KER-012, A Modified ActRIIB Ligand Trap, Administered to Healthy Postmenopausal Women Was Generally Well Tolerated and Increased Biomarkers of Bone Formation, Supportive of A Bone Anabolic Mechanism (P1053)

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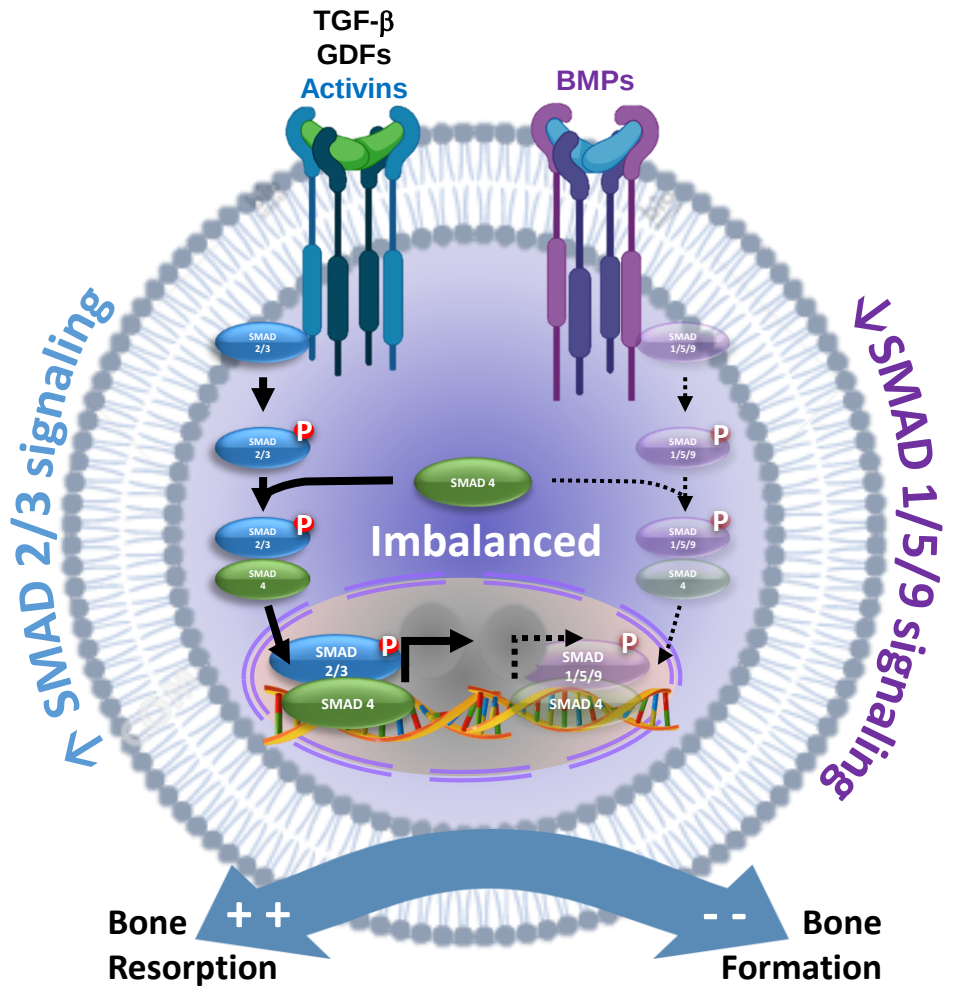
Disclosures

- Harveen Natarajan, Ying Jiang, Jennifer Lachey, Jasbir Seehra, Enrikas Vainorius and Simon Cooper are employees of and security holders in Keros Therapeutics, Inc.
- Sylvain Bedard is engaged as an independent contractor for Keros Therapeutics, Inc.
- Richard Friend - no disclosures

Dysregulated TGF-β Superfamily Signaling Underlies Bone Loss Associated With Multiple Disease States

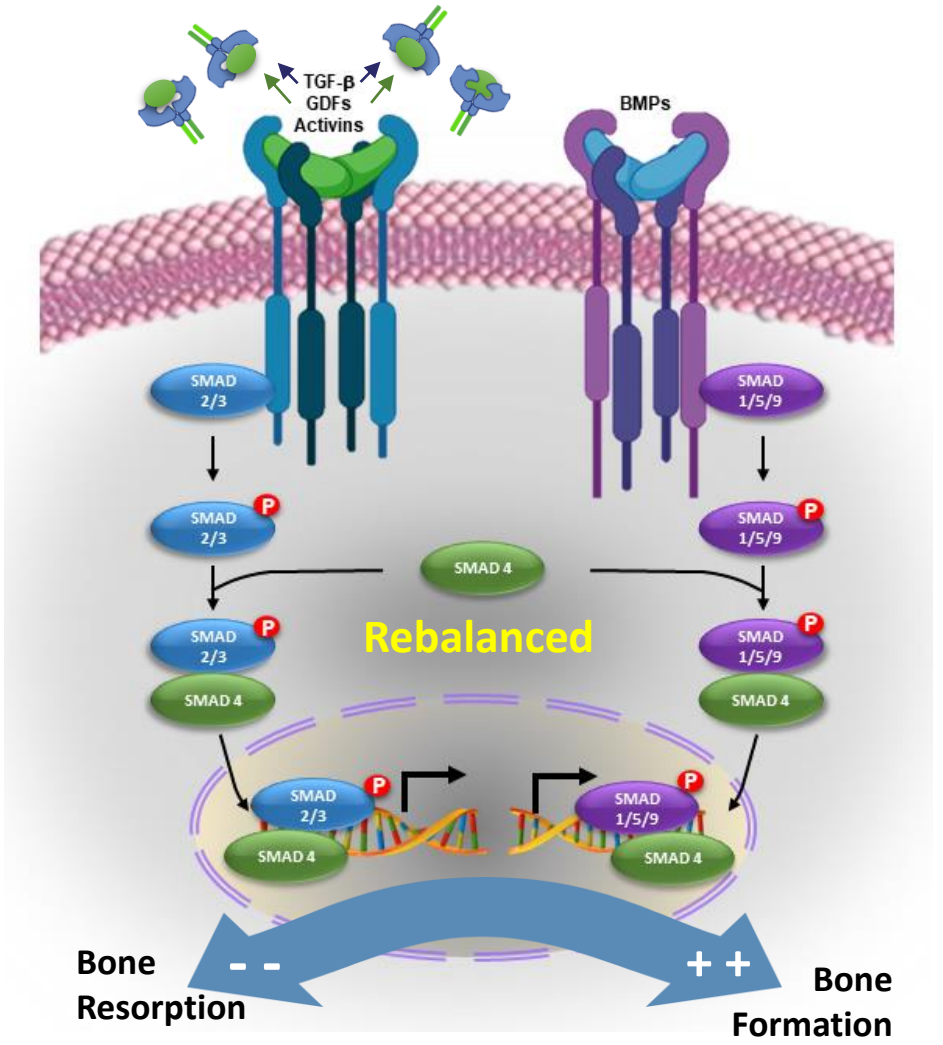
- **Transforming growth factor-beta (TGF-β) superfamily ligands regulate bone remodeling and growth**
  - **Activins: promote osteoclasts, inhibit osteoblast formation and mineralization activity via SMAD 2/3 signaling[1]**
  - **Bone morphogenetic proteins (BMP): promote bone formation via SMAD 1/5/9 signaling[2]**
- **Activin signaling is increased in aging, cardiac diseases, cancer and disorders that result in bone loss (e.g., pulmonary arterial hypertension, chronic kidney disease)[3-5]**



