KER-050, A NOVEL MODIFIED ACTRIIA LIGAND TRAP, INCREASES RED BLOOD CELL PRODUCTION IN CYNOMOLGUS MONKEYS

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INTRODUCTION

- The transforming growth factor beta (TGFß) superfamily consists of over 30 ligands including growth differentiation factors, bone morphogenic proteins, and activins that function to regulate several physiological processes, including muscle function, bone growth, vascular remodeling, and hematopoiesis.
- The action of TGFβ-like ligands is transduced through the cells by a class of molecules known as the mothers against decapentaplegic homologs (SMADs). Canonical TGBFβ-like signaling is mediated by phosphorylation of either SMAD 1/5/8 or SMAD 2/3[1].
- Studies have found that certain TGFβ-like ligands regulate red blood cell production by promoting progression of precursor cells through the stages of hematopoiesis, while others delay progression and maintain precursor cells in a quiescent state.
- Generally, bone morphogenic proteins signal through SMAD 1/5/8/9 to promote progression, while GDFs, such as GDF11, and activins signal through SMAD 2/3 to act as quiescence factors[2].
- KER-050, a novel activin type 2A receptor (ActRIIA) ligand trap comprised of a modified ActRIIA extracellular domain fused to the Fc of a human IgG, is designed to inhibit GDF8, GDF11, activin A, and activin B thereby reducing SMAD 2/3 activation and resulting in increased red blood cell (RBC) production.
- In mice, KER-050 has been shown to affect both early and late stage maturation, resulting in increases in RBCs, hematocrit (Hct), hemoglobin (Hgb), and reticulocytes (RET). **Visit poster EP786 for more information**.

OBJECTIVE

Our objective was to test the pharmacodynamic activity of KER-050 on hematopoietic response in cynomolgus monkeys.

METHODS

- **Animals**
  - Female and male 2-4-year-old monkeys (n=6/group).
- **Procedure**
  - KER-050 (0, 3, 10, 50 mg/kg) administered subcutaneously every other week for 3 months.
  - Baseline and end-of-study blood samples were analyzed for RBCs, Hgb, Hct, and RETs.
- **Statistics**
  - Data were analyzed using Prism 8 (GraphPad Software, San Diego, CA, USA) using either t-test or ANOVA.

RESULTS

KER-050 increased RBCs, Hgb, Hct and RET in female monkeys.

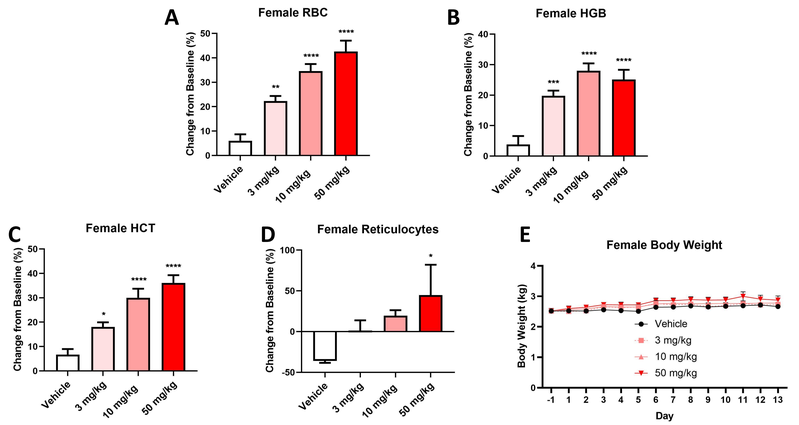

Figure 1. *KER-050 treatment resulted in significantly increased RBC number, Hgb, Hct, and RET in female monkeys.* ***(A)*** *RBC numbers increased by 22.3%, 34.6%, and 42.6% at 3, 10, and 50 mg/kg relative to the baseline values, respectively, whereas a 6.1% change was observed in the vehicle cohort (all p<0.005 compared to vehicle).* ***(B)*** *Hgb was also increased after KER-050 treatment with increases of 19.8%, 28.0%, and 25.1% with increasing dose compared to a 3.8% change in the vehicle cohort (all p<0.005).* ***(C)*** *Additionally, KER-050 increased Hct at doses of 3 (18.0%), 10 (30.0%) and 50 mg/kg (36.1%) [both p<0.05 vs. vehicle 7.0%)].* ***(D)*** *RET also increased [44.8% compared to a reduction in vehicle (-35.9%); p = 0.03] at the 50 mg/kg dose.* ***(E)*** *KER-050 did not affect body weight gain at any dose *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.*

KER-050 increased RBCs, Hgb, Hct and RET in male monkeys.

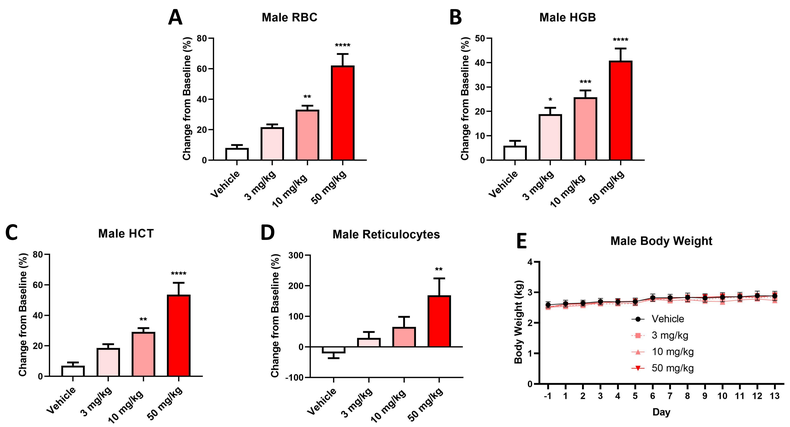

Figure 2. *KER-050 treatment resulted in significantly increased RBC number, Hgb, Hct, and RET in male monkeys.* ***(A)*** *RBC numbers increased by 21.7%, 33.2% and 62.1% at doses of 10 and 50 mg/kg, respectively, [3 mg/kg, p = 0.09; 10 and 50 mg/kg p<0.05 vs. vehicle (8.1%)].* ***(B)*** *Hgb was also increased by 18.9%, 25.9%, and 40.9% at doses of 3, 10 and 50 mg/kg, respectively, compared to vehicle (6.0%; all p<0.05).* ***(C)*** *Additionally, KER-050 increased Hct at doses of 3 (18.6%; p = 0.18), 10 (29.2%) and 50 mg/kg (53.6%) [both p<0.05 vs. vehicle 7.0%)].* ***(D)*** *RET also increased in males [168.9% compared to a reduction in vehicle (-21.3%); p = 0.003] at the 50 mg/kg dose. (E) KER-050 did not affect body weight gain at any dose. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.*

CONCLUSIONS

- KER-050 is a modified ActRIIA extracellular domain fused to the Fc of a human IgG designed to inhibit SMAD 2/3 resulting in increased RBC production.
- Similar to effects in mice, KER-050 robustly increased RBCs, Hgb, Hct, and RET in monkeys by as much as 169%.
- These data demonstrate KER-050's effects translate to primates.
- In a Phase 1 clinical trial in healthy participants, treatment with KER-050 also led to robust increases in hematologic parameters. **Visit poster EP806 for more information.**

ACKNOWLEDGEMENTS

We would like to thank Charles River Laboratories (Mattawan, MI, USA) for conducting the cynomolgus monkey studies.

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