A modified ActRIIB ligand trap dose-dependently increased trabecular bone by enhancing bone growth and attenuating bone resorption

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INTRODUCTION

- Osteoporosis is a bone disorder estimated to affect over 200 million people worldwide and is characterized by low bone mineral density, reduced bone strength, deterioration of bone, and high risk of bone fracture which can lead to increased mortality[1].
- TGF-β superfamily ligands, including activins A and B, are negative regulators of bone remodeling and suppress bone growth[2,3].
- KER-012 and its research form, RKER-012, are investigational modified activin receptor II ligand traps designed to bind and inhibit activins and promote bone growth.
- **Our aims were to characterize the dose response of RKER-012 on bone and to investigate RKER-012's mechanism of action.**

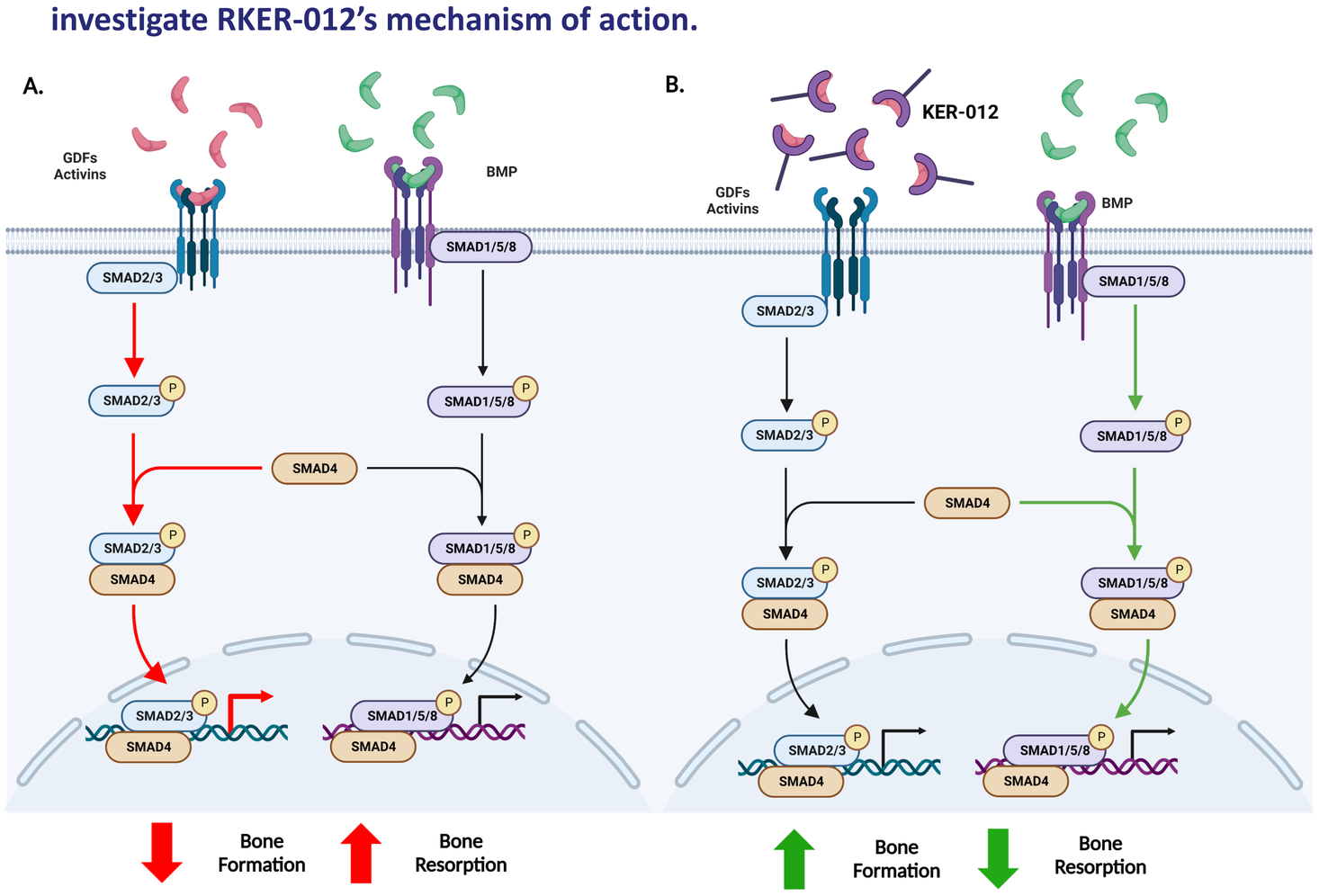

Figure 1. KER-012 is designed to inhibit SMAD2/3 signaling. (A) TGF-β ligands bind ActRII which phosphorylates SMAD2/3 causing it to complex with SMAD4 and regulate gene expression. The regulation of target genes in this manner leads to decreased bone formation and increased bone resorption. (B) KER-012 is designed to bind TGF-β superfamily ligands, including activins A and B, and to inhibit SMAD2/3 signaling. The inhibition of SMAD2/3 increases bone formation and reduces bone resorption[6]. Figure made using BioRender.

