Seralutinib Treatment in Adult Subjects With Pulmonary Arterial Hypertension: Results From the TORREY Study

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ATS 2023

Washington, DC May 19-24

Disclosures

Financial relationships with “ineligible companies” within the past 24 months:

Company name: Aerovate Therapeutics
Type of relationship: Data safety and monitoring board

Company name: Gossamer Bio, Inc.
Type of relationship: Advisory Committee

Company name: Insmed
Type of relationship: Advisory Committee

Company name: Janssen
Type of relationship: Advisory Committee, Consultant

Company name: Liquidia
Type of relationship: Advisory Committee, Consultant

Company name: Merck
Type of relationship: Advisory Committee

Company name: ShouTi
Type of relationship: Advisory Committee

Company name: Tenax Therapeutics
Type of relationship: Advisory Committee

Pulmonary Vascular Remodeling: A Key Structural Alteration in PAH

Pathological mechanisms

Vascular remodeling of the small pulmonary arteries

- Peri-vascular inflammation
- Neointimal proliferation of endothelial cells and myofibroblasts
- Proliferation and hypertrophy of pulmonary artery smooth muscle cells
- Perivascular fibrosis

Leading to

- Increased pulmonary vascular resistance
- Decreased pulmonary artery compliance
- Right ventricular hypertrophy and right heart failure

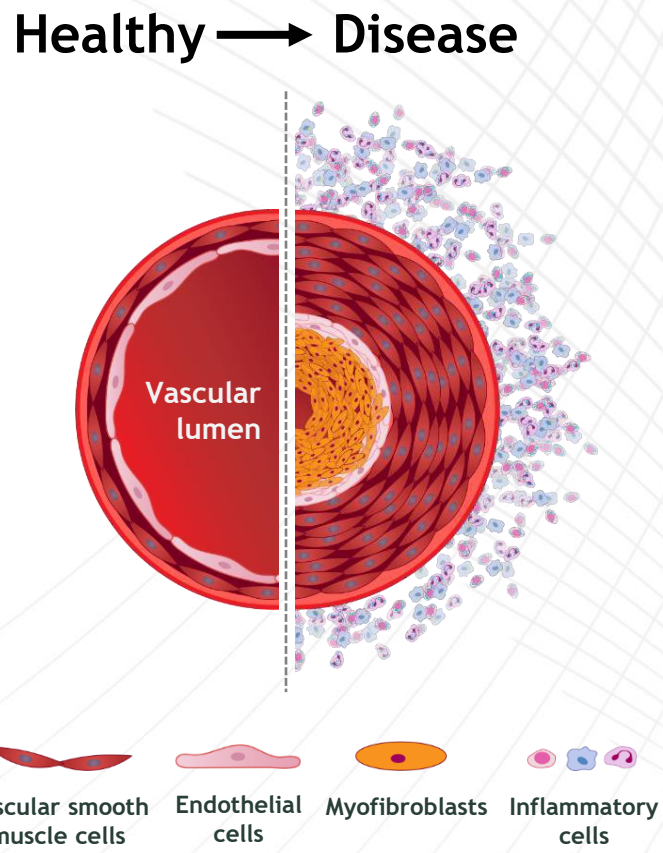

Figure adapted from; Schermuly RT et al. *Nat Rev Cardiol*. 2011;8(8):443-455.

Chen J et al. *BMC Genomics*. 2016;17(1):781.; Grimminger F, Schermuly RT. *Adv Exp Med Biol*. 2010;661:435-446.; Montani D et al. *Am J Respir Crit Care Med*. 2011;184(1):116-123.; Schermuly RT et al. *Nat Rev Cardiol*. 2011;8(8):443-455.; Zhou X et al. *Cell*. 2018;172(4):744-757.e17. PAH, pulmonary arterial hypertension.

