KER-012, a Novel Modified ActRII Ligand Trap, Attenuated Cardiac Pathology in a Pulmonary Arterial Banding Model of Right Ventricle Overload

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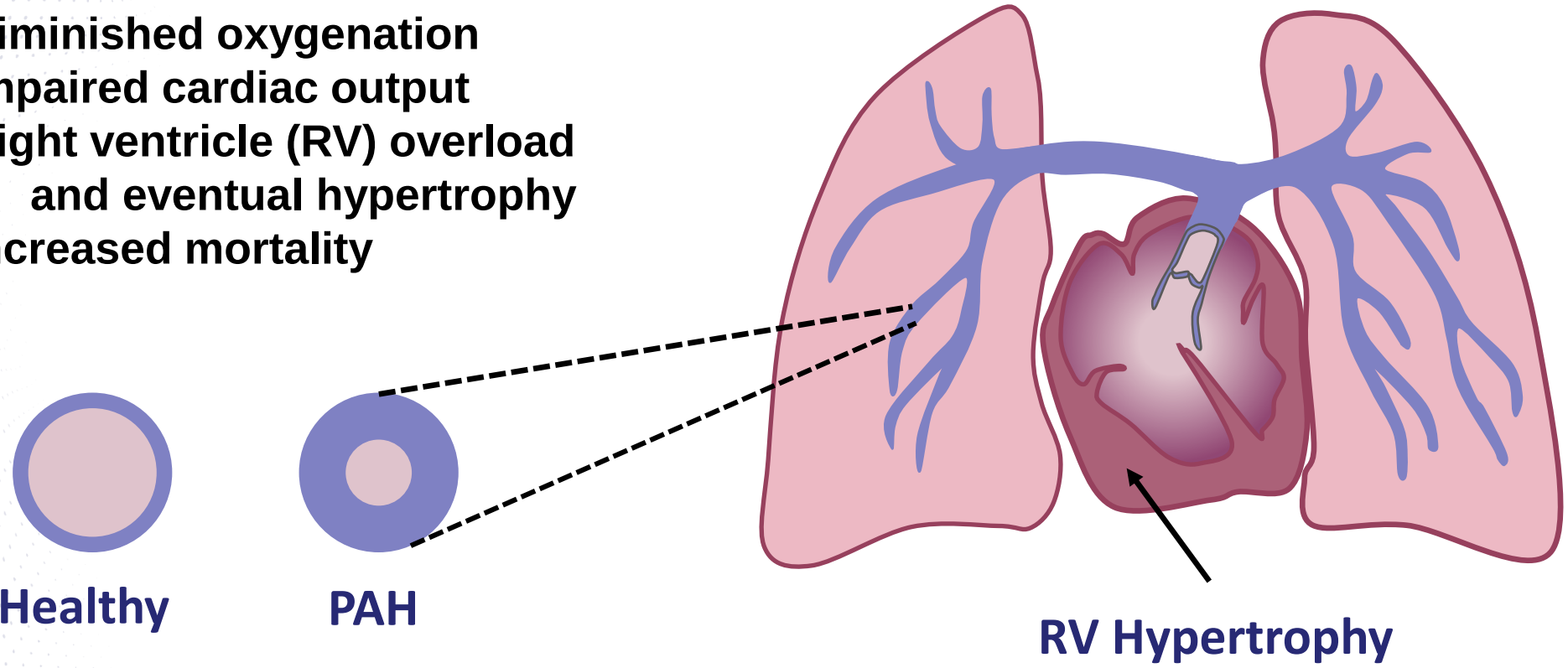
Disclosures

Keith Babbs, Chris Materna, ffolliott Fisher, Jasbir Seehra, and Jennifer Lachey are employees and stockholders of Keros Therapeutics, Inc.

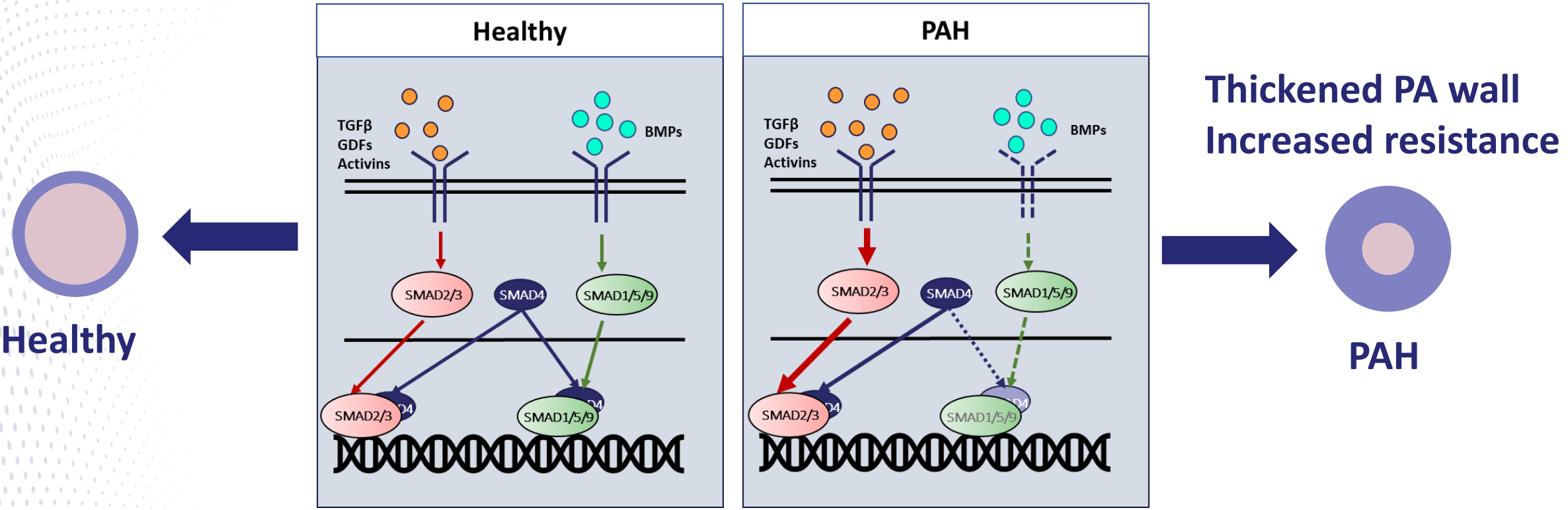
Overview: Pulmonary Arterial Hypertension (PAH)

