Effects of Inhaled Seralutinib on Right Ventricular-Pulmonary Arterial Coupling and Right Heart Function in Pulmonary Arterial Hypertension

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27 August 2023

Pulmonary Vascular Remodeling in PAH Impacts Right Heart Function

Pathological mechanisms of pulmonary vascular remodeling

Vascular remodeling of the small pulmonary arteries

- Peri-vascular inflammation
- Neointimal proliferation of endothelial cells and myofibroblasts
- Proliferation and hypertrophy of PASMCs
- Perivascular fibrosis

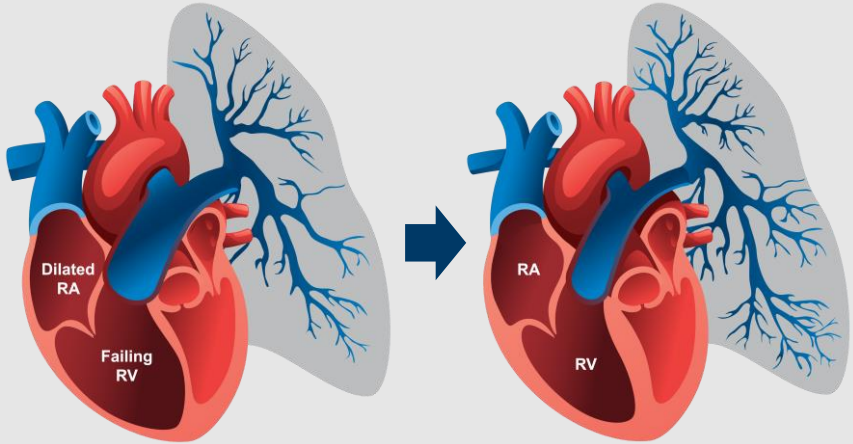
Seralutinib, a potent PDGFRα/ß, CSF1R, and c-KIT inhibitor targets inflammation, proliferation and fibrosis associated with pulmonary vascular remodeling

Pulmonary vascular remodeling

Increased PVR, decreased PAC, increased RV afterload, and increased RV strain may cause eventual RA & RV dilation and RV failure.

Reverse pulmonary vascular remodeling

Reduced PVR and increased PAC reduce RV afterload and RV strain and may delay, prevent, or reverse RV failure.

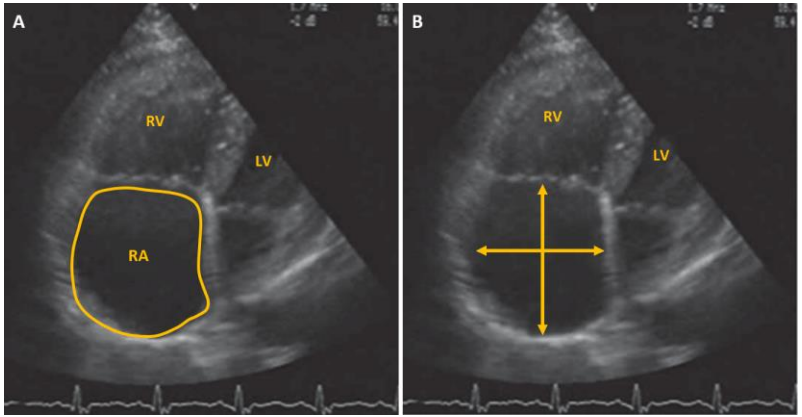


PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cell; PVR, pulmonary vascular resistance; RA, right atrial/atrium; RV, right ventricular/ventricle.

RAA, RVFWS and RVFWS:sPAP Are Important Measures of Right Heart Function in PAH

- Imaging-based assessment of the right atrium provides important prognostic information
  - An increase of 1 cm^2 in RAA increased the risk of death by 6%[1]

Measurement of A) the right atrial area and B) dimensions in an apical four-chamber view[2]