Seralutinib Targets Key Factors of Vascular Remodeling: Role of PDGFR, CSF1R, c-KIT, and Interaction With BMPR2

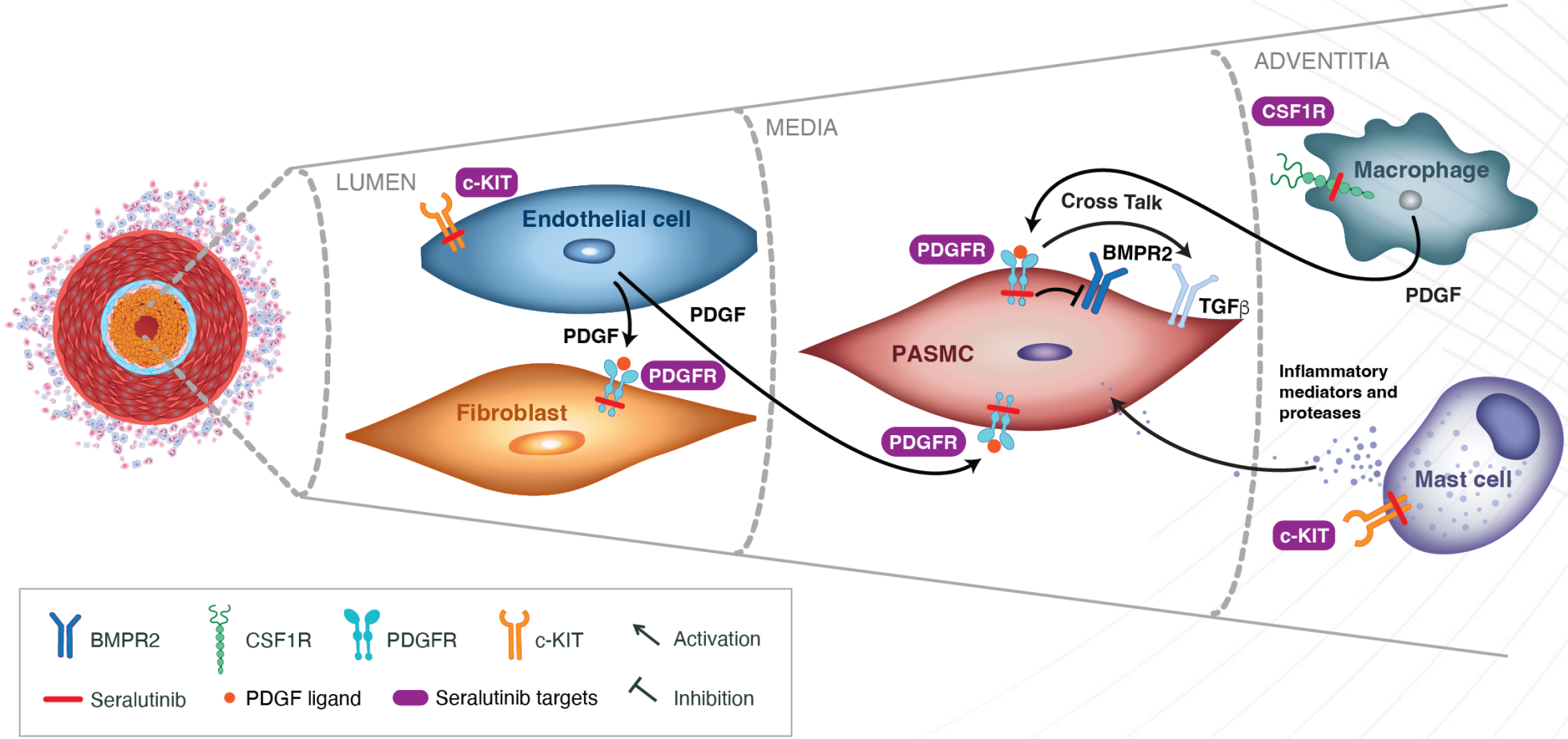

Figure: Frantz RP et al. *Pulm Circ*. 2021;11(4):20458940211057071.
BMPR2, bone morphogenetic protein receptor type 2; CSF1R, colony stimulating factor 1 receptor; PASMC, pulmonary arterial smooth muscle cell; PDGFR, platelet-derived growth factor receptor.