- Debilitating disorder with an estimated prevalence of 10,000 to 20,000 cases in the U.S. (Prins 2016, Wijeratne 2018)
- Driven by pulmonary endothelial dysfunction and vascular remodeling leading to increased wall thickening and resistance to blood flow (Maron 2016).
- Elevated pulmonary vascular resistance and progressive obliteration of pulmonary vessels leads to:
  - Diminished oxygenation
  - Impaired cardiac output
  - Right ventricle (RV) overload and eventual hypertrophy
  - Increased mortality



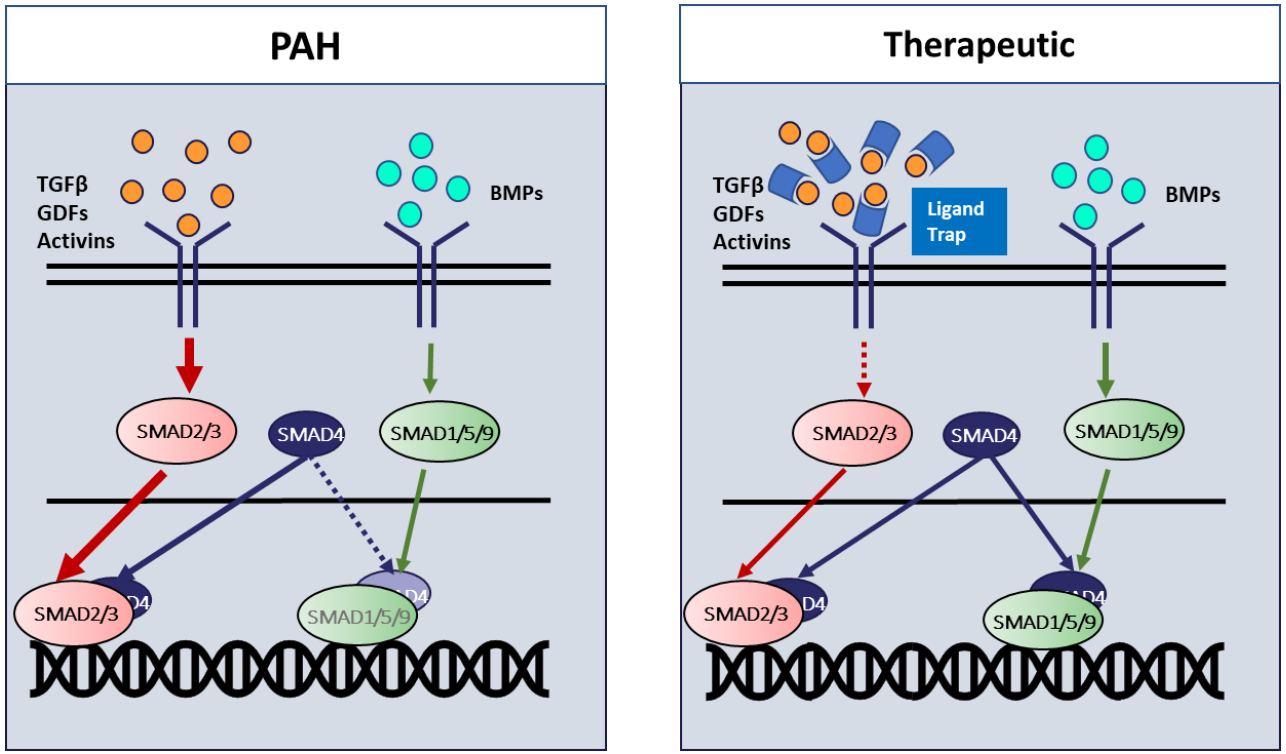
Overview: PAH and TGF-β signaling

- In healthy vasculature, homeostasis is achieved by balanced signaling through SMAD1/5/9 and SMAD2/3, the canonical signaling proteins for the TGF-β superfamily.
- PAH has been associated with dysregulated TGF-β signaling, favoring signaling through SMAD2/3 (Machado 2006, Yang 2017, Ynestad 2009)
  - Diminished BMP signaling – familial form (Lane 2000)
  - Increased SMAD2/3 ligands (Yung 2020)
  - Increased signaling through SMAD2/3 further reduces SMAD1/5/9.
- Unbalanced signaling may lead to enhanced myogenic and fibrogenic differentiation of blood vessels.



