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

TORREY STUDY

7th World Symposium on Pulmonary Hypertension
Barcelona, Spain
29 June - 1 July 2024

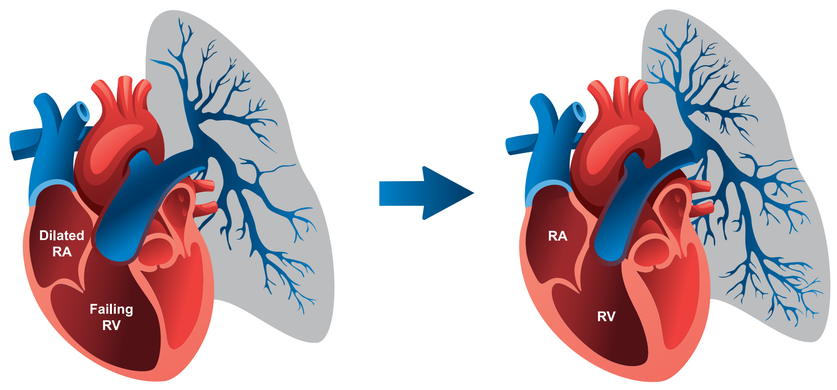
Robert P. Frantz[1], Khodr Tello[2], Victor M. Moles[3], Scott D. Solomon[4], Roberto Badagliacca[5], Raymond L. Benza[6], Richard N. Channick[7], Kelly M. Chin[8], Anna R. Hemnes[9], Luke S. Howard[10], Vallerie V. McLaughlin[3], Olivier Sitbon[11], Roham T. Zamanian[12], Matt Cravets[13], Robin Osterhout[13], Robert F. Roscigno[13], Richard Aranda[13], Lawrence S. Zisman[13], Hossein-Ardeschir Ghofrani[14], Jean-Luc Vachiéry[15]

[1]Mayo Clinic, Rochester, MN, USA; [2]Justus-Liebig-University Giessen, Giessen, Germany; [3]University of Michigan, Ann Arbor, MI, USA; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [5]Sapienza University of Rome, Rome, Italy; [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]University of California Los Angeles, UCLA Medical Center, Los Angeles, CA, USA; [8]UT Southwestern Medical Center, Dallas, TX, USA; [9]Vanderbilt University, Vanderbilt University Medical Center, Nashville, TN, USA; [10]Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK; [11]Hôpital Bicêtre (AP-HP), Université Paris-Saclay, Le Kremlin-Bicêtre, France; [12]Stanford University School of Medicine, Stanford Medicine, Stanford, CA, USA; [13]Gossamer Bio, Inc., San Diego, CA, USA; [14]Universities of Giessen and Marburg Lung Center (UGMLC), Institute for Lung Health (ILH); Cardio-Pulmonary Institute (CPI); Member of the German Center for Lung Research (DZL), Giessen, Germany; [15]Université Libre de Bruxelles, HUB – Hôpital Erasme, Brussels, Belgium

BACKGROUND

- Pulmonary vascular remodeling in PAH increases pulmonary vascular resistance (PVR) and decreases pulmonary arterial 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)[4]
- 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 right heart 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 RVFWS
- Statistical analysis was performed using analysis of covariance (ANCOVA)

