted in decreases in serum hepcidin and ferritin, and increases in serum iron and transferrin, that are consistent with inhibition of ALK2 signaling.
- Increases in reticulocyte hemoglobin content are indicative of increased iron mobilization and incorporation into hemoglobin.

KER-047's differentiated pharmacologic effect on hepcidin and iron mobilization has the potential to treat anemia of iron imbalance