Rebalancing Signaling

- Increasing SMAD1/5/9 signaling or decreasing SMAD2/3 signaling may restore homeostasis.
  - Promoting SMAD1/5/9 by administration of BMP9 reversed RV and pulmonary dysfunction in models of PAH (Long 2015).
  - Inhibition of TGF-β2 and 3 by administration of TGFβRII-Fc reduced PAH-associated pathologies (Yung 2016).
  - Inhibition of SMAD2/3 by ActRIIA-Fc (Sotatercept), an activin A, activin B, GDF8 and GDF11 investigational ligand trap, reduced cardiac and pulmonary dysfunction (Yung 2020).



ActRII Ligand Traps Affect Bone, Vasculature, and Erythropoiesis

- **Signaling through SMAD1/5/9 and SMAD2/3 are known to regulate multiple systems, including bone, vasculature and erythropoiesis (Zhang 2017, Itoh 2012, Blank 2011, Song 2009).**

- **Acceleron has disclosed that Sotatercept (ActRIIA-Fc) has been observed to:**
  - **Treat PAH in phase 2 clinical trial**
  - **Increased bone in phase 1 clinical trial**
  - **Increase erythropoiesis in phase 1 and 2 clinical trials**

Sotatercept for the Treatment of Pulmonary Arterial Hypertension

Marc Humbert, M.D., Ph.D., Vallerie McLaughlin, M.D., J. Simon R. Gibbs, M.D., Mardi Gomberg-Maitland, M.D., Marius M. Hoeper, M.D., Ioana R. Preston, M.D., Rogerio Souza, M.D., Ph.D., Aaron Waxman, M.D., Ph.D., Pilar Escribano Subias, M.D., Ph.D., Jeremy Feldman, M.D., Gisela Meyer, M.D., David Montani, M.D., Ph.D., et al., for the PULSAR Trial Investigators*

April 1, 2021
N Engl J Med 2021; 384:1204-1215
DOI: 10.1056/NEJMoa2024277

A soluble activin Type IIA receptor induces bone formation and improves skeletal integrity

R. Scott Pearsall, Ernesto Canalis, Milton Cornwall-Brady, Kathryn W. Underwood, Brendan Haigis, Jeffrey Ucran, Ravindra Kumar, Eileen Pobre, Asya Grinberg, Eric D. Werner, Vaida Glatt, Lisa Stadmeyer, Deanna Smith, Jasbir Seehra, and Mary L. Bouxsein

PNAS May 13, 2008 105 (19) 7082-7087; https://doi.org/10.1073/pnas.0711263105

Multiple-dose, safety, pharmacokinetic, and pharmacodynamic study of sotatercept (ActRIIA-IgG1), a novel erythropoietic agent, in healthy postmenopausal women

Matthew L. Sherman MD, Niels G. Borgstein MD, Louisa Mook MD, Dawn Wilson BS, Yijun Yang ScD, Nianhang Chen PhD, Ravindra Kumar PhD, Kenneth Kim MD, Abderrahmane Laadem MD

First published: 12 August 2013 | https://doi.org/10.1002/jcph.160 | Citations: 29

- **Erythropoietic effects may be dose-limiting in indications not involving deficient erythropoiesis.**

Research Questions

- **Are the effects on bone, RBC and vasculature dependent on one another (i.e., can you have a therapeutic with more selective biology)?**

KER-012 is an investigational, modified ActRIIB ligand trap designed to inhibit SMAD2/3. Keros has previously demonstrated in preclinical studies that KER-012 or its research form, RKER-012:

- **Increased bone in healthy and osteoporotic mice and in rats with hypoxia-associated bone loss.**
- **Reduced cardiopulmonary dysfunction in a SUGEN/hypoxia model of PAH**

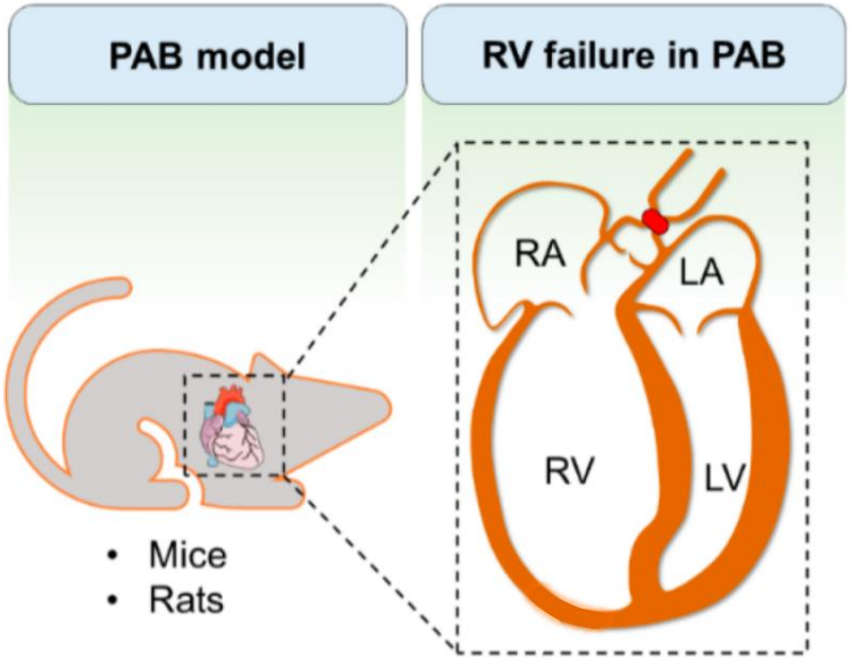
- **Does a therapeutic that affects bone and benefits PAH have direct cardioprotective effects independent of pulmonary vascular benefit?**

