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EFFECTS OF INHALED SERALUTINIB ON RIGHT VENTRICULAR-PULMONARY ARTERIAL (RV-PA) COUPLING AND RIGHT HEART FUNCTION IN PULMONARY ARTERIAL HYPERTENSION (PAH)

TORREY STUDY

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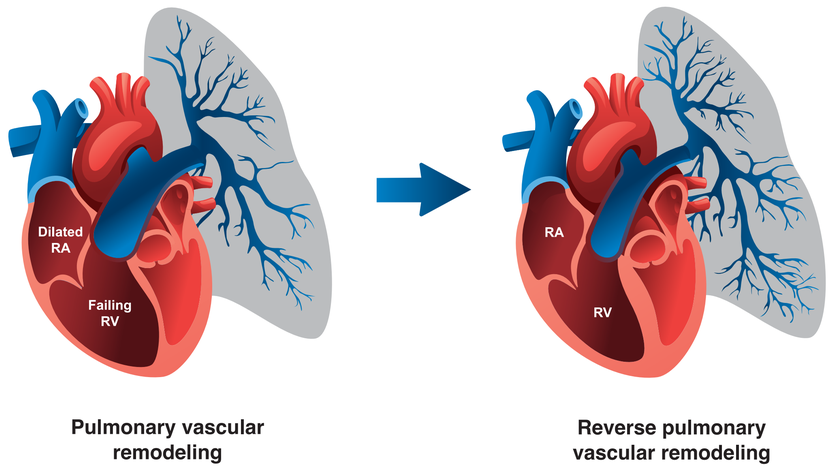
BACKGROUND

- Pulmonary vascular remodeling in PAH increases pulmonary vascular resistance (PVR) and decreases pulmonary artery compliance (PAC)
- As a result, right ventricular (RV) afterload and RV strain are increased, leading to right atrial and RV dilation and eventual right heart (RH) failure (**Figure 1**)
- Right atrial area (RAA), right ventricular free wall strain (RVFWS), and RVFWS:systolic pulmonary arterial pressure (sPAP) ratio are important prognostic measures of RH function[1,2]
- Therapies that have the potential to reverse-remodel the pulmonary vasculature may prevent or reverse RH failure
- Seralutinib, a potent PDGFRα/ß, CSF1R, and c-KIT inhibitor targets inflammation, proliferation and fibrosis associated with pulmonary vascular remodeling[3]
- The phase 2 TORREY study of inhaled seralutinib in patients with PAH met its primary endpoint of reduction in PVR at 24 weeks (NCT04456998)
- One exploratory endpoint in TORREY was the change from baseline to Week 24 in RV function measured by echocardiography

Figure 1. Pulmonary vascular remodeling impacts RH function.



METHODS

- Phase 2, randomized, double-blind, placebo-controlled, multicenter study in patients with World Health Organization (WHO) Group 1 PH, Functional Class (FC) II or III, on standard background therapies, 6-minute walk distance (6MWD) ≥ 150 m and ≤ 550 m, PVR ≥ 400 dyne*s/cm^5
- 2D and color Doppler echocardiography was performed at baseline, Week 12 and Week 24, and analyzed at a core laboratory in a blinded fashion
- Key parameters included RAA, RVFWS, and RVFWS:sPAP; Speckle tracking with TOMTEC software was used to calculate RVWFS
- Statistical analysis was performed using analysis of covariance (ANCOVA)

RESULTS

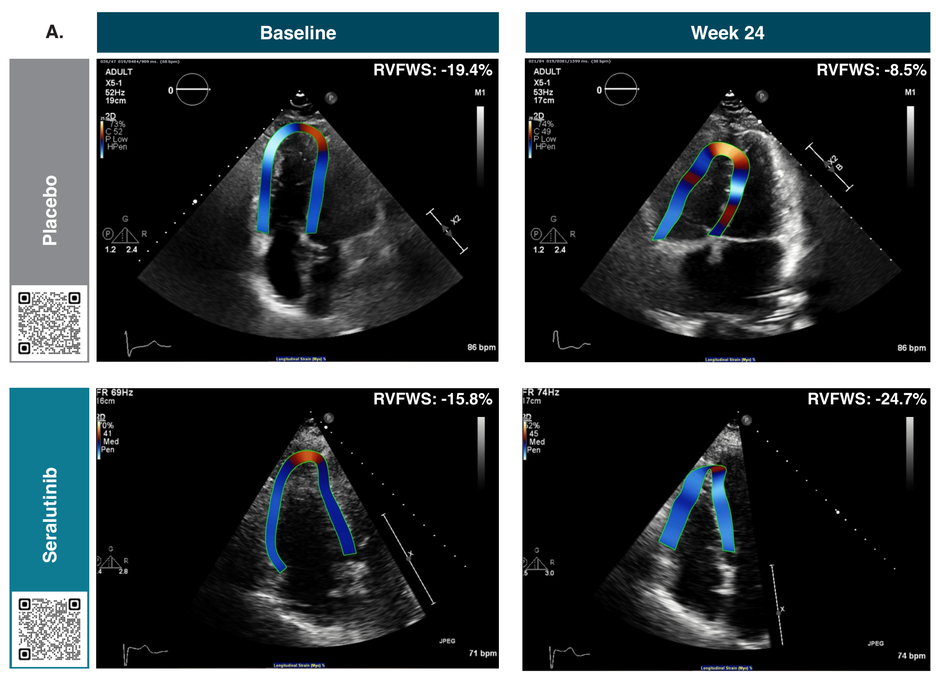
- 86 patients were randomized to study treatment at 40 sites worldwide; 80 patients completed the study
- Treatment groups were balanced except for WHO FC II/III: seralutinib, 68%/32%; placebo, 48%/52%
- For an overview of TORREY topline results,[4] please scan the QR code in the poster's Conclusions section

Table 1. Baseline echocardiography parameters.