1. Lodberg A. Cytokine and Growth Factor Reviews (2021); 60:1-17; 2. Bharadwaz A. *Mater Sci Eng C Mater Biol Appl* (2021): 111748. doi:10.1016/j.msec.2020.111748; 3. Roh *et al*., *Sci. Transl. Med.* 11, eaau8680 (2019); 4. Bian X, *et al*. *BMJ Open Diab Res Care*2019;7:e000720. doi:10.1136/bmjdrc-2019-000720; 5. Ries A. *Exp Opin Ther Targets*. (2020); 24(10):985–996

Proof of Concept Established for Targeting TGF-β Superfamily in Diseases Characterized by Bone Loss

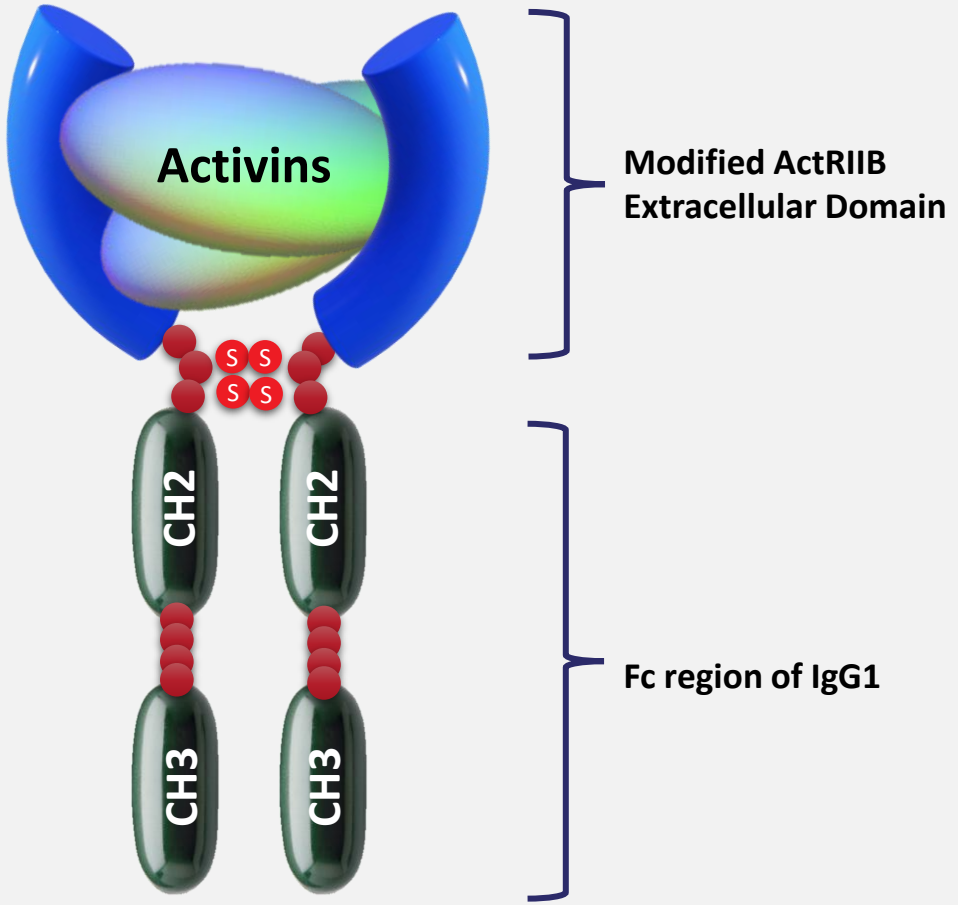
- Pharmacologic inhibition of activin signaling has been shown to reverse bone loss in multiple myeloma[1] and neuromuscular diseases[2]
- Investigational activin receptor (ActR) ligand traps have been shown to increase bone mineral density in postmenopausal women[3]
  - Accompanied by a rapid and sustained increase in RBC that required halting of further dosing
- Demonstrated POC in patients with pulmonary arterial hypertension (PAH)[4]
  - Dosing in PAH has been limited to low doses due to potential for increased hemoglobin[3]
  - Limited target engagement at low doses may prevent full benefit



1.Abdulkadyrov et al. British Journal of Haematology, 2014, 165, 814–8231. 2.Campbell et. al. Muscle and Nerve 2017 Apr;55(4):458-464.; 3.Sherman et al 2013 The Journal of Clinical Pharmacology 53(11) 1121–1130; 4.Humbert M, et al. *New Eng J Med* 2021; 384:1204-15

KER-012: A Novel, Investigational Activin Receptor Type IIB Ligand Trap

KER-012 Structure



- **Designed to inhibit TGF-β superfamily ligands with specificity for activins to:**
  - **Maximally inhibit SMAD 2/3 signaling via activins**
  - **Permit SMAD 1/5/9 signaling via BMPs**