Seralutinib Preclinical Research

- Inhaled seralutinib was an effective treatment of severe PAH in two preclinical animal models[1] with
  - ➢ Improved cardiopulmonary hemodynamic parameters
  - ➢ Reduced NT-proBNP
  - ➢ Reversed remodeling of pulmonary vascular pathology
  - ➢ Improved inflammatory biomarkers

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
A. GALKIN ET AL.

Inhaled seralutinib exhibits potent efficacy in models of pulmonary arterial hypertension

Anna Galkin[1,5], Ravikumar Sitapara[1,2,5], Bryan Clemons[1], Eduardo Garcia[1], Michael Kennedy[1], David Guimond[1], Laura L. Carter[1], Ashley Douthitt[1], Robin Osterhout[1], Aneta Gandjeva[3], Deborah Slee[1], Luisa Salter-Cid[1], Rubin M. Tuder[3] and Lawrence S. Zisman[1,4]

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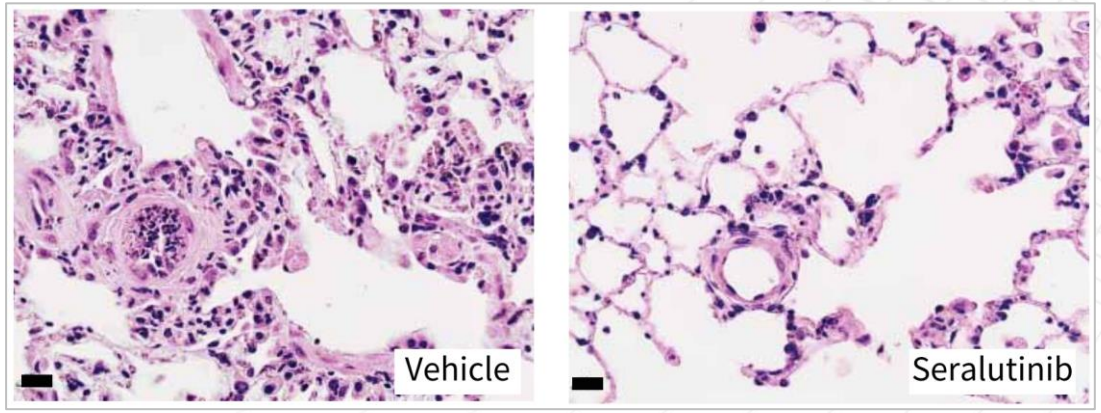


Representative photomicrographs of histological changes in lung by haematoxylin and eosin stain (rat MCT/PN model). Scale bars: 20 µm.

1. Galkin A et al. *Eur Respir J.* 2022;60(6):2102356.
MCT/PN, monocrotaline pneumonectomy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension.

TORREY Phase 2, Randomized, Double-blind, Placebo-controlled Multicenter Study

- **Objective:** To evaluate the efficacy and safety of inhaled seralutinib in PAH over 24 weeks

Selected Inclusion Criteria

- WHO Group 1 PH
- 6MWD ≥ 150 meters and ≤ 550 meters
- WHO FC II or III
- Standard of care PAH background therapies
- PVR ≥ 400 dyne·s/cm^5

Selected Exclusion Criteria

- WHO Pulmonary Hypertension Group 2–5
- HIV-associated PAH
- Inhaled prostanoids
- Use of anticoagulants

Endpoints

- Primary: Change in PVR from BL to Week 24
- Secondary: Change in 6MWD from BL to Week 24
- Exploratory: NT-proBNP, RH structure and function by echocardiography
- Safety assessed during scheduled visits