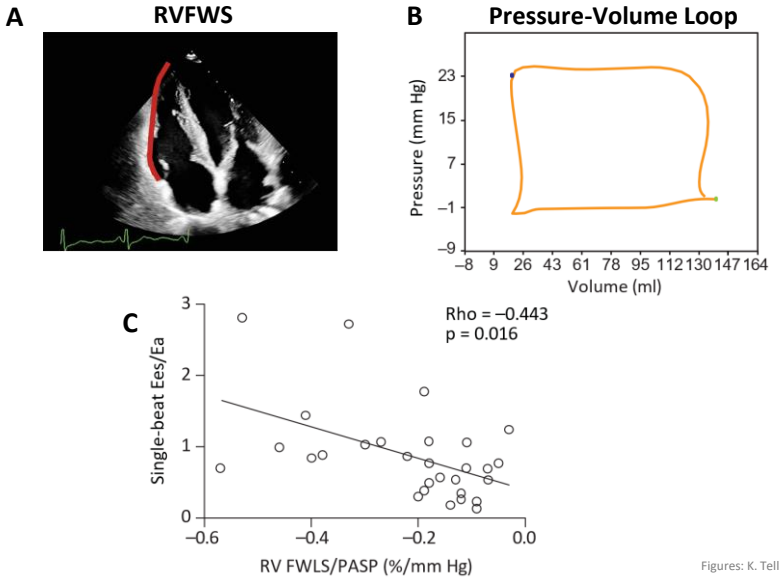


Right atrial area (N<20 cm^2)

Right atrial transverse and supero-inferior diameters

Figure adapted from Habib G, Torbicki A. 2010

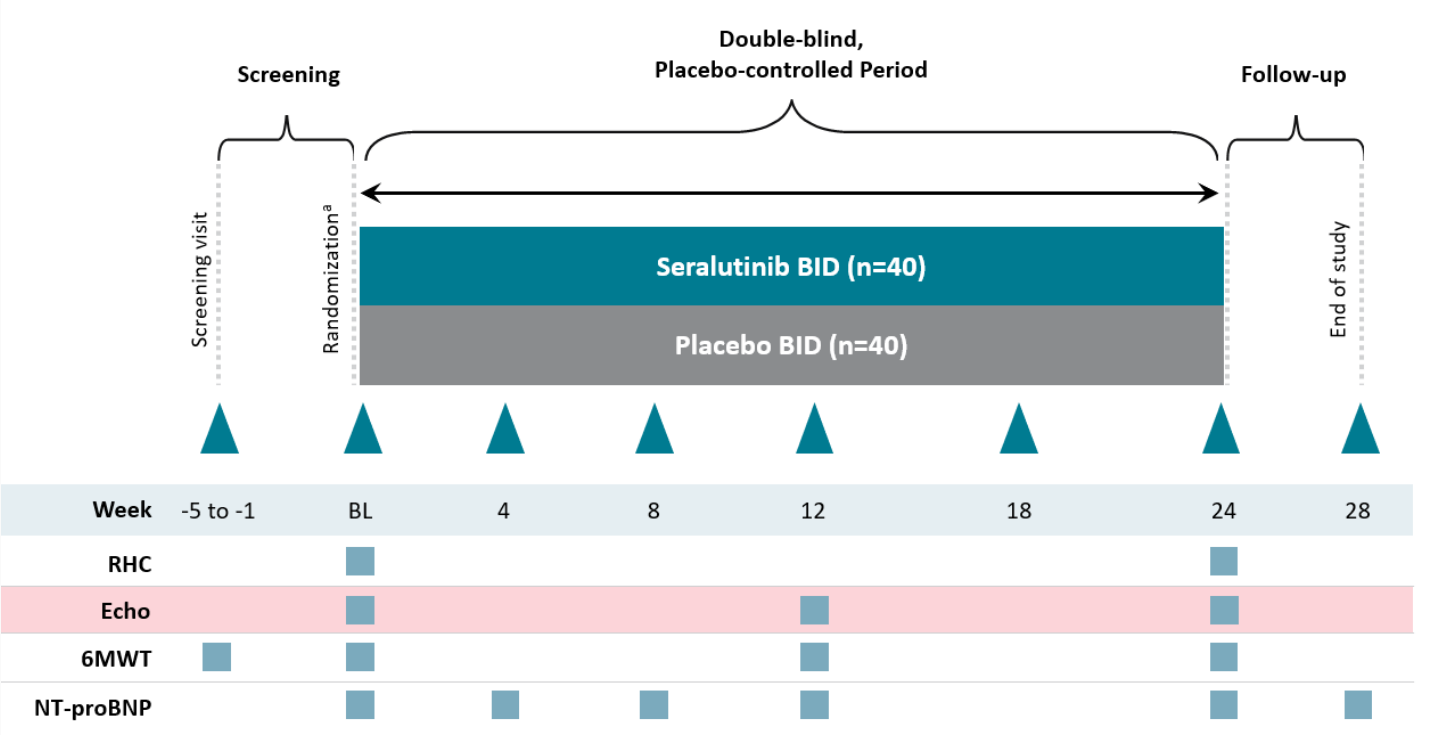
- RVFWS:sPAP has been reported as a measure of RV-PA coupling[3]
- RV-PA coupling is associated with prognosis[4]