RESULTS

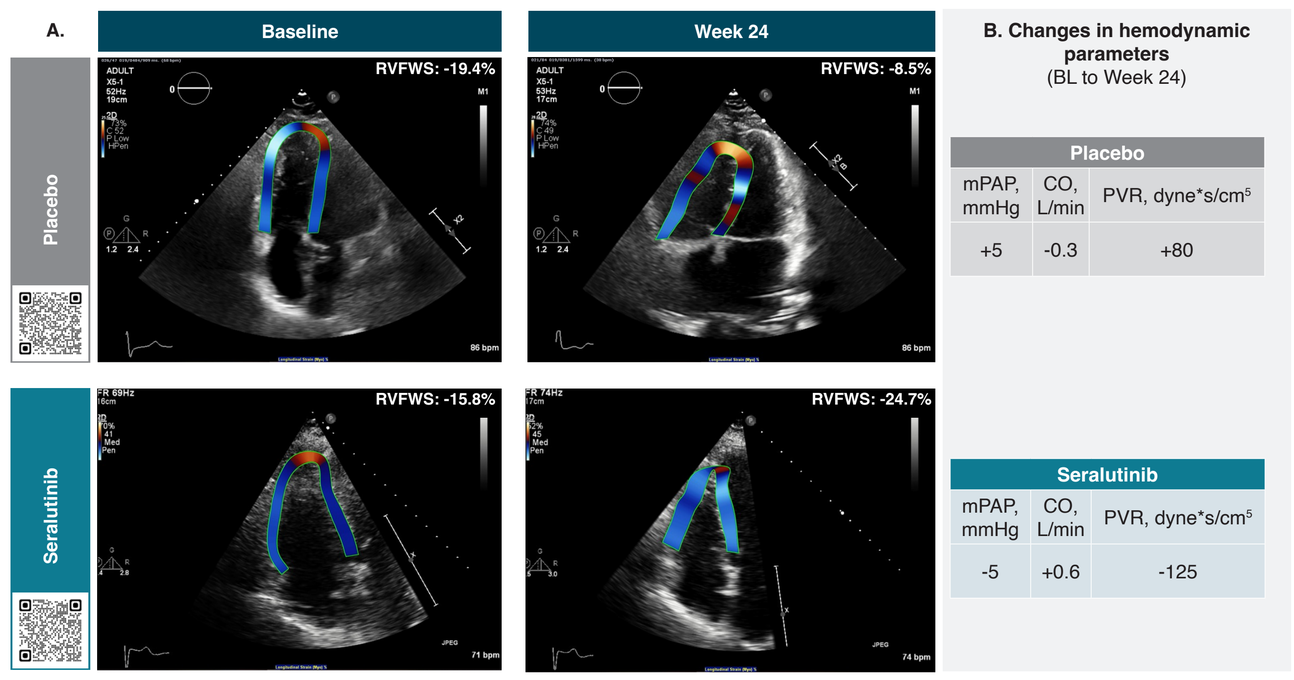
- 86 patients were randomized to study treatment at 40 sites worldwide; 80 patients completed the study
- Treatment groups were balanced except for WHO FC II/III: seralutinib, 68%/32%; placebo, 48%/52%
- For an overview of TORREY topline results,[4] please scan the QR code in this poster's Conclusions 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 arterial 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 (BL) to Week 24 in TORREY. Scan the QR codes below to view the animated echocardiograms.

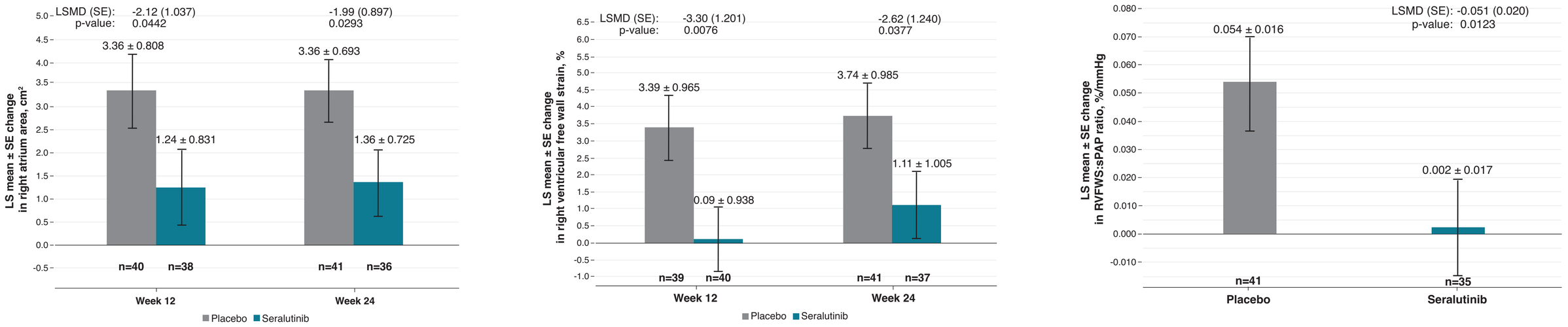


B. Changes in hemodynamic parameters
(BL to Week 24)

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. *Lancet Resp Med* Published online May 2, 2024. doi: 10.1016/S2213-2600(24)00072-9

Acknowledgements: We thank all patients, their families, and all the TORREY study investigators and study coordinators who participated in TORREY.
Research supported by: Gossamer Bio, Inc.

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

TORREY study echocardiography results