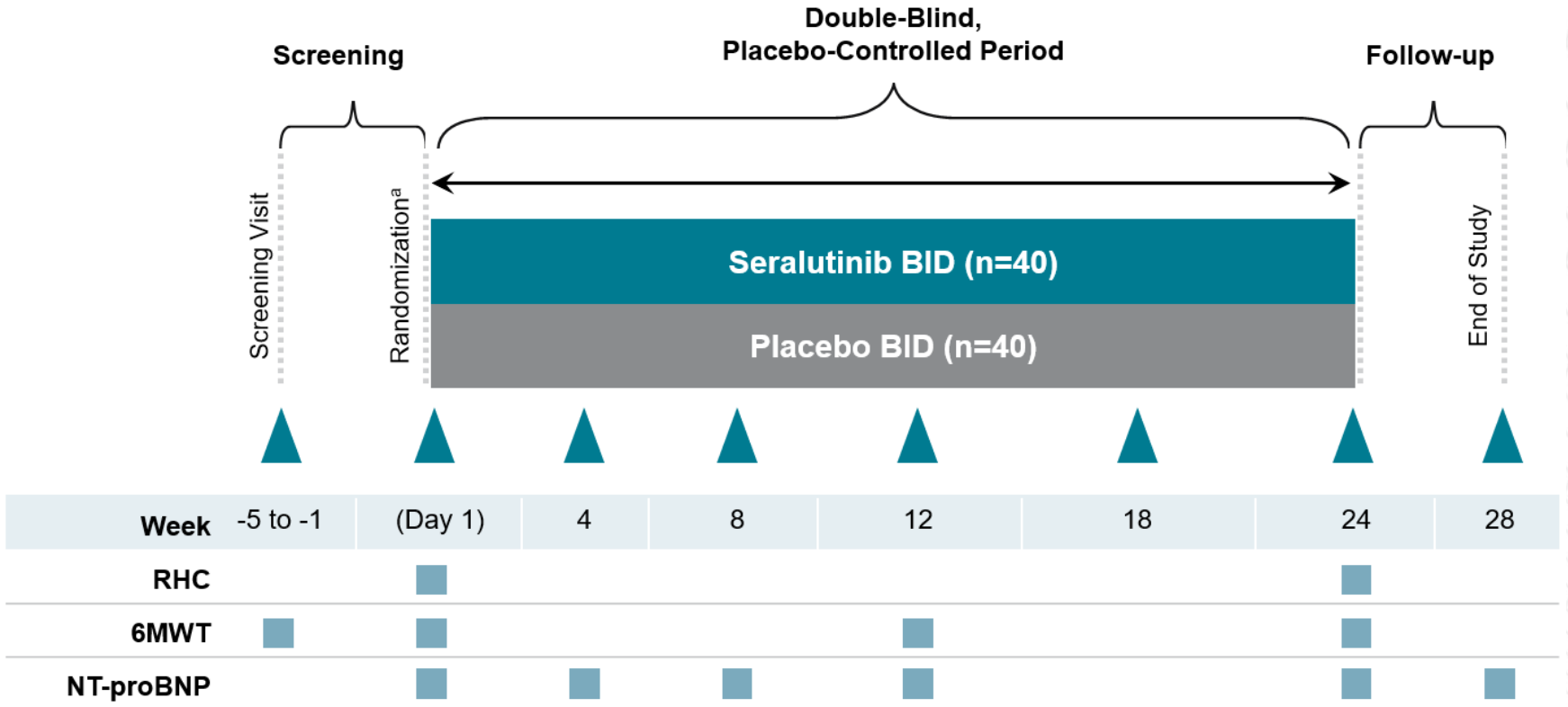
RHC Analyses

- PAC and other cardiopulmonary hemodynamic parameters

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; BL, baseline; FC, functional class; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary artery compliance (stroke volume/[pulmonary artery pulse pressure]); PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RH, right heart; RHC, right heart catheterization; WHO, World Health Organization. NCT04456998.

