

RKER-050, a Novel Activin Receptor Type II Ligand Trap, Improved Bone Loss in a Myelodysplastic Syndrome Mouse Model

Chris Materna¹, Remya Nathan¹, Tandicka Nurse¹, Joe Worrall¹, Keith Babbs¹, ffolliott Fisher¹, Jasbir Seehra¹, Jennifer Lachey¹

¹Keros Therapeutics, Inc., Lexington, MA, USA



INTRODUCTION

- Myelodysplastic syndromes (MDS) are hematological stem cell diseases characterized by ineffective hematopoiesis, peripheral blood cytopenia and dysplasia^{1,2}.
- Osteoporosis and osteopenia are associated comorbidities of MDS leading to reduced bone mineral density (BMD) and bone loss³.
- Increased bone loss alters the bone microenvironment that may further contribute to the ineffective hematopoiesis in MDS patients.
- TGF- β superfamily ligands are important in the regulation of hematopoiesis and are dysregulated in MDS⁴.
- KER-050 is a modified ActRII ligand trap designed to alter signaling of TGF- β superfamily ligands, restoring balance to the osteo-hematopoietic niche and promoting differentiation of erythroid and megakaryocytic precursors.
- ActRII ligand traps have been demonstrated to increase hematopoiesis and bone in healthy mice^{5,6}.
- The goal of the study was to determine the efficacy of a research form of KER-050 (RKER-050) on bone loss in a model of MDS, the NUP98/HOXD13 MDS mouse model.**