Figures: K. Tello

1 Sanz J et al. *J Am Coll Cardiol.* 2019;73(12):1463-1482. **2** Habib G, Torbicki A. *Eur Respir Rev.* 2010;19(118):288-299. **3** Vonk Nordegraaf A et al. *J Am Coll Cardiol.* 2017;69(2):236-243. **4** Richter MJ et al. *J Heart Lung Transplant.* 2023;42(4):433-446. LV, left ventricular/ventricle; PA, pulmonary artery; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; RAA, right atrial area; RVFW(L)S, right ventricular free wall (longitudinal) strain; RV-PA, right ventricular-pulmonary arterial; sPAP, systolic pulmonary arterial pressure

TORREY Phase 2, Randomized, Double-blind, Placebo-controlled Multicenter Study of Inhaled Seralutinib in PAH



[a] Randomization stratified by PVR (< 800 dyne·s/cm^5 vs. ≥ 800 dyne ·s/cm^5)

6MWD, six-minute walk distance; 6MWT, six-minute walk test; BID, twice daily; BL, baseline; echo, echocardiogram; FC, Functional Class; NT-proBNP, N-terminal pro-brain natriuretic peptide; RHC, right heart catheterization; WHO, World Health Organization. NCT04456998.

Echocardiography: Methods

- 2D and color Doppler echocardiography was performed at baseline, Week 12, and Week 24
- Data were analyzed at a core laboratory in a blinded fashion
- Key echocardiographic parameters included RAA, RVFWS, RVFWS/sPAP
  - Speckle tracking with TOMTEC software was used to calculate RVFWS
- Analysis of RVFWS:sPAP used sPAP from RHC
- Echocardiographic endpoints were analyzed using ANCOVA

2D, two-dimentional; ANCOVA, analysis of covariance; FC, functional class; PVR, pulmonary vascular resistance; RAA, right atrial area; RVFWS, right ventricular free wall strain; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; WHO, World Health Organization.

TORREY Baseline and Disease Characteristics

Characteristic	Placebo (N=42)	Seralutinib (N=44)	Total (N=86)
Age, y	49.5 (11.81)	48.3 (12.70)	48.8 (12.22)
Female, n (%)	38 (90.5)	40 (90.9)	78 (90.7)
Race, n (%)			
White	37 (88.1)	37 (84.1)	74 (86.0)
Other	5 (11.9)	7 (15.9)	12 (14.0)
Years since PAH diagnosis	8.78 (7.218)	8.07 (7.074)	8.41 (7.111)
WHO FC, n (%)			
Class II	20 (47.6)	30 (68.2)	50 (58.1)
Class III	22 (52.4)	14 (31.8)	36 (41.9)
PVR, dyne·s/cm^5	661.3 (164.91)	675.8 (240.35)	668.7 (205.90)
6MWD, m	407.1 (107.02)	408.6 (75.11)	407.9 (91.54)
NT-proBNP, ng/L	645.6 (1158.75)	611.0 (714.58)	628.3 (956.83)
Number of background therapies, n (%)			
< 3	18 (42.9)	19 (43.2)	37 (43.0)
3	24 (57.1)	25 (56.8)	49 (57.0)
Prostacyclin/Prostacyclin receptor agonist use, n (%)			
Parenteral	19 (45.2)	19 (43.1)	38 (44.2)
Oral	10 (23.8)	10 (22.7)	20 (23.3)

Frantz RP et al. *Am J Respir Crit Care Med* 2023;207:A6726. doi.org/10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A6726

LSMD, least squares mean difference; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary artery compliance; PVR, pulmonary vacular resistance; SE, standard error

Baseline Echocardiography Parameters

Parameter	Placebo		Seralutinib	
	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.

