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KER-012, A NOVEL ACTIVIN RECEPTOR TYPE II LIGAND TRAP INCREASED BONE IN MICE VIA A UNIQUE MECHANISM OF ACTION

Keith Babbs[1], Chris Materna[1], Evan Lema[1], Claire Tseng[1], ffolliott Fisher[1], Jasbir Seehra[1], Jennifer Lachey[1]

[1]*Keros Therapeutics, Lexington, MA, USA*

KEROS THERAPEUTICS

INTRODUCTION

- Osteoporosis affects over 200 million people worldwide and is characterized by low bone mineral density (BMD), reduced bone strength, deterioration of bone, and high risk of fracture leading to increased mortality[1].
- TGF-ß superfamily ligands, including activin A and B, negatively regulate bone remodeling and suppress bone growth[2,3]. Moreover, activins enhance synthesis and secretion of follicle-stimulating hormone, which stimulates bone resorption[4].
- KER-012 is a novel modified activin receptor type 2 (ActRII) ligand trap designed to bind and inhibit activins and SMAD 2/3 signaling to increase bone growth.

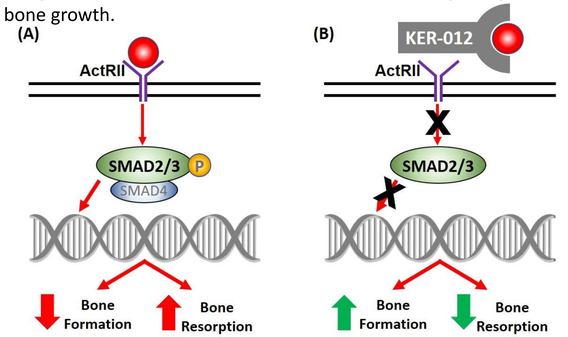

Figure 1. KER-012 is designed to inhibit SMAD 2/3 signaling. **(A)** TGF-ß ligands bind ActRIIA or B which phosphorylates SMAD 2/3 causing it to complex with SMAD 4 and regulate gene expression. The regulation of target genes in this manner leads to decreased bone formation and increased bone resorption. (B) KER-012 is designed to bind to TGF-ß superfamily ligands, including activin A and B, inhibiting SMAD 2/3 signaling. The inhibition of SMAD 2/3 increases bone formation[5] and reduces bone resorption.

AIMS

To evaluate the efficacy of KER-012 in increasing bone and to investigate the mechanism of action in mice.

METHODS

- KD values for TGF-ß superfamily ligands were obtained by kinetic evaluation by Biacore.
- KER-012's ability to inhibit TGF-ß ligands was measured using luciferase reporter cell assays.
- 13-week-old male mice (C57Bl/6; n=10/grp) were administered either vehicle or KER-012 (20 mg/kg) I.P. twice-weekly.
- After 5 weeks, skeletal labeling was performed *in vivo* using declomycin followed by calcein.
- At study termination, tibias were fixed in 10% NBF and stored in EtOH.
- Trabecular bone at the proximal tibial metaphysis was evaluated using static and dynamic histomorphometry.

RESULTS

KER-012 observed to bind SMAD 2/3 signaling ligands and inhibit their activity

A

K_D Values			
GDF-11	**Activin A**	**Activin B**	**BMP-9**
172 pM	64 pM	105 pM	24 nM

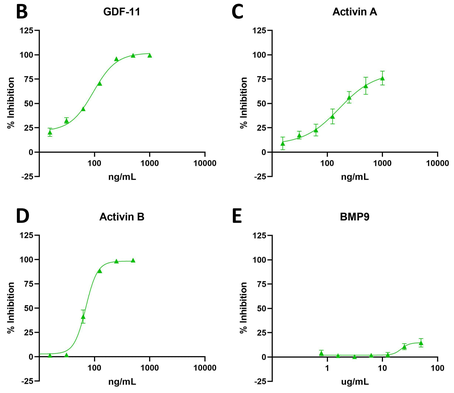

Figure 2. (A) Dissociation constant (K_D) concentrations GDF-11, Activin A, Activin B, and BMP-9. KER-012 observed to inhibit TGF-ß superfamily ligands (B) GDF-11, (C) activin A, and (D) activin B which normally signal through SMAD 2/3 and suppress bone production. KER-012 did not inhibit (E) BMP-9 which signals through SMAD 1/5/8 to promote osteogenesis and regulate vascular remodeling, indicating lack of effect of KER-012 on normal vasculature. Data displayed are mean ± SEM.