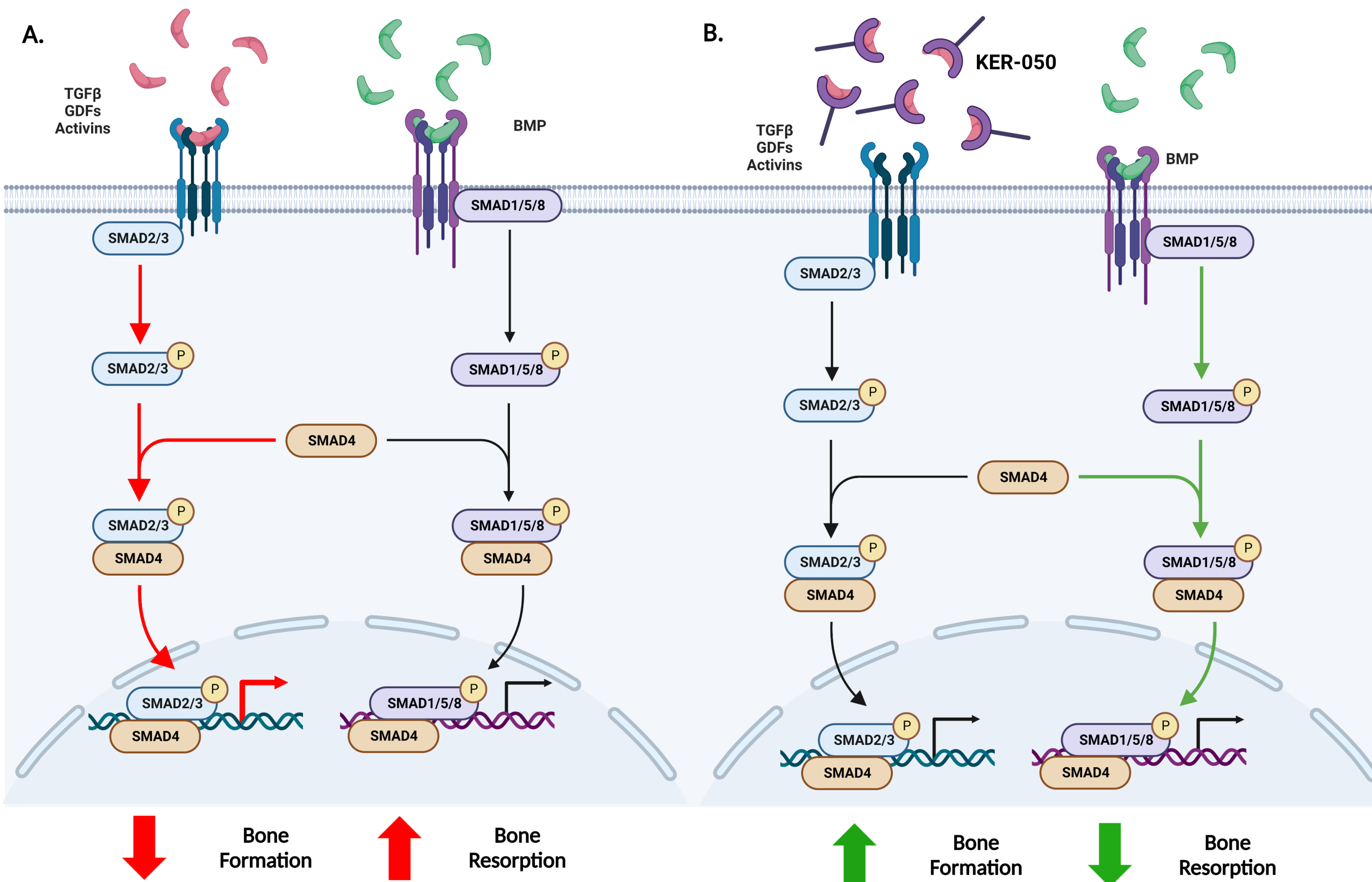


Figure 1. KER-050 is designed to inhibit SMAD2/3 signaling. (A) TGF- β ligands bind ActRII which phosphorylates SMAD2/3 causing it to complex with SMAD4 and regulate gene expression. The regulation of target genes in this manner leads to decreased bone formation and increased bone resorption. (B) KER-050 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 resorption⁶. Figure made using BioRender.

METHODS

- 5-month-old male MDS (NUP98/HOXD13) were treated IP with vehicle (MDS+VEH, n=10) or RKER-050 (7.5 mg/kg, MDS+RKER-050, n=9) once weekly for 6 weeks along with a wildtype (WT) control group treated IP with vehicle (WT+VEH, n=4).
- Femurs were scanned using GX2 μ CT (10 mm FOV, 90 kV, 88 μ A, 4 minutes, Perkin Elmer).
- Trabecular bone at the distal and cortical bone at the mid-diaphysis femur were evaluated using Analyze 14.0 Bone Micro-architecture Analysis software (AnalyzeDirect).
- Dissected femurs were scanned using InAlyzer 2.0 (MediKors) for bone mineral density (BMD) measurements.
- Representative images produced using Scanco Software (Scanco Medical AG, Brüttisellen, Switzerland).