	Placebo		Seralutinib	
Parameter	n	Mean (SD)	n	Mean (SD)
Right atrial area (RAA), cm^2	41	17.4 (6.80)	42	17.0 (4.33)
Right ventricular free wall strain (RVFWS), %	42	-16.2 (5.47)	44	-17.8 (4.84)
RVFWS:sPAP[a] ratio, %/mmHg	42	-0.2 (0.09)	44	-0.2 (0.11)
Tricuspid annular peak systolic velocity (TAS'), cm/s	37	10.6 (1.98)	43	10.8 (2.48)
Right ventricular fractional area change (RVFAC)	39	33.9 (8.81)	44	36.9 (11.67)
Tricuspid annular plane systolic excursion (TAPSE), mm	38	17.0 (3.60)	41	16.9 (4.22)
Systolic pulmonary artery pressure (sPAP[a]), mmHg	42	81.9 (16.63)	44	84.8 (17.85)
TAPSE:sPAP[a] ratio, mm/mmHg	38	0.2 (0.06)	41	0.2 (0.09)
RV:LV basal diameter ratio	37	1.2 (0.27)	41	1.1 (0.21)
Left ventricular ejection fraction (LVEF), %	38	68.5 (6.19)	42	69.5 (6.64)

[a]sPAP values obtained from right heart catheterization.

Figure 3. Case study: Seralutinib reduced RVFWS (**A.**) and improved hemodynamic parameters (**B.**) from baseline to Week 24 in TORREY. Scan the QR codes below to view the animated echocardiograms.

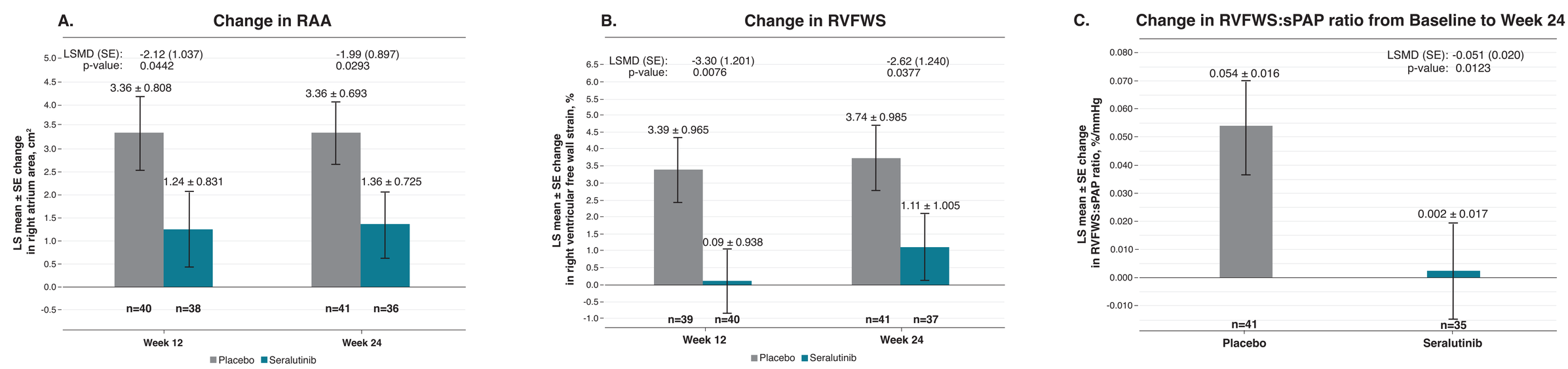


B. Changes in hemodynamic parameters
(BL to Week 24)

Placebo		
mPAP, mmHg	CO, L/min	PVR, dyne*s/cm^5
+5	-0.3	+80

Seralutinib		
mPAP, mmHg	CO, L/min	PVR, dyne*s/cm^5
-5	+0.6	-125

Figure 2. A. Seralutinib treatment resulted in a significantly lower increase in RAA vs placebo both at Week 12 (p = 0.0442) and Week 24 (p = 0.0293). **B.** Seralutinib prevented worsening of RVFWS both at Week 12 (p = 0.0076) and Week 24 (p = 0.0377) and **C.** was associated with a significant reduction of RVFWS:sPAP at Week 24 (p = 0.0123). These treatment effects support improved RV-PA coupling and RH function. In conjunction with concordant reductions in PVR and NT-proBNP, these data suggest potential favorable effects of seralutinib in PAH.



CONCLUSIONS

- In the phase 2 TORREY study, inhaled seralutinib treatment showed a significant benefit on right atrial area at Weeks 12 and 24 compared to placebo
- Seralutinib prevented worsening of right ventricular free wall strain at Weeks 12 and 24
- Seralutinib treatment was associated with a significant reduction of RVFWS:sPAP after 24 weeks
- These data support improved RV-PA coupling and right heart function after 24 weeks with seralutinib

References: 1 Richter MJ et al. *J Heart Lung Transplant* 2023 Apr;42(4):433-446. **2** Ünlü S et al. *Eur Heart J Cardiovasc Imaging* 2023;24(5):635-642. **3** Galkin A et al. *Eur Respir J* 2022; 60(6):2102356. **4** Frantz RP et al. *Am J Respir Crit Care Med* 2023;207:A6726.

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Seralutinib for the Treatment of PAH: Results from the Ph2 TORREY Study

TORREY study echocardiography results