TORREY Phase 2, Randomized, Double-blind, Placebo-controlled Multicenter Study

- **Dosing:** Subjects started on 60 mg BID and after 2 weeks escalated to 90 mg BID as tolerated
- After completing the Week 24 visit, subjects had the option to roll into an **open-label extension study**



[a] Randomization stratified by PVR (< 800 dyne*s/cm5 vs. ≥ 800 dyne*s/cm5)

6MWT, 6-minute walk test; BID, twice daily; NT-proBNP, N-terminal pro-brain natriuretic peptide; RHC, right heart catheterization; NCT04456998.

TORREY Baseline & 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 (12.0)	7 (15.9)	12 (14.0)
Years since PAH diagnosis	8.78 (7.218)	8.07 (7.074)	8.41 (7.111)
PAH classification, n (%)			
Idiopathic	22 (52.4)	20 (45.5)	42 (48.8)
Heritable	5 (11.9)	10 (22.7)	15 (17.4)
Associated with CTD	11 (26.2)	6 (13.6)	17 (19.8)
Drug or toxin-induced	4 (9.5)	5 (11.4)	9 (10.5)
Associated with congenital shunts	0	3 (6.8)	3 (3.5)
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)

ITT Population. Data presented as mean (SD) unless otherwise noted.
CTD, connective tissue disease; FC, functional class; ITT, intention-to-treat; PAH, pulmonary arterial hypertension; SD, standard deviation; WHO, World Health Organization.

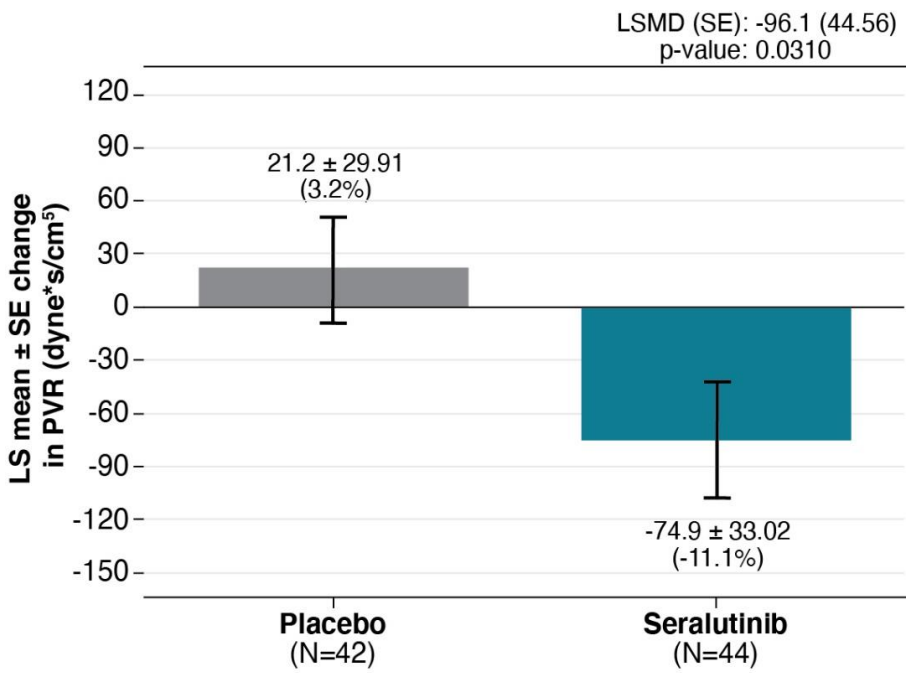
TORREY Baseline & Disease Characteristics (cont.)