RESULTS

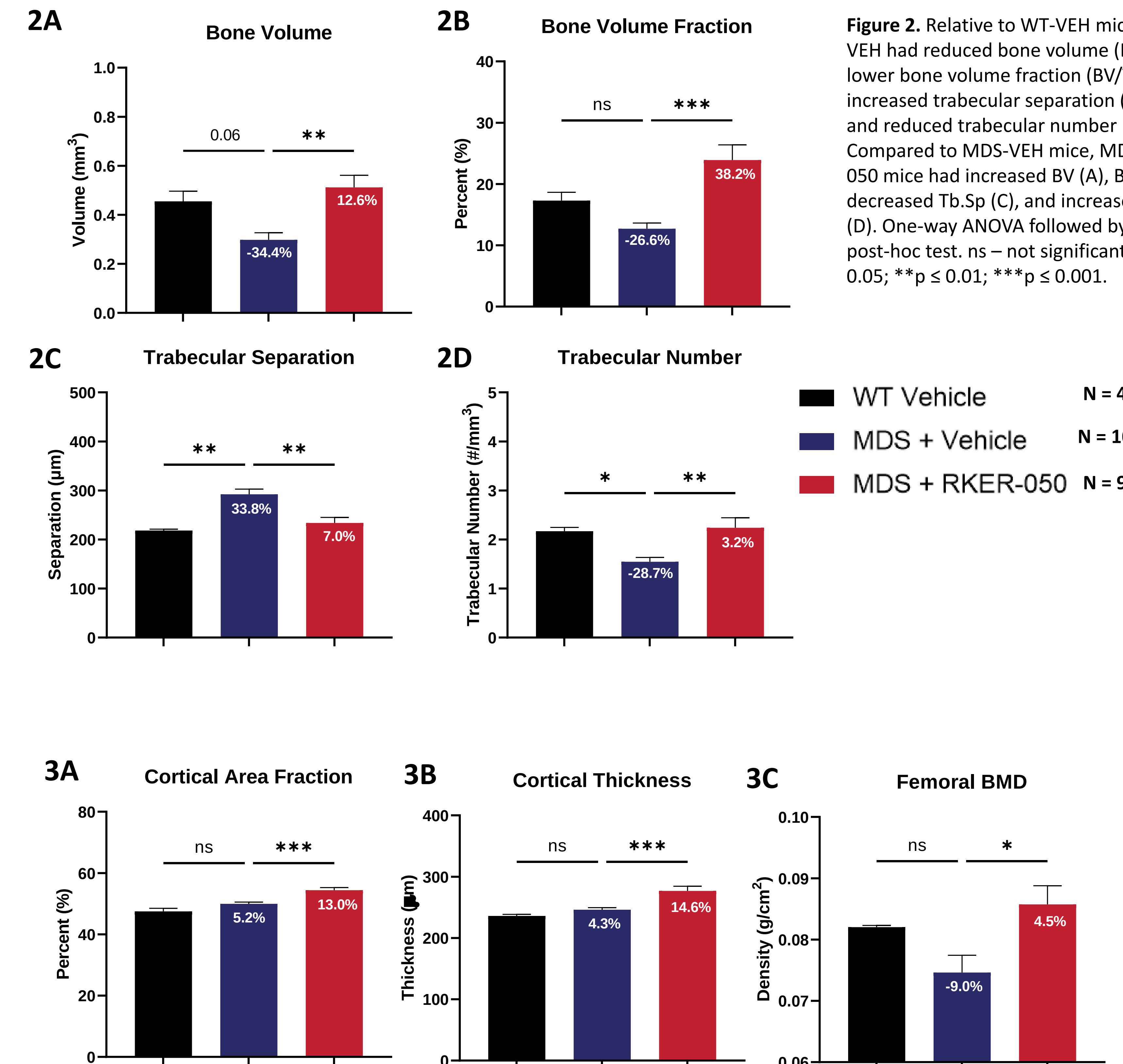


Figure 3. Relative to MDS+VEH, MDS+RKER-050 mice had increased cortical bone area fraction (A), cortical thickness (B) and femoral bone mineral density (C). No MDS related changes were observed in cortical bone area fraction, cortical thickness and bone mineral density. One-way ANOVA followed by Sidak post-hoc test. ns – not significant; * $p \leq 0.05$; *** $p \leq 0.001$.



Figure 4. (A) Representative three-dimensional image of the femur where trabecular architecture is reduced in MDS+VEH compared to WT+VEH and MDS+RKER-050. (B) Transverse cross section of the distal femur depicting trabecular (red) and cortical (opaque) bone; Scale bar = 1 mm.

CONCLUSIONS

- MDS+VEH showed bone loss with decreased bone volume and trabecular number, and increased trabecular separation compared to WT controls.
- Treatment with RKER-050 prevented loss of bone volume, bone volume fraction and trabecular number, and reduced trabecular separation compared to MDS+VEH mice.
- Modified ActRII ligand traps have been demonstrated to increase bone mineral density in WT and osteoporotic mice through increased bone formation and repression of bone resorption (ASBMR2020; CERRM2022).
- RKER-050 treatment has been demonstrated to increase RBCs in mouse model of MDS (ASH2020) and correct anemia in MDS patients (EHA2021).
- These data support the potential of RKER-050 to restore hematopoiesis and bone health, which may restore a healthier bone microenvironment in patients with MDS**

REFERENCES

- Cazzola, M. Myelodysplastic Syndromes. *N. Engl. J. Med.* 2020, 383, 1358-74.
- Adès, L., Itzykson, R., Fenaux, P. Myelodysplastic Syndromes. *Lancet Lond. Engl.* 2014, 383, 2239-52.
- Weidner, H., Rauner, M., ..., Platzbecker, U. Myelodysplastic syndromes and bone loss in mice and men. *Leukemia*. 2017, 31, 1003-7.
- Komrokji, R.S. Activin Receptor II Ligand Traps: New Treatment Paradigm for Low-Risk MDS. *Curr Hematol Malig Rep.* 2019, 14, 346-51.
- Carrancio, S., Markovics, J., ..., Sung, V. An activin receptor IIA ligand trap promotes erythropoiesis resulting in a rapid induction of red blood cells and haemoglobin. *Brit Jour Haematol*, 2014, 165, 870-82.
- Pearsall, R.S., Canalis, E., Cornwall-Brady, M., Underwood, K. W., ... Bouxsein, M. L. (2008) A soluble Type IIA receptor induces bone formation and improves skeletal integrity. *PNAS* 105(19), 7082-7087.

ACKNOWLEDGEMENTS

We would like to thank Dr. Mary Bouxsein for her scientific advice and Daniel Brooks for his expertise on Scanco Medical Imaging software.

CONTACT INFORMATION

Justin Frantz
jfrantz@soleburytrout.com
617-921-9660