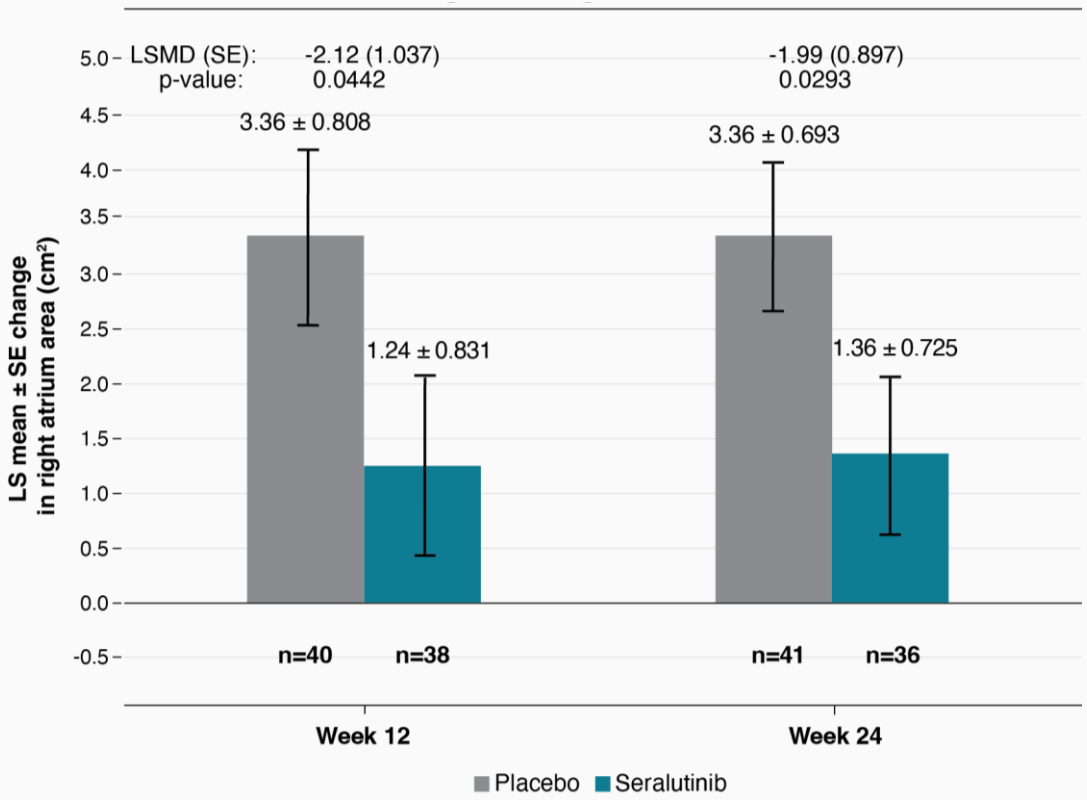
LV, left ventricular; RV, right ventricular

TORREY: Seralutinib Improved Pulmonary Hemodynamics and NT-proBNP

- TORREY met primary end point of significant reduction in PVR at Week 24 (14.3%, p=0.0310)
- PVR reduction mainly driven by a significant reduction in mPAP (p=0.0094)
- Significant reduction in NT-proBNP in seralutinib group vs placebo at Week 12 (LSMD -309.6 ng/L, p=0.0116) and Week 24 (LSMD -408.3 ng/L, p=0.0012)*
- Seralutinib treatment was associated with a significant improvement in PAC (p=0.0410)*

*NT-proBNP and PAC were exploratory endpoints.
mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary artery compliance; PVR, pulmonary vacular resistance