Characteristic	Placebo (N=42)	Seralutinib (N=44)	Total (N=86)
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)

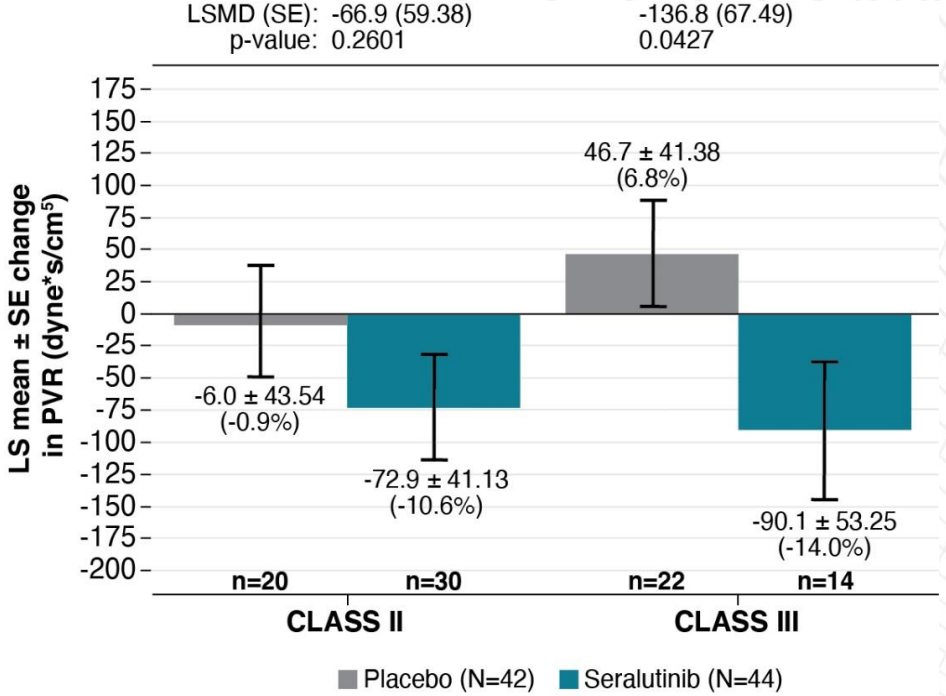
ITT Population. Data presented as mean (SD) unless otherwise noted.
6MWD, 6-minute walk distance; ITT, intention-to-treat; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; SD, standard deviation.