KER-012 increased trabecular bone in proximal tibia

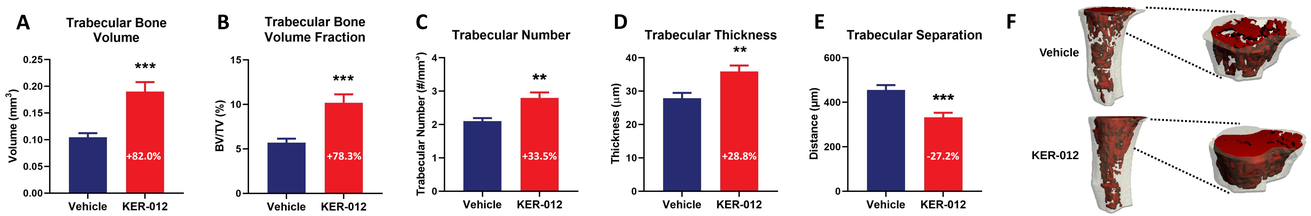

Figure 3. Relative to vehicle-treated mice, KER-012-treated mice had increased trabecular bone. Specifically, we observed increased (A) trabecular bone volume, (B) trabecular bone volume fraction, (C) trabecular number, and (D) trabecular thickness. (E) Moreover, KER-012-treated mice had reduced trabecular separation. (F) Representative µCT images from vehicle- and KER-012-treated mouse tibias**p < 0.01; ***p < 0.001 versus vehicle. Data are displayed as mean + SEM.

KER-012 inhibited trabecular bone catabolism and enhanced trabecular bone anabolism

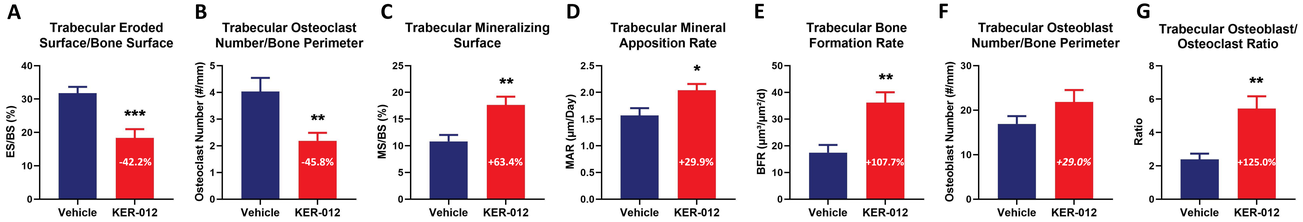

Figure 4. KER-012-treated mice had reduced bone catabolism and enhanced bone anabolism in proximal tibia (relative to vehicle-treated mice). Specifically, we observed reductions in (A) trabecular eroded surface and (B) trabecular osteoclast number. Moreover, we observed significant increases in (C) trabecular mineralizing surface, (D) mineral apposition rate, (E) bone formation rate, and (G) ratio of osteoblasts to osteoclasts, and a trend for increased (F) osteoblast number. * p < 0.05; **p < 0.01; ***p < 0.001 versus vehicle. Data displayed are mean + SEM.

CONCLUSIONS

- KER-012 is a modified ActRII ligand trap designed to bind and inhibit activins and reduce SMAD 2/3 signaling.
- In WT mice, KER-012 increased trabecular bone volume, bone volume fraction, trabecular number, trabecular thickness and reduced trabecular separation.
- KER-012 reduced trabecular eroded surface and osteoclast number.
- KER-012 increased trabecular mineralizing surface, mineral apposition rate, and bone formation rate.
- Together, these results indicate that KER-012 increased trabecular bone by reducing its catabolism and enhancing its anabolism.
- **These data provide support that KER-012 is a potential treatment for bone loss, including cancer-induced bone loss, osteogenesis imperfecta, and osteoporosis.**

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CONTACT INFORMATION

Julia Balanova
jbalanova@soleburytrout.com
646-378-2936

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