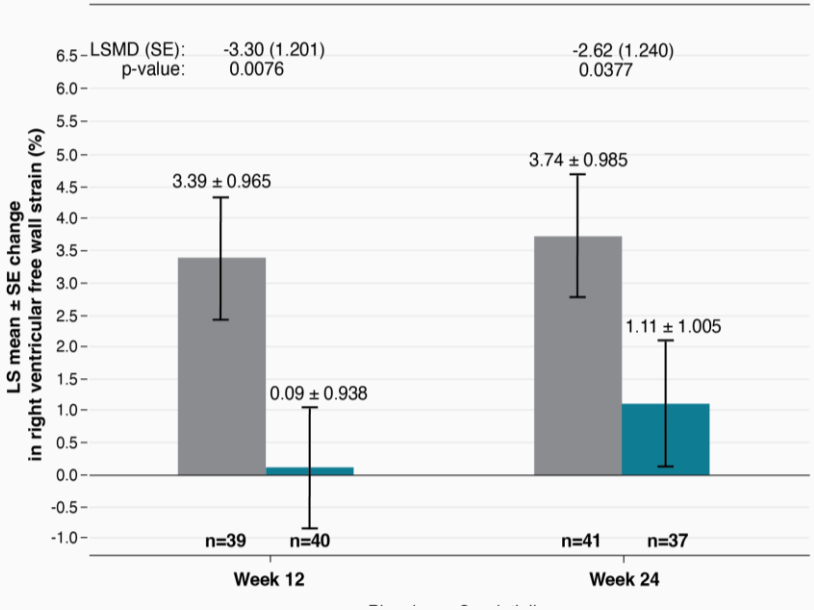
Seralutinib Delayed Worsening of RAA Compared to Placebo



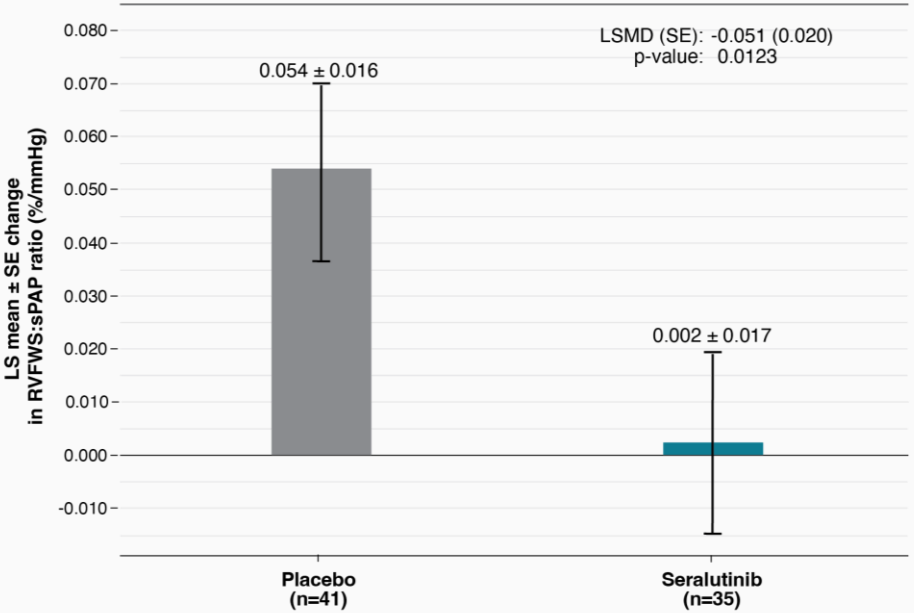
LSMD, least squares mean difference; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary artery compliance; PVR, pulmonary vacular resistance; RAA, right atrial area; RHC, right heart catheterization; SE, standard error.