Primary Endpoint: Change in PVR From Baseline to Week 24

A. Overall population



B. Subgroup analysis: WHO Functional Class

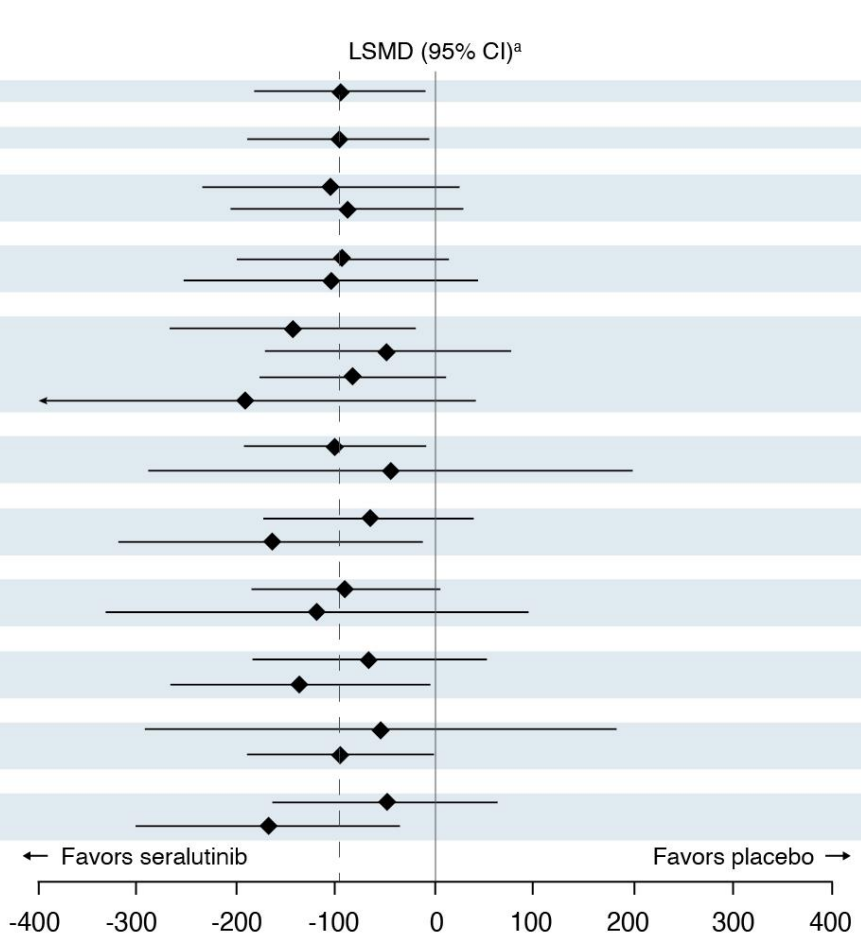


- In the overall population, seralutinib significantly reduced PVR at Week 24 vs placebo (14.3%, p=0.0310) (**A**)
- Seralutinib had a more pronounced effect on PVR in FC III patients: 20.8% reduction (p=0.0427) (**B**)

Based on an ANCOVA model with multiple imputation.
ANCOVA, analysis of covariance; FC, functional class; LS, least squares; LSMD, least squares mean difference; ITT, intention-to-treat; PVR, pulmonary vascular resistance; SE, standard error; WHO, World Health Organization.

Change in PVR From Baseline to Week 24 by Pre-specified Subgroups: Strong Concordance of Benefit

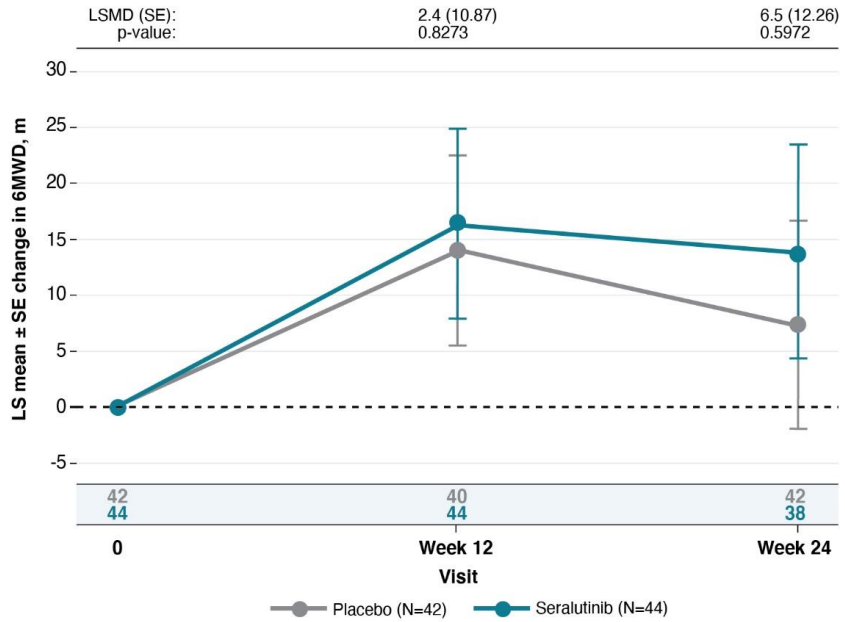
Subgroup	Placebo N	Seralutinib N	LSMD (95% CI)[a]	p-value[a]
Overall	42	44	-96.1 (-183.5, -8.8)	0.0310
Sex				
Female	38	40	-97.5 (-190.2, -4.9)	0.0390
PAH background medications				
< 3	18	19	-105.8 (-235.4, 23.9)	0.1099
≥ 3	24	25	-89.1 (-205.8, 27.5)	0.1343
Prostacyclins at baseline				
Yes	29	29	-93.9 (-201.9, 14.1)	0.0885
No	13	15	-105.4 (-252.8, 41.9)	0.1609
Age groups				
< Median (47 y)	19	24	-143.6 (-268.1, -19.0)	0.0239
≥ Median (47 y)	23	20	-49.1 (-171.1, 72.9)	0.4303
< 65 y	37	36	-84.0 (-178.1, 10.1)	0.0801
≥ 65 y	5	8	-192.2 (-423.9, 39.5)	0.1040
Race				
White	37	37	-100.3 (-192.1, -8.4)	0.0324
Non-White	5	7	-44.8 (-290.7, 201.1)	0.7210
Region				
North America	30	29	-65.9 (-172.6, 40.8)	0.2262
Rest of world	12	15	-164.7 (-316.8, -12.7)	0.0337
PVR strata				
< 800 dyne*s/cm^5	34	34	-91.0 (-186.1, 4.1)	0.0606
≥ 800 dyne*s/cm^5	8	10	-119.6 (-332.9, 93.6)	0.2712
WHO functional class				
II	20	30	-66.9 (-183.3, 49.5)	0.2601
III	22	14	-136.8 (-269.1, -4.5)	0.0427
Connective tissue disease				
Yes	11	6	-55.8 (-294.4, 182.7)	0.6459
No	31	38	-95.5 (-190.3, -0.8)	0.0482
REVEAL 2.0 risk score				
< 6	25	24	-49.0 (-162.3, 64.4)	0.3972
≥ 6	17	20	-168.4 (-301.7, -35.0)	0.0134



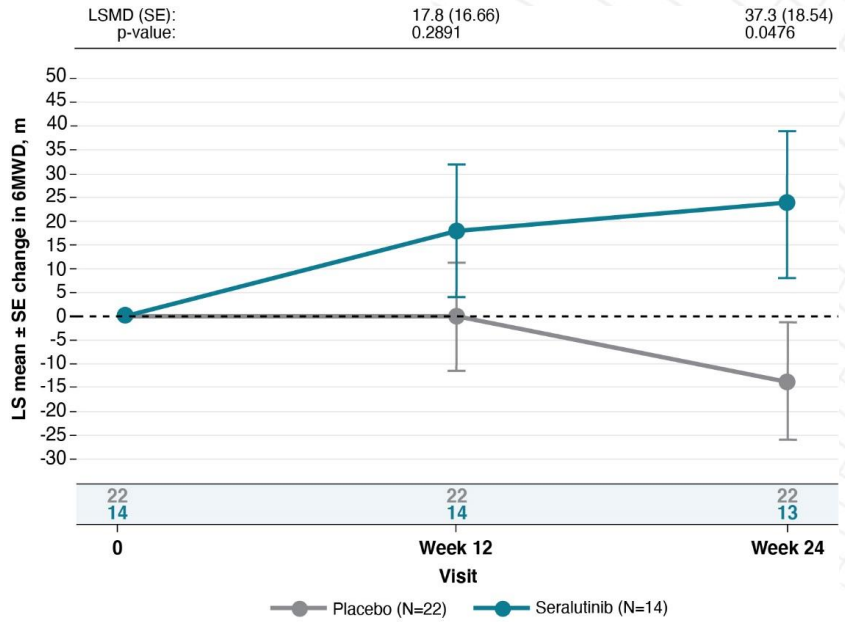
ITT Population. [a] Based on an ANCOVA model with multiple imputation. ANCOVA, analysis of covariance; ITT, intention-to-treat; LSMD, least squares mean difference; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; WHO, World Health Organization.

Secondary Endpoint: Change in 6MWD From Baseline to Week 24

A. Change in 6MWD from BL to each visit for overall population