- **Does KER-012 affect RBCs as part of its mechanism of action?**

Pulmonary Arterial Banding (PAB)

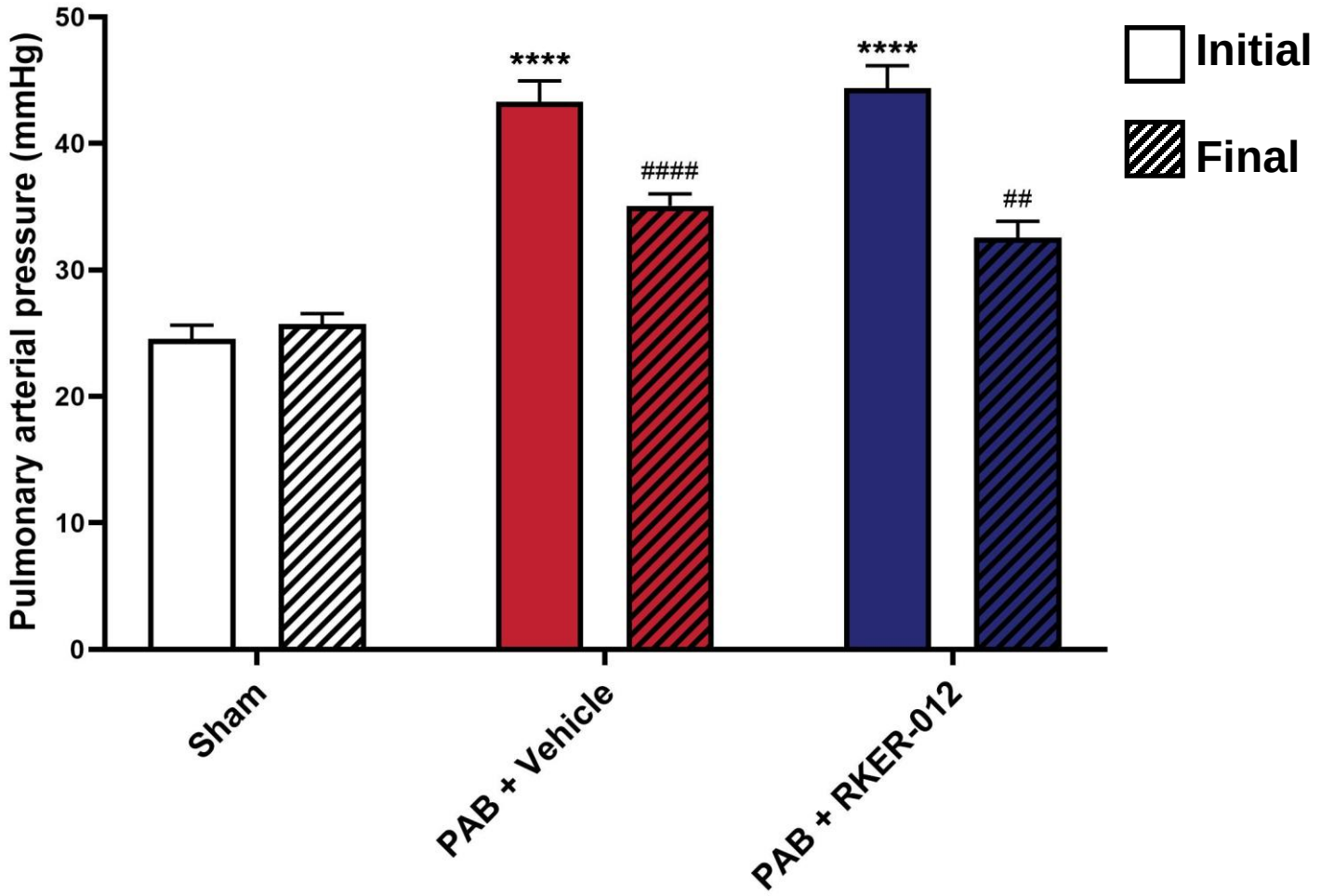
RKER-012, a research form of KER-012, was evaluated in the PAB model to evaluate its effect on dysfunction resulting from RV overload

- PAB increases RV pressure by mechanically restricting blood flow through the pulmonary artery.
- 8 w.o. male C57Bl/6 mice (n=14-16/grp) received either Sham or PAB surgery
  - Ligature applied to the pulmonary artery trunk
  - Pressure was confirmed at PASP > 33 mgHg
- Sham-operated mice received vehicle (VEH) and PAB-operated mice received either VEH or 10 mg/kg of RKER-012 twice weekly for 3 weeks.
- Endpoints
  - *In vivo* cardiac function assessed by echocardiography
  - RV hemodynamics assessed via Millar pressure-volume loop catheter
  - Fibrosis was assessed in formalin-fixed embedded hearts stained with Masson's trichrome



Adapted from Mamazhakypov 2021.