METHODS

STUDY 1: Dose Response

- Healthy adult wild-type C57Bl/6 females (n=10/group).
- KER-012 doses of 0, 0.3, 1, 3, 10, or 20 mg/kg IP twice weekly for 8 weeks.
- Terminal assessment of bone mineral density (BMD), bone volume, and bone quality.
- Data were compared by one-way ANOVA and presented as mean + SEM.

STUDY 2: Mechanism of Action

- Healthy adult wild-type C57Bl/6 males (n=10/group).
- Doses of 0 or 20 mg/kg RKER-012 IP twice weekly for 4 weeks.
- Prior to termination, skeletal staining was performed with declomycin and calcein (15 mg/kg) three days apart.
- Terminal assessment of bone dynamic histomorphometry.
- Data were compared with t-tests and are presented as mean + SEM.

CONCLUSIONS

- **KER-012 and its research form, RKER-012, are investigational modified activin receptor II ligand traps designed to bind and inhibit activins and promote bone growth.**
- **KER-012 dose-dependently increased bone in healthy wild-type mice**
- **RKER-012 increased bone in healthy wild-type mice through both pro-anabolic and anti-catabolic processes.**

Taken together, we believe these results provide early evidence that KER-012 has the potential to treat human diseases of bone loss, such as osteoporosis.

RESULTS

STUDY 1: KER-012 dose-dependently increased bone in healthy mice.

