RKER-012 Therapy Prevented Increased Pulmonary Arterial Pressure And Right Ventricle Hypertrophy In A Rat Model Of PAH

Keith Babbs, Chris Materna, ffolliott Fisher, Sebastien Sannajust, Dan Aleksandrowicz, Jasbir Seehra, Jennifer Lachey
Keros Therapeutics, Lexington, MA, USA

Introduction

- Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary vascular resistance, impaired cardiac output, and right ventricle (RV) overload and hypertrophy[1].
- PAH is associated with imbalanced TGF-ß signaling, including insufficient activation of SMAD1/5/9 and/or inappropriately high SMAD2/3 signaling which is associated with inflammation, fibrosis, and eventual heart failure (HF)[1].
- In preclinical studies and clinical trials, treatment with an investigational ActRIIA ligand trap (ActRIIA-Fc) demonstrated benefits concomitant with an observed dose-limiting increase in red blood cells (RBCs)[2,3].
- RKER-012 is a research form of KER-012, which is an investigational, modified ActRIIB ligand trap, designed to target ActRII signaling to favor SMAD1/5/9 without affecting RBCs.

Aim: To investigate the mechanism of RKER-012's prevention of PAH pathology and evaluate potential RBC effects.

Methods

- Sprague Dawley rats (241-295g) received either vehicle (DMSO; n=6/group) or SU54216 (200 mg/kg; n=12/group) SQ once and placed in either normoxic (Nx; ~21% O_2) or hypoxic (Hx; ~13% O_2) conditions.
  - Nx rats were treated with vehicle (TBS), while Hx rats were treated with vehicle (TBS), ActRIIA-Fc (10 mg/kg) or RKER-012 (10 mg/kg) SQ twice weekly for 3 weeks.
  - Rats were assessed terminally for RV and lung expression of markers of PAH pathology. Histopathology for lung inflammation, fibrosis, and smooth muscle hypertrophy was scored. RV histopathology is pending.
- 2- to 4-year-old cynomolgus monkeys (n=6/sex/group) were dosed every other week for 190 days. RBC number was assessed at the beginning and end of the study.

Results

RKER-012 reduced right ventricle (RV) hypertrophy and reduced pulmonary arterial pressure in the rat PAH model

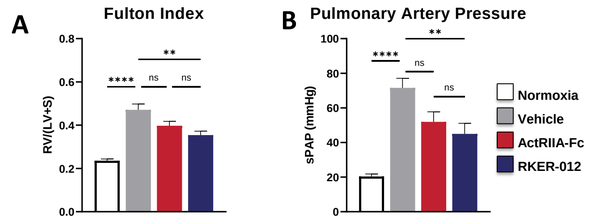

Figure 1. Vehicle-treated Hx rats had (A) RV hypertrophy and (B) elevated pulmonary arterial pressure. Treatment with RKER-012 significantly reduced both of these pathologies. **p<0.01; ****p<0.0001, ns p>0.05.

RKER-012 reduced lung inflammation, fibrosis and smooth muscle hypertrophy

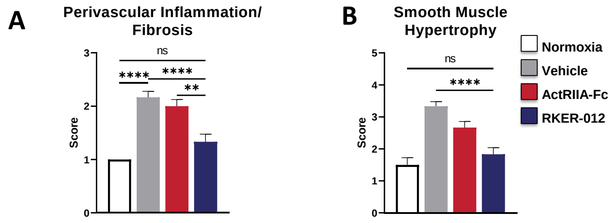

Figure 2. Vehicle-treated Hx rats had increased (A) lung inflammation and (B) smooth muscle hypertrophy. Treatment with RKER-012 prevented these pathologies. **p<0.01; ****p<0.0001, ns p>0.05.

RKER-012 reduced markers of heart failure in the RV

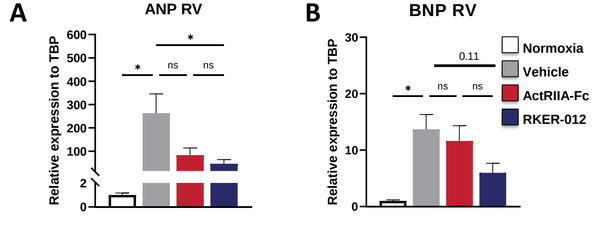

Figure 3. Vehicle-treated Hx rats had elevated RV expression of (A) atrial natriuretic peptide (ANP) and (B) brain natriuretic peptide (BNP), which are markers of heart failure. Treatment with RKER-012 significantly reduced expression of both genes. *p<0.05, ns p>0.12.

RKER-012 reduced expression of genes associated with the development of PAH pathology in lung and RV

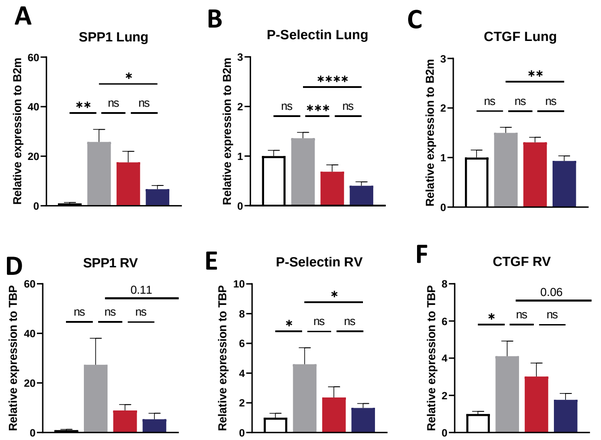

Figure 4. Vehicle-treated Hx rats had elevated expression of lung and RV expression of genes associated with PAH pathology, including lung secreted phosphoprotein 1 (SPP1; A,D), RV P-selectin (B,E) and lung and RV connective tissue growth factor (CTGF; C,F). Treatment with RKER-012 significantly reduced expression of all of these genes. B2M=bet-2-macroglobulin, TBP=tata-box binding protein *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns p>0.05.

6 months of treatment with KER-012 did not increase RBCs in non-human primates

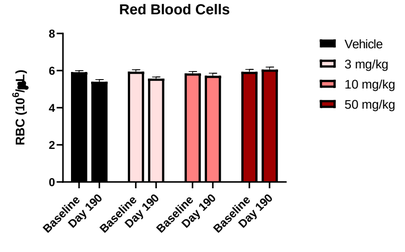

Figure 5. In a non-human primate model that is believed to be highly predictive of response in humans, KER-012 did not increase RBC number in any of the doses evaluated.

Conclusions

- **RKER-012 is a modified ActRIIB ligand trap designed to inhibit SMAD 2/3 signaling, favoring SMAD 1/5/9.**
- **In a Sugen hypoxia rat model of PAH, relative to vehicle Nx, RKER-012:**
  - **reduced pulmonary arterial pressure and right ventricle hypertrophy;**
  - **reduced lung fibrosis, inflammation and smooth muscle hypertrophy;**
  - **reduced markers of heart failure in RV; and**
  - **reduced changes in gene expression of markers of PAH-associated pathology.**
- **KER-012 did not alter RBCs in non-human primates.**

These results provide early evidence that KER-012 has the potential to benefit lung and heart tissues in PAH, and support continued clinical development in patients.

References

1. Yung et al. 2020 (PMID: 32404506)
2. Sherman et al. 2012 (PMID: 23939631)
3. Humbert el al. 2021 (PMID: 33789009)

Contact

Justin Frantz
jfrantz@soleburytrout.com
617-221-9100

Disclosures

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