Seralutinib Prevented Worsening of RVFWS and RVFWS:sPAP

Change in RVFWS



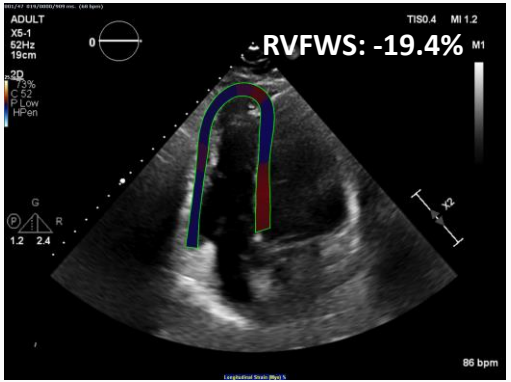
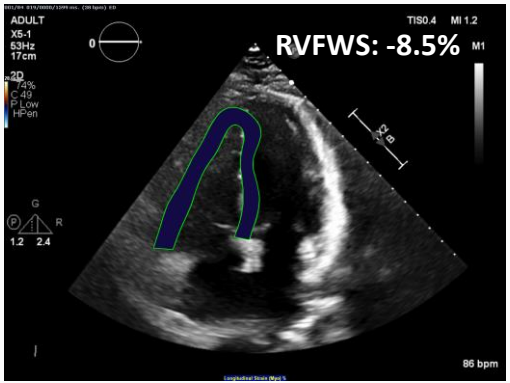
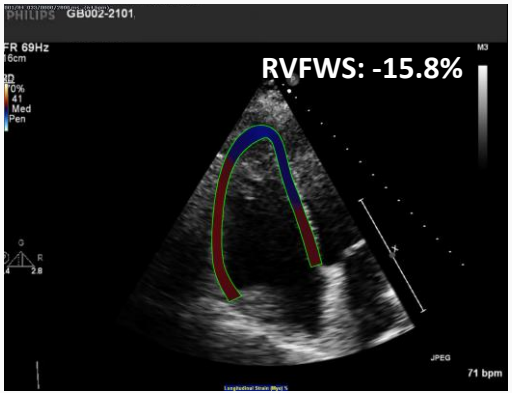
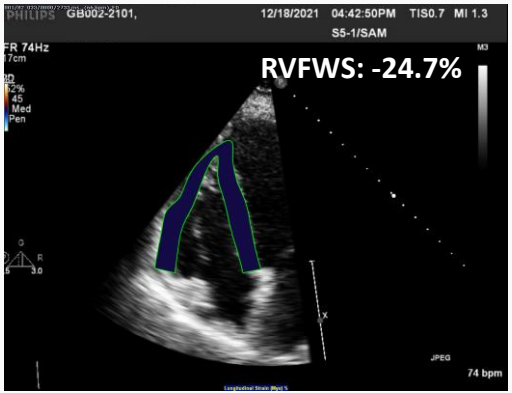
Change in RVFWS:sPAP ratio from Baseline to Week 24



RVFWS:sPAP was calculated using the PASP from RHC.

ITT Population. ANCOVA – Observed cases.
ANCOVA, analysis of covariance; LS, least squares; LSMD, least squares mean difference; PASP, pulmonary artery systolic pressure; RHC, right heart catheterization; RVFWS, right ventricular free wall strain; SE, standard error; sPAP, systolic pulmonary artery pressure

Change in RVFWS in TORREY Patients

	Baseline	Week 24
Placebo		
Seralutinib		

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

BL, baseline; CO, cardiac output; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RVFWS, right ventricular free wall strain.

Summary

- In the phase 2 TORREY Study, inhaled seralutinib treatment showed a significant benefit on **RAA** at Weeks 12 and 24 compared to placebo
- Seralutinib prevented worsening of **RVFWS** 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

TORREY STUDY

Acknowledgments

- We thank all patients, their families, and all the TORREY study investigators and study coordinators who participated in the trial
    - Study Investigators: Y. Adir, T. Baillie, D. Baratz, R.L. Benza, C. Burger, M.M. Chakinala, R.N. Channick, K.M. Chin, J.M. Cifrián Martínez, M Delcroix, N. Dwyer, J. Elwing, P. Escribano-Subías, M. Fisher, V. Franco, R.P. Frantz, H.-A. Ghofrani, A.R. Hemnes, E. Grünig, K. Highland, N. Hill, N. Hirani, M. Hoeper, L.S. Howard, P. Jansa, A. Keogh, J. Kingrey, M. Lopez-Meseguer, J.W. McConnell, V.V. McLaughlin, S. Mehta, L. Melendres-Groves, C. Opitz, J. Pepke-Zaba, P. Pillutla, F.F. Rahaghi, A. Raina, Y. Raviv, J. Robinson, J. Ryan, J. Sager, S. Sahay, S.M. Shapiro, M. Simon, O. Sitbon, K. Smith, I.R. Sobol, N. Sood, L.A. Spikes, S. Stadler, W. Stevens, R. Sulica, J.-L. Vachiéry, R.J. White, R.T. Zamanian, R.L. Zolty

- The TORREY study was sponsored by Gossamer Bio, Inc., San Diego, CA, USA
    - Gossamer Bio, Inc., personnel: R. Aranda, J-M. Bruey, M. Cravets, R. Osterhout, R.F. Roscigno, L.S. Zisman