***In vitro* binding assays[1]**

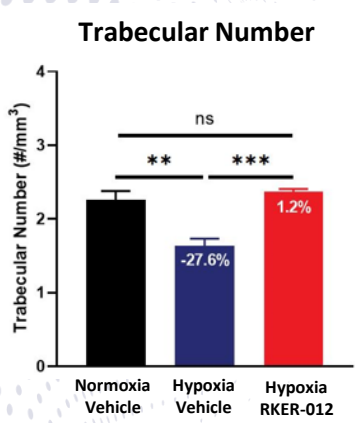
	K_D (pM)			
	Activin A	Activin B	GDF-11	BMP-9
KER-012	120	132	77	30,000

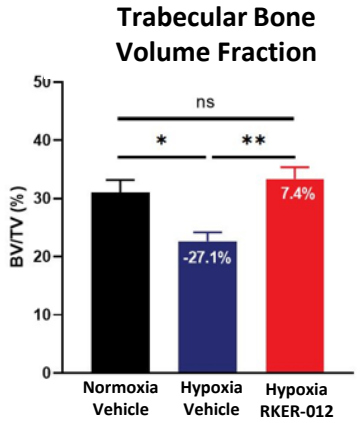
- **Designed to lack effect on erythropoiesis**

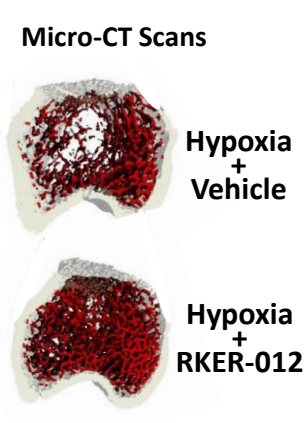
1. Babbs K, *et al.*, Pulmonary Hypertension Association Int. Conference 2022; GDF-11 = Growth differentiation factor 11; BMP-9 = bone morphogenetic protein 9

KER-012 Not Only Prevented, But Reversed Bone Loss in Multiple Preclinical Models of Bone Dysfunction

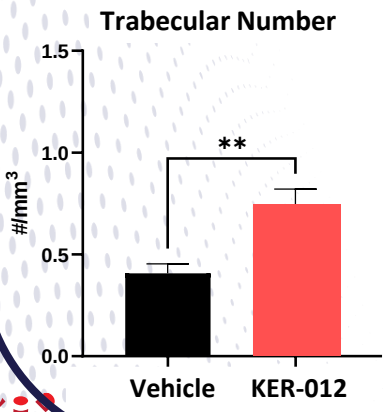
Preventive: Sugen—hypoxia rat (PAH)[1]

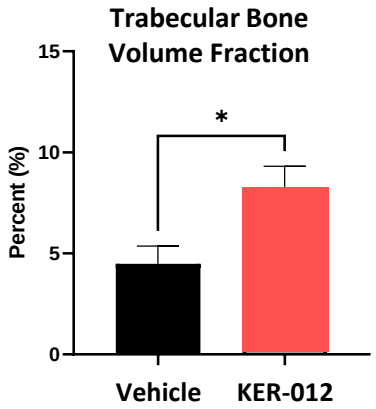


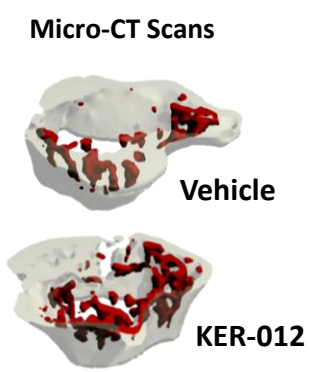




Reversal: orchiectomized mouse (osteoporosis)







P value *<0.05, **<0.01, ***<0.001; ns= non significant; RKER = Research KER-012

KER-012 administration increased trabecular bone in multiple preclinical models of bone loss:

- **Prevented bone loss in a Sugen-hypoxia model of PAH, as evidenced by normalization of trabecular number and bone volume fraction (top panels)[1]**
- **Reversed bone loss in orchiectomized mice as evidenced by increased trabecular number and bone volume fraction (bottom panels)**
- **Taken together, these observations support exploring potential effects of KER-012 on bone remodeling in humans**

1. Materna C et al., Am Society Bone Mineral Res 2021 Annual Meeting. Sept 9-12, 2021

Phase 1 Trial of KER-012 in Healthy Postmenopausal Women

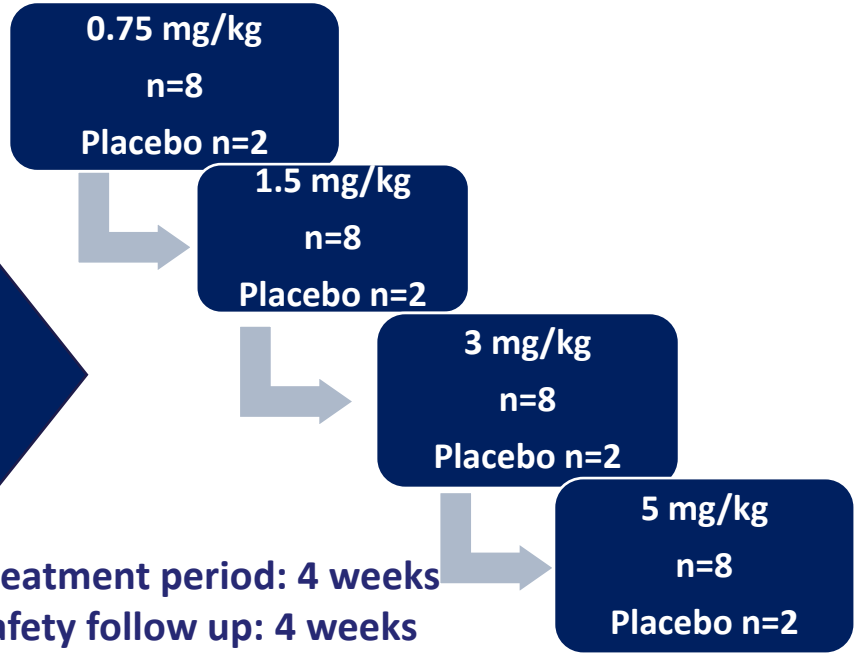
Key Inclusion:

Postmenopausal females*
- 45 to 70 years (inclusive)
- Serum FSH > 40 IU/L
- BMI >18.5 kg/m^2 to <32.0 kg/m^2

Key Exclusion:

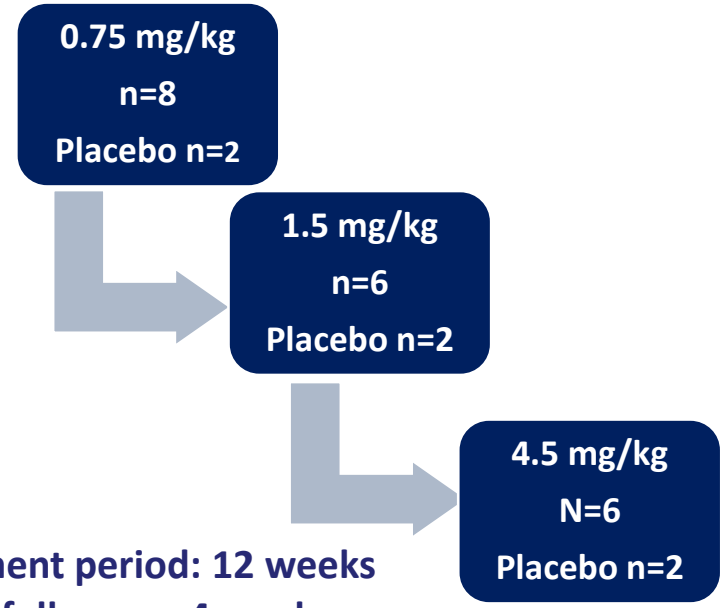
- History of or any past treatment for osteoporosis
- Systemic hormone replacement therapy within 3 months

Part 1: Single Ascending Dose (Double-blinded)



Treatment period: 4 weeks
Safety follow up: 4 weeks
Single subcutaneous dose

Part 2: Multiple Ascending Dose (Double-blinded)



Treatment period: 12 weeks
Safety follow up: 4 weeks
Three subcutaneous doses (28 days apart)

Endpoints:
Safety, PK, PD (including serum biomarkers of bone formation & resorption)

*≥ 6 months of spontaneous amenorrhea OR 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy
FSH= Follicle Stimulating Hormone, BMI=Body Mass Index

Demographics and Disposition (Part 1 SAD)

	PBO (N=8)	0.75 mg/kg (N=8)	1.5 mg/kg (N=8)	3.0 mg/kg (N=8)	5.0 mg/kg (N=8)	All Subjects (N=40)
Age, years mean (range)	56.0 (48 – 60)	58.3 (52 -70)	54.9 (50 - 59)	57.8 (50 - 66)	59.3 (53 - 68)	57.2 (48 - 70)
Race, n (%)						
White	8 (100)	8 (100)	8 (100)	7 (87.5)	8 (100)	39 (97.5)
Multiple[&]	0	0	0	1 (12.5)	0	1 (2.5)
Weight, kg mean (SD)	68.4 (10.09)	71.6 (9.60)	67.5 (8.05)	68.1 (9.49)	67.1 (10.35)	68.6 (9.19)
FSH, IU/L mean (SD) [range]						
at Screening	88.9 (16.34) [62, 107]	75.5 (19.87) [56, 112]	95.0 (22.93) [64, 133]	77.9 (26.31) [60, 127]	91.0 (35.02) [45, 146]	85.6 (25.02) [45, 146]
at C1D1	70.4 (28.91) [18, 105]	53.3 (28.16) [26, 103]	86.5 (16.64) [64, 109]	49.5 (23.65) [21, 92]	87.1 (35.49) [63, 162]	68.9 (30.18) [18, 162]
%chg from SCRN	-16.9 (35.65) [-83.2, 11.9]	-31.9 (23.02) [-58.3, 1.1]	-7.7 (8.78) [-18.3, 7.1]	-33.3 (24.57) [-83.5, 2.6]	4.4 (17.71) [-17.0, 40.0]	-17.7 (26.38) [-83.5, 40.0]
Disposition						
Completed Study, n (%)	8 (100%)	8 (100%)	7 (87.5%)	8 (100%)	8 (100%)	39 (97.5)
Discontinuation, n (%)	0	0	1[#] (12.5%)	0	0	1[#] (2.5)

& More than one race was reported.
# 1 subject prematurely discontinued after receiving KER-012 due to withdrawal of consent.

Demographics and Disposition (Part 2 MAD)

	PBO (N=6)	0.75 mg/kg (N=8)	1.5 mg/kg (N=6)	4.5 mg/kg (N=6)	All Subjects (N=26)
Age, years mean (range)	59.5 (51 – 68)	59.1 (52 – 65)	55.7 (52 – 59)	61.2 (52 – 71)	58.9 (51 – 71)
Race, n (%)					
White	6 (100.0)	7 (87.5)	5 (83.3)	6 (100.0)	24 (92.3)
Asian	0	1 (12.5)	0	0	1 (3.8)
Australian Aborigine or Torres Strait Islander	0	0	1 (16.7)	0	1 (3.8)
Weight, kg mean (SD)	68.2 (12.20)	67.8 (7.02)	71.0 (9.05)	71.9 (12.08)	69.6 (9.61)
FSH, IU/L mean (SD) [range]					
at Screening	80.7 (17.50) [59, 108]	69.3 (40.52) [41, 164]	82.7 (32.01) [42, 121]	92.5 (32.65) [48, 137]	80.3 (31.86) [41, 164]
at C1D1	82.8 (20.29) [51, 114]	65.4 (28.75) [40, 126]	80.7 (23.65) [52, 116]	83.8 (21.40) [61, 119]	77.2 (24.15) [40, 126]
%chg from SCRN	5.8 (34.66) [-26, 73]	-1.5 (12.94) [-23, 12]	1.7 (14.34) [-19, 24]	-4.5 (23.81) [-19, 44]	0.2 (21.35) [-26, 73]
Disposition					
Completed Study, n (%)	5 (83.3)	8 (100.0)	5 (83.3)	6 (100.0)	24 (92.3)
Discontinuation, n (%)	1 (16.7)[&]	0	1 (16.7)[#]	0	2 (7.7) [& #]

& 1 subject prematurely discontinued after receiving 2 doses of placebo due to physician's decision
# 1 subject withdrew consent after receiving 2 doses of KER-012