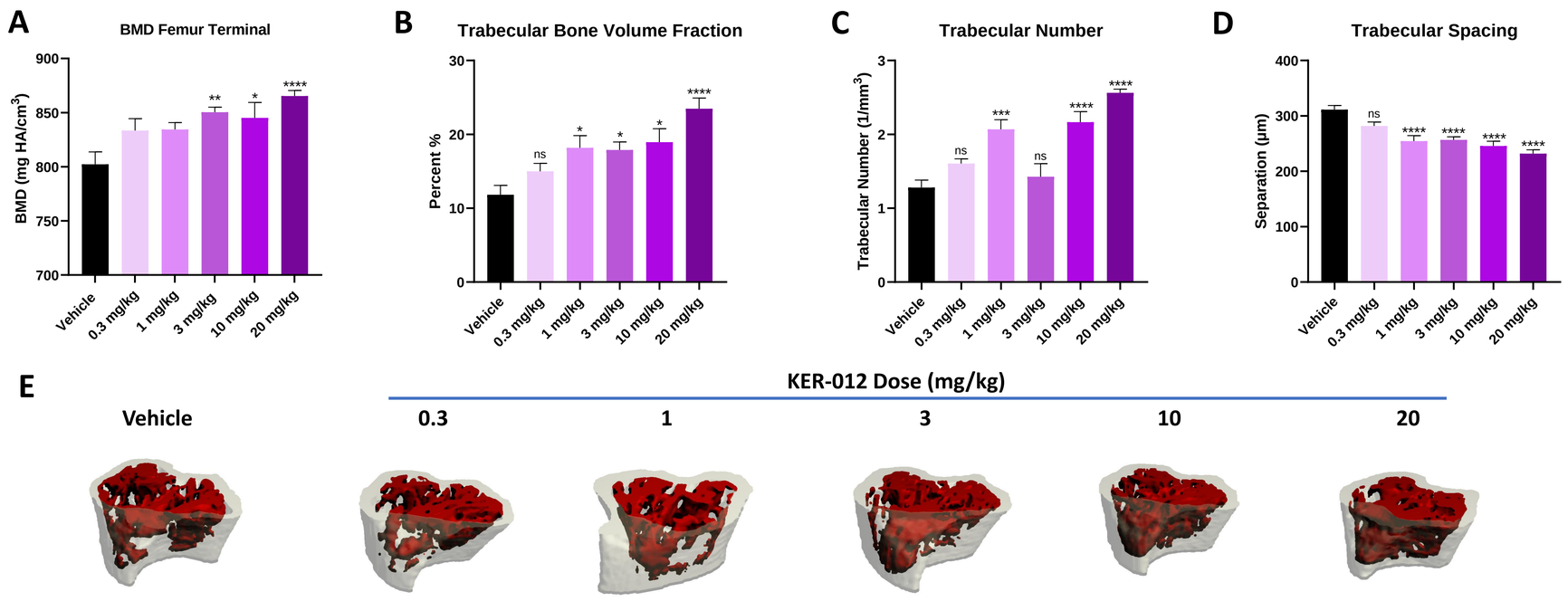

Figure 2. Treatment with KER-012 significantly and dose-dependently increased (A) BMD, (B) trabecular bone volume fraction (1-20mg/kg), and (C) trabecular number (1, 10, and 20mg/kg), and significantly and dose-dependently decreased (D) trabecular spacing (1-20mg/kg), relative to vehicle. (E) Representative µCT images or proximal tibia trabecular bone. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

STUDY 2: RKER-012 increased bone growth and decreased bone resorption in healthy mice.

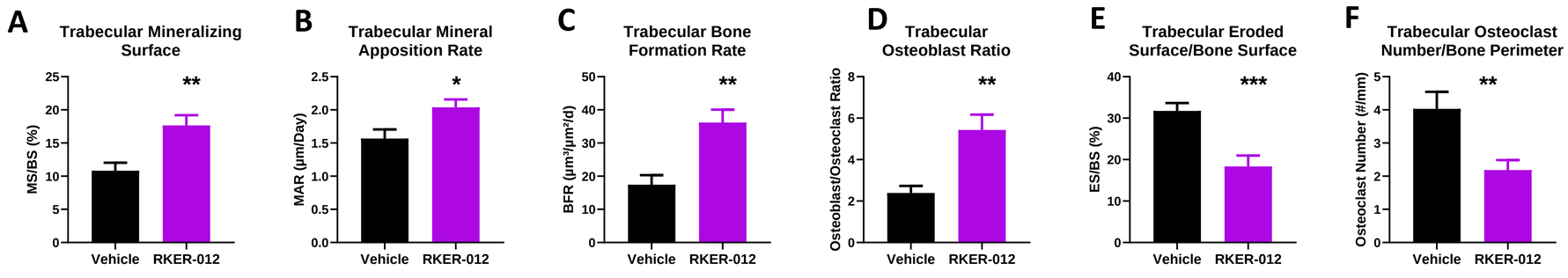

Figure 3. Relative to vehicle, RKER-012-treated mice had significantly greater (A) trabecular mineralizing surface, (B) apposition rate, (C) bone formation rate, and (D) osteoblast/osteoclast ratio, as well as significantly decreased (E) trabecular eroded surface and (F) osteoclast number. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

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DISCLOSURES

All authors are employees and stockholders of Keros Therapeutics, Inc.