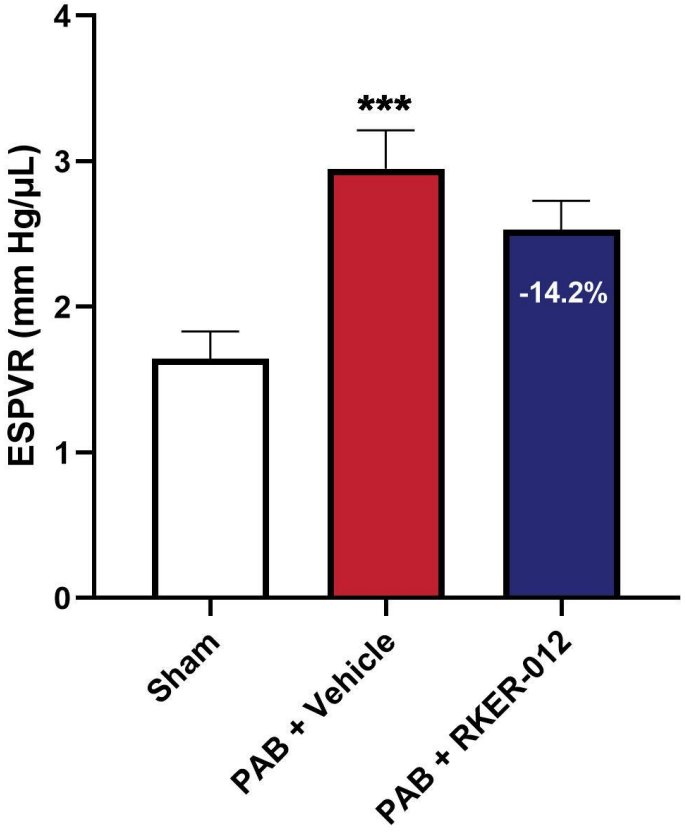
Increased PAP was confirmed in all PAB groups, verifying pressure overload



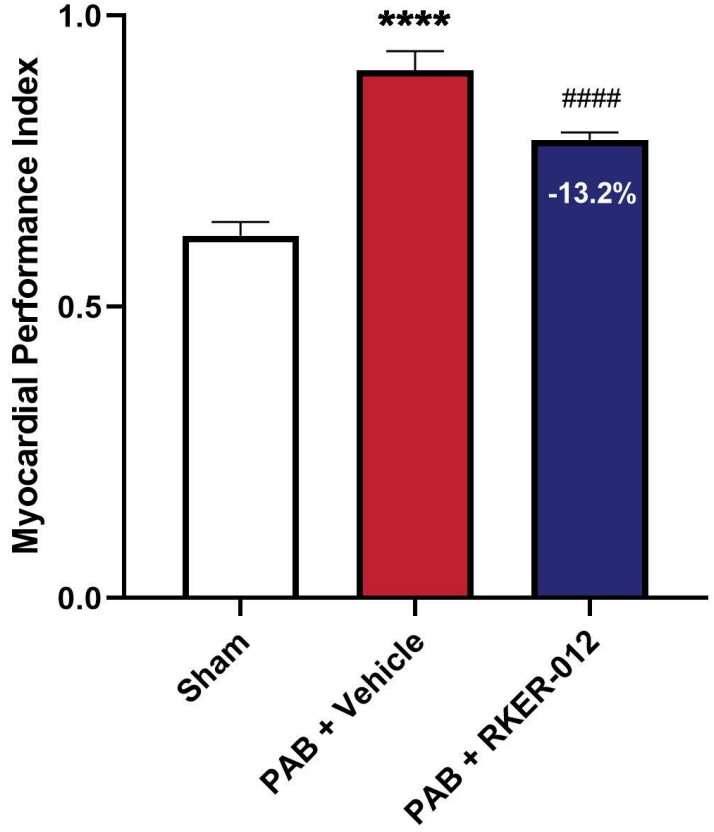
Values depicted are mean + SEM. ****p<0.0001 vs. Sham Initial; ##p<0.01, ####p<0.0001 vs. Sham Final

RKER-012 treatment resulted in improved cardiac dysfunction

End Systolic Pressure-Volume Relationship



Myocardial Performance Index



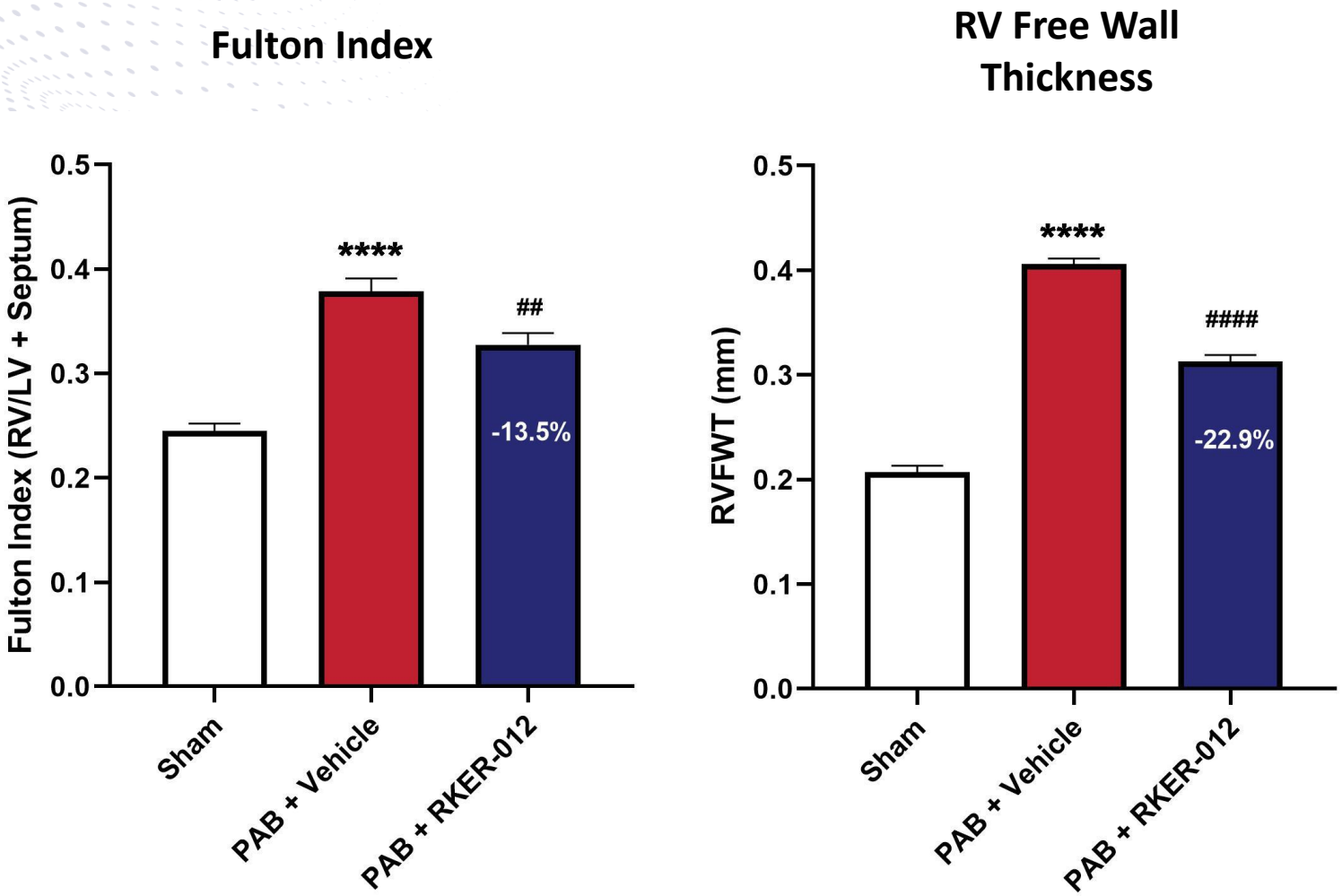
PAB induced cardiac dysfunction:

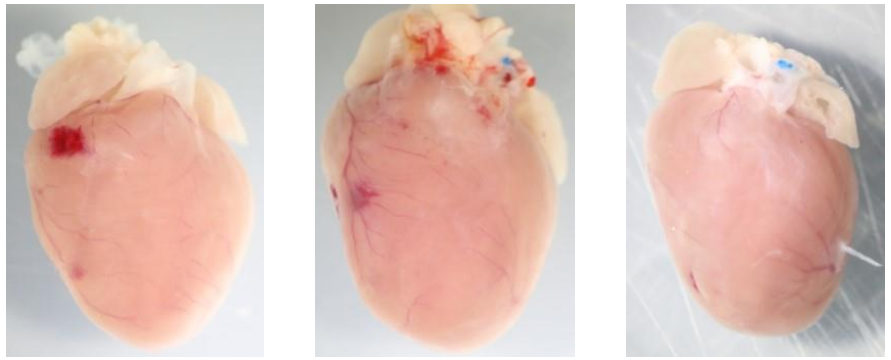
- **Increased ESPVR**
- **Increased MPI**

RKER-012 decreased ESPVR and MPI.

Values depicted are mean + SEM. ***p<0.001; ****p<0.0001 vs. Sham; ####p<0.0001 vs. Vehicle.

RKER-012 decreased cardiac remodeling





SHAM | PAB+VEH | PAB+ RKER-012

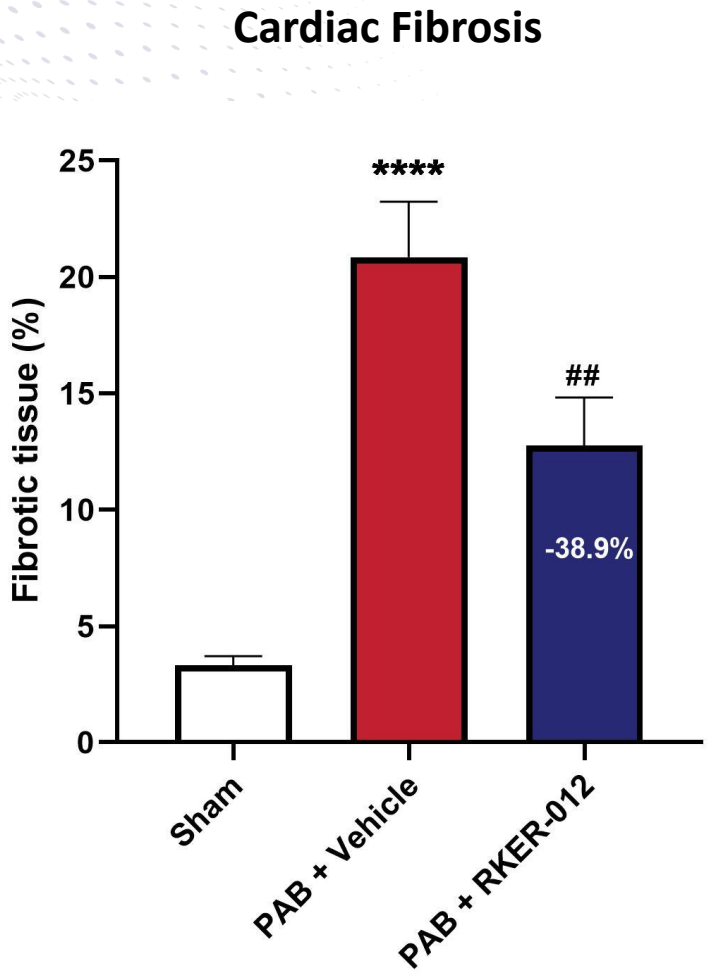
PAB induced cardiac remodeling:

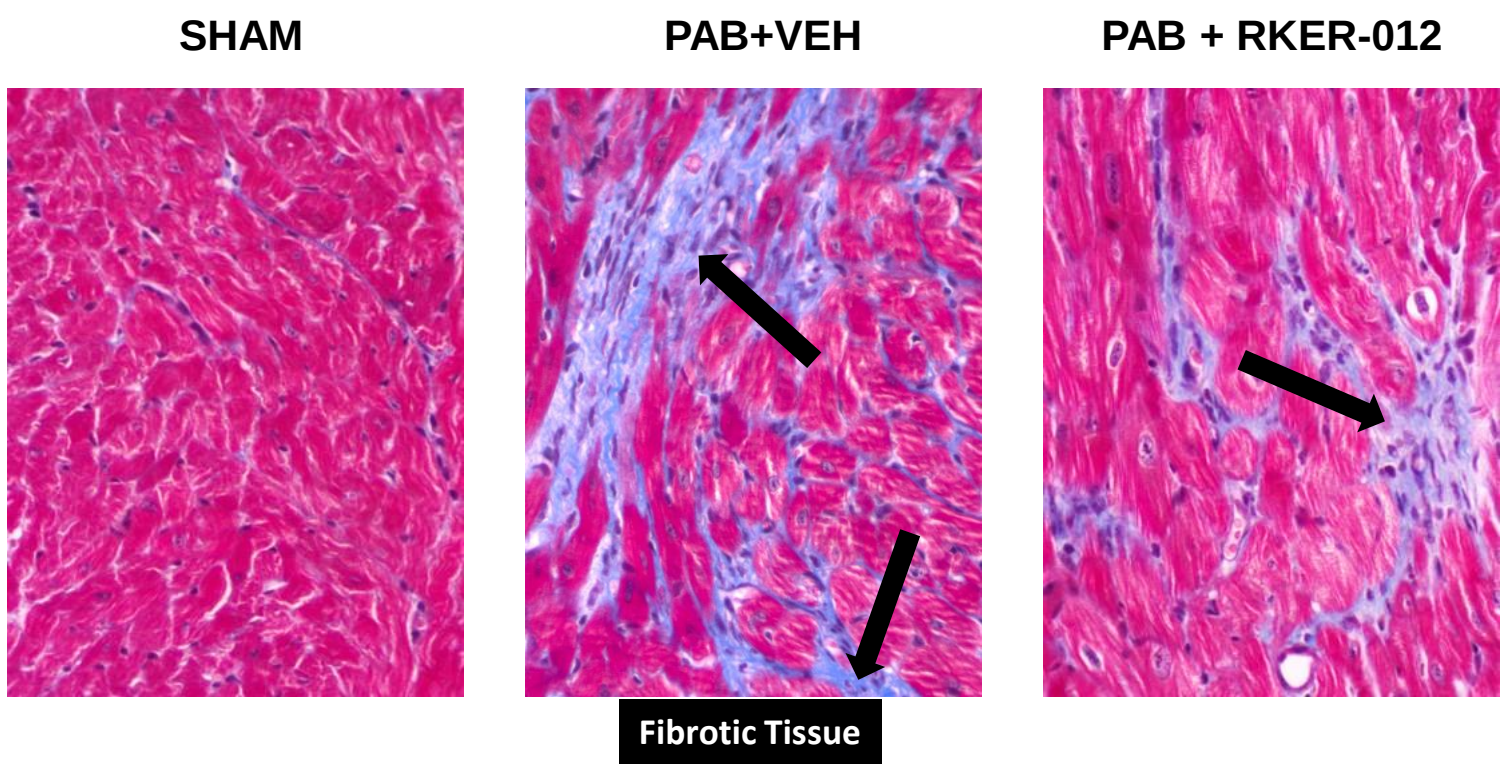
- **Increased Fulton Index**
- **Increased RV free wall thickness**

RKER-012 decreased Fulton Index and RV free wall thickness.

Values depicted are mean + SEM. ****p<0.0001 vs. Sham; ##p<0.01, ####p<0.0001 vs. Vehicle

RKER-012 decreased cardiac fibrosis





- PAB induced formation of fibrotic tissue.
- RKER-012 decreased cardiac fibrotic tissue.

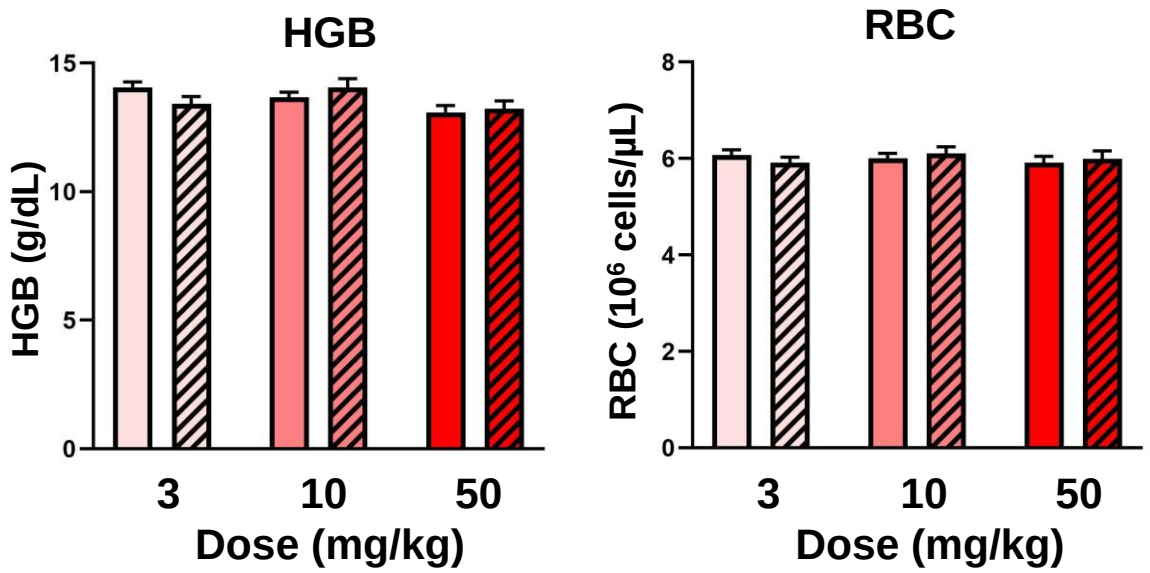
Values depicted are mean + SEM. ****p<0.0001 vs. Sham; ##p<0.01 vs. PAB + Vehicle

KER-012 Did Not Affect Hemoglobin (HGB) or Red Blood Cells (RBC) in Non-human Primates

- As discussed earlier, ActRII ligand traps have also been demonstrated to have pro-erythropoietic effects in humans, an effect which could be dose limiting in non-erythropoiesis-related diseases
- Ligand traps that elevate RBCs and HGB in humans have also been reported as increasing RBCs and HGB in NHP, demonstrating that NHP studies have been predictive models for what will be expected in humans (Sherman 2013, Piga 2019, Suragani 2014, Attie 2012)

Therapeutic	HGB in NHPs	HGB in Human
ACE-011 (Sotatercept)	↑	↑
ACE-536 (Reblozyl®; Luspatercept)	↑	↑
KER-050	↑	↑
ACE-031 (ActRIIB-Fc)	Not Reported	No Change
KER-012	No Change	TBD*

*KER-012 healthy volunteer trial is ongoing. Data expected to be reported in 2022.



Values depicted are mean + SEM.

Summary/Conclusions

- KER-012 is an investigational modified ActRIIB ligand trap designed to inhibit ligands that signal through SMAD2/3 to promote restoration of vascular homeostasis.

- In a PAB model of RV pressure overload, RKER-012 showed direct cardiac benefit by decreasing:
  - Cardiac dysfunction
  - Cardiac remodeling
  - Fibrosis

- KER-012 did not increase HGB or RBCs in nonhuman primates.

Taken together, these data provide preliminary preclinical evidence that the biological effects on bone, blood, and vasculature are separable. Moreover, we believe KER-012 has the potential to provide benefit in PAH without affecting RBCs or HGB.

Phase 1 clinical trial of KER-012 in healthy volunteers is ongoing.