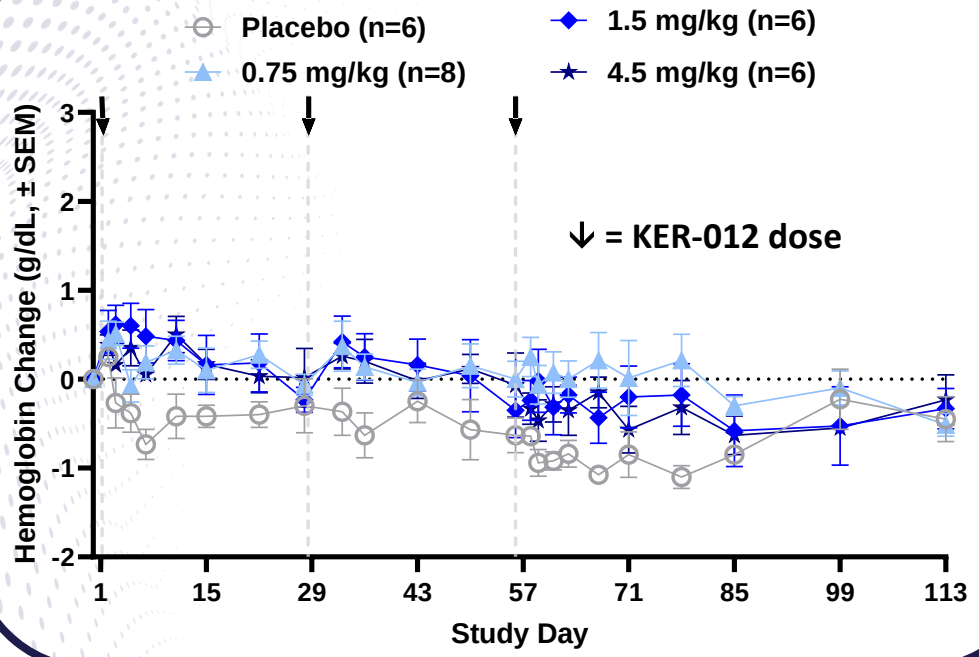
KER-012 was Generally Well Tolerated after Single and Repeated Dosing

Adverse Event	Part 1: Single Ascending Dose KER-012 Dose (mg/kg)					Part 2: Multiple Ascending Doses KER-012 Dose (mg/kg)			
	PBO (N = 8)	0.75 (N = 8)	1.5 (N = 8)	3.0 (N = 8)	5.0 (N = 8)	PBO (N = 6)	0.75 (N = 8)	1.5 (N = 6)	4.5 (N = 6)
Any TEAE	6 (75%)	7 (87.5%)	3 (37.5%)	6 (75%)	3 (37.5%)	6 (100%)	5 (62.5%)	5 (83.3%)	6 (100%)
Any SAE	-	-	-	-	-	1 (16.7%)	-	-	-
Injection site erythema	-	1 (12.0%)	-	2 (25.0%)	-	-	2 (25.0%)	3 (50.0%)	4 (66.7%)
Headache	1 (12.0%)	2 (25.0%)	-	-	1 (12.5%)	2 (33.3%)	2 (25.0%)	1 (16.7%)	2 (33.3%)
Back pain	2 (25.0%)	-	1 (12.5%)	3 (37.5%)	-	-	-	1 (16.7%)	-
COVID-19	-	-	-	-	1 (12.5%)	-	-	1 (16.7%)	1 (16.7%)
Diarrhoea	1 (12.0%)	-	-	1 (12.5%)	1 (12.5%)	-	-	-	-
Pain in extremity	-	-	-	1 (12.5%)	-	1 (16.0%)	-	-	1 (16.7%)

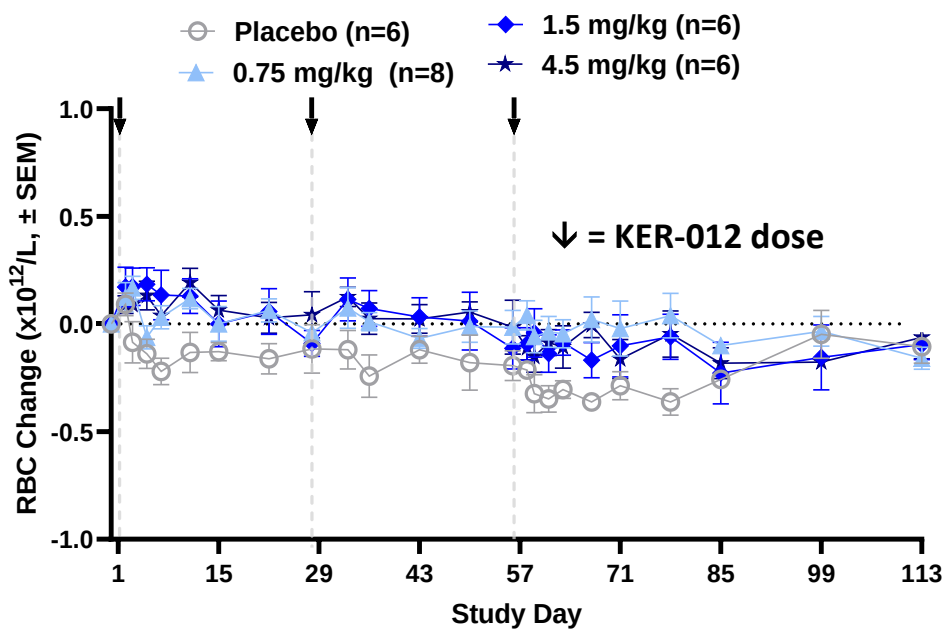
1. AE occurring in $\geq$ 3 participants combined, 2. Data shown as count and (percent) of participants reporting AE, 3. Data as of Aug 4, 2022

Multiple Doses of KER-012 Did Not Elicit Changes in Erythropoiesis

Mean Hemoglobin Change



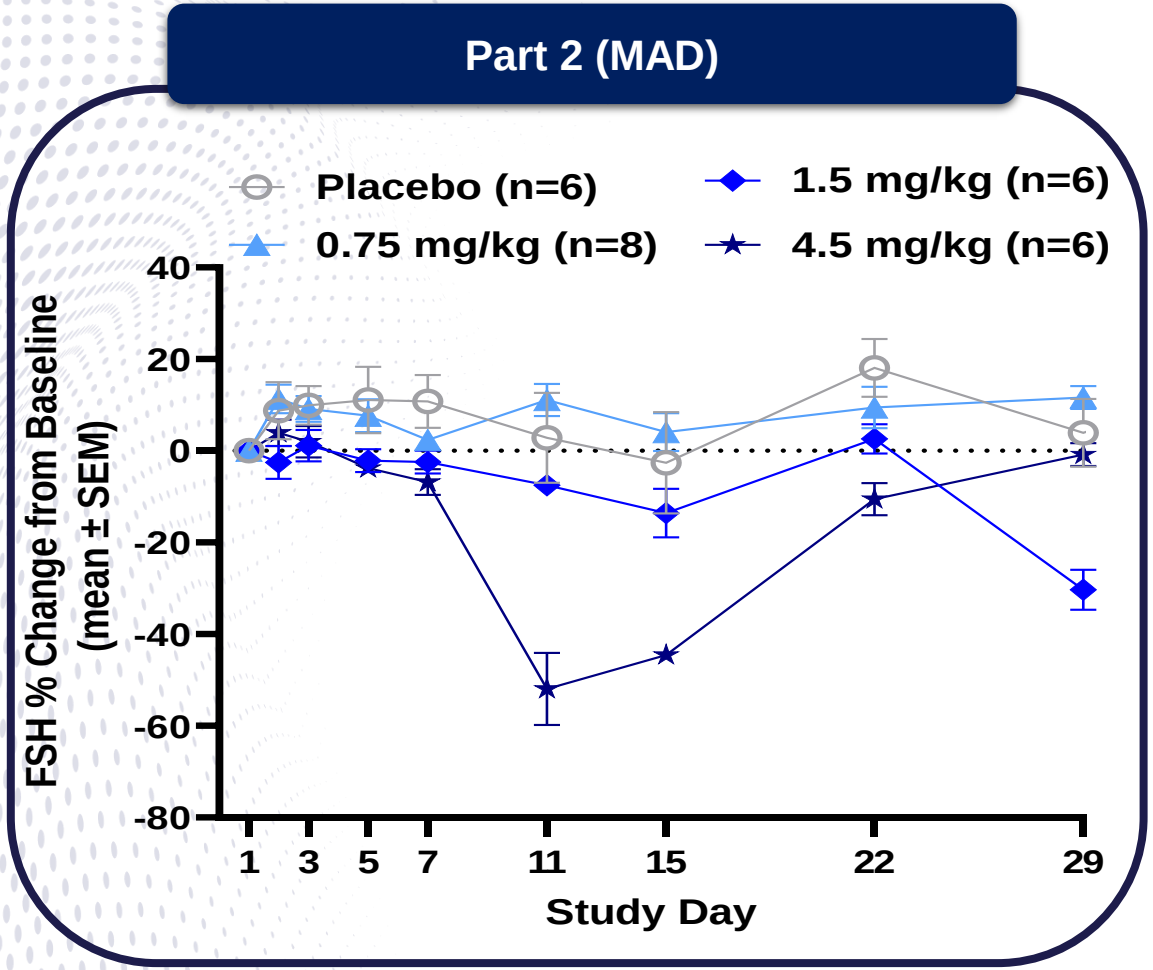
Mean RBC Change



- Treatment with three doses of KER-012 at 28-day intervals did not elicit changes in hemoglobin or red blood cells
- The lack of effect on erythropoiesis in humans was consistent with lack of effect in multiple preclinical models[1,2]

1. Babbs K, et al. American Thoracic Society 2021 Annual Meeting; 2. Babbs K, et al. American Thoracic Society 2022 Annual Meeting

KER-012 Elicited Dose-Dependent Reductions in Serum FSH

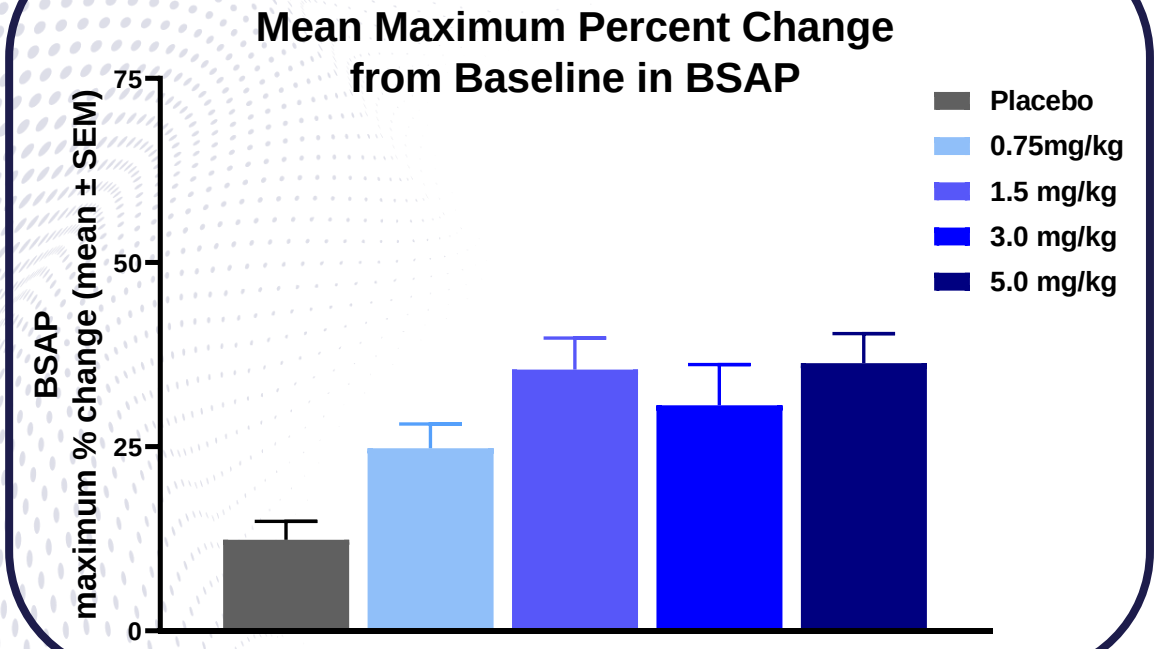


- **Follicle stimulating hormone (FSH) secretion by the pituitary is controlled through signaling by the activin receptor and Gonadotropin Releasing Hormone (GnRH)**
  - Approximately 50% of the FSH secretion is regulated via activin signaling and the other 50% by GnRH[1]
  - Complete inhibition of activin signaling therefore would be expected to reduce FSH by ~50% in postmenopausal women, who have elevated FSH levels
- **KER-012 treatment resulted in suppression of FSH**
  - FSH suppression was observed in Part 1 (SAD) and Part 2 (MAD) of the study
  - In Part 2, maximal suppression was observed at the 4.5 mg/kg dose level with 5 of 6 subjects achieving ≥ 40% reduction in FSH
- **The magnitude of FSH reduction in the highest doses tested suggest that KER-012 treatment maximally inhibited activin signaling.**

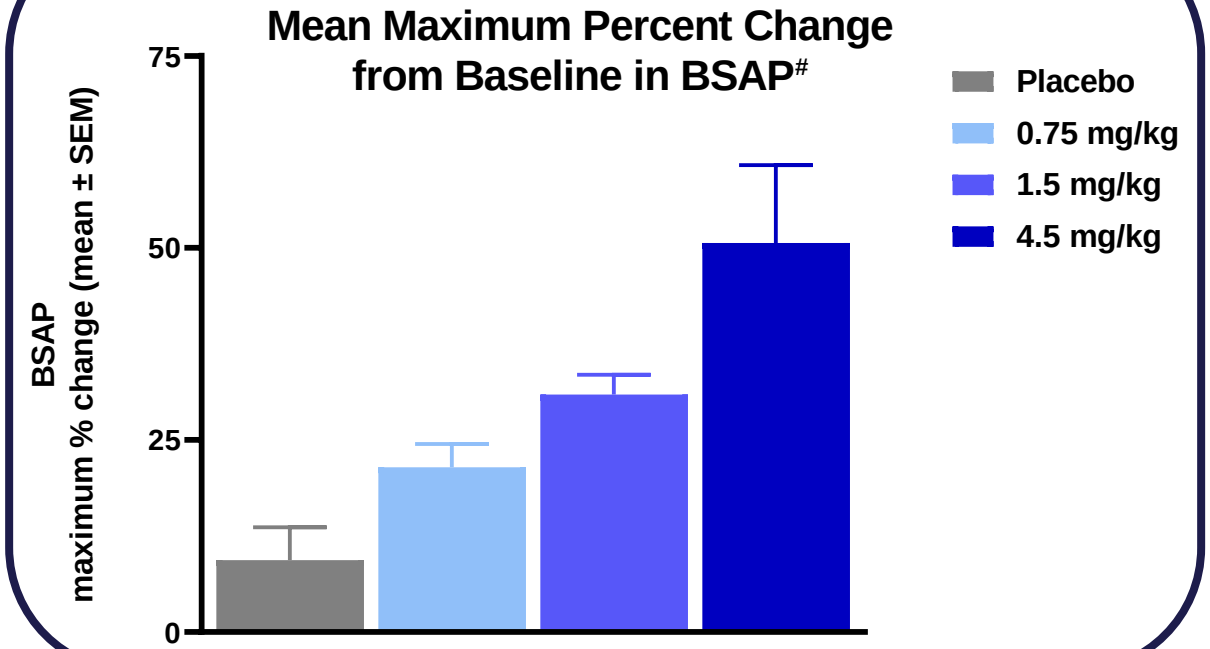
1.Rivier and Vale, Endocrinology 1991;129: 2160-2165

Dose-Dependent Increases in Serum BSAP with Maximal Effects Seen at Highest Doses of KER-012 Tested

Part 1 (SAD)



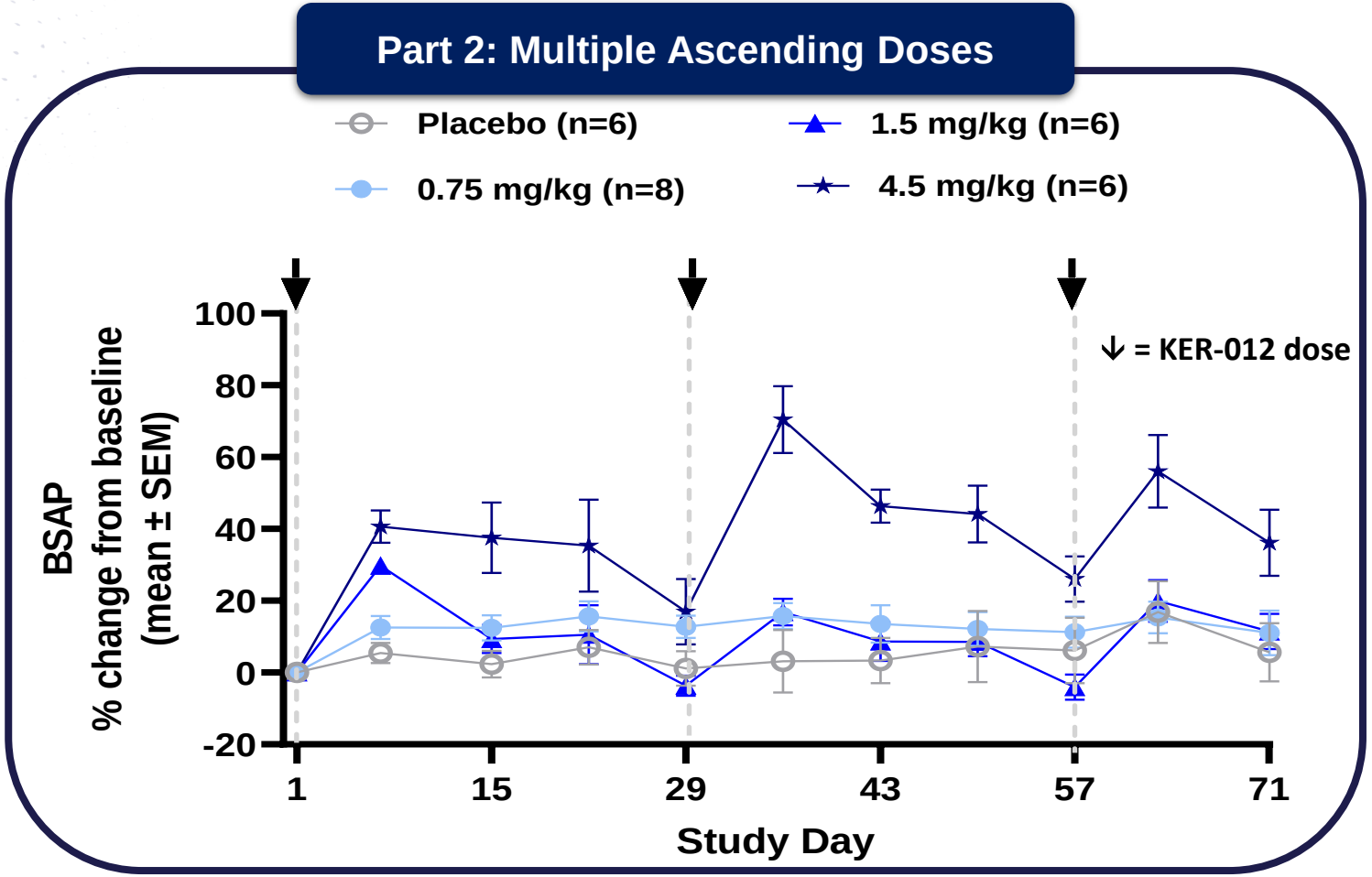
Part 2 (MAD)



- KER-012 is designed to inhibit activins and GDFs in bone, which potentially results in reduced SMAD 2/3 signaling and increased signaling of the bone morphogenetic protein (BMP) pathway (SMAD 1/5/9)
- The increased BMP signaling potentially promotes bone formation through a dual mechanism of activation/recruitment of bone forming osteoblasts and repression of osteoclasts, as demonstrated in preclinical studies[1]
- Increases in BSAP, a marker of osteoblast activity, were observed starting at the lowest dose tested in this trial

1. Materna C et al., Am Society Bone Mineral Res 2021 Annual Meeting. Sept 9-12, 2021, # Data shown post first dose only

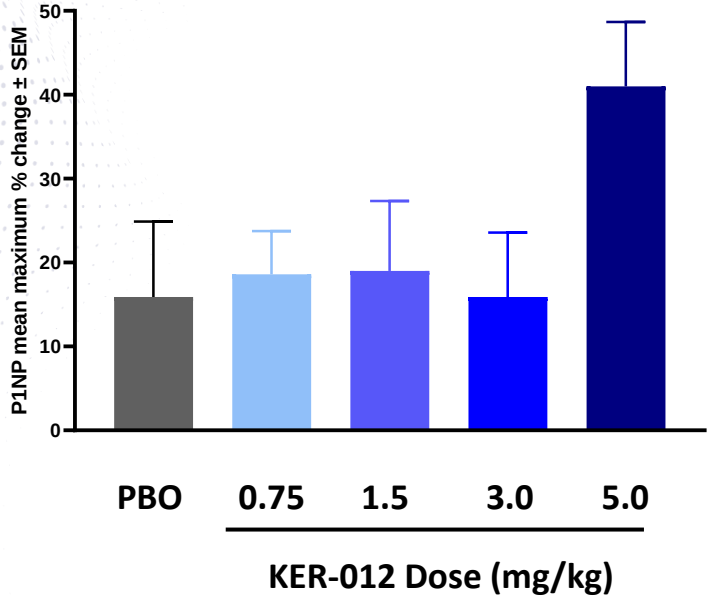
Serum BSAP Increased After Administration of Each Dose of KER-012



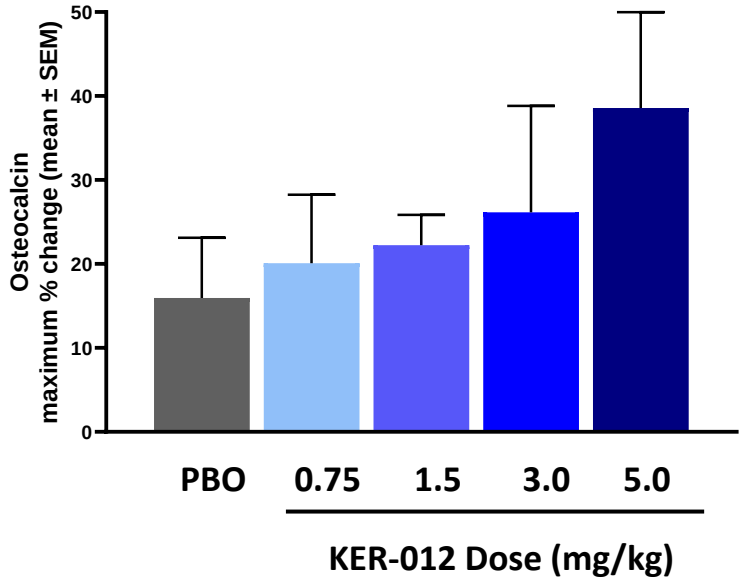
Administration of KER-012 at a 28-day interval resulted in increases in BSAP after each dose in Part 2 (MAD), supportive of activation of osteoblast after each dose

Robust Increases in Additional Markers of Bone Formation Were Elicited by a Single Dose of KER-012 (Part 1)

Procollagen Type 1 N-Terminal Propeptide



Osteocalcin



KER-012 administration elicited increases in:

- **Osteocalcin: indicative of late osteoblastic activity**
- **Procollagen Type 1 N-Terminal Propeptide: indicative of osteoblast activity and new bone formation**

Summary

- KER-012 is a novel, investigational activin receptor type IIB ligand trap designed to correct SMAD 2/3 and SMAD 1/5/9 signaling imbalances in multiple degenerative disease states
  - Demonstrated ability to not only prevent, but reverse bone loss in multiple preclinical models of induced bone dysfunction
- In this Phase 1 study, KER-012 was generally well tolerated at multiple doses up to 4.5 mg/kg; adverse events generally mild
- Consistent with preclinical studies, no clinically meaningful changes in Hb or RBCs were observed
- FSH reduction is suggestive of maximum activin target engagement
- Robust changes in multiple markers of bone formation were observed, starting at the lowest dose (0.75 mg/kg) and maximized at the highest doses administered (4.5 and 5.0 mg/kg)

KER-012 has a tolerability profile suitable for further development in multiple disease states characterized by dysfunctional activin signaling, such as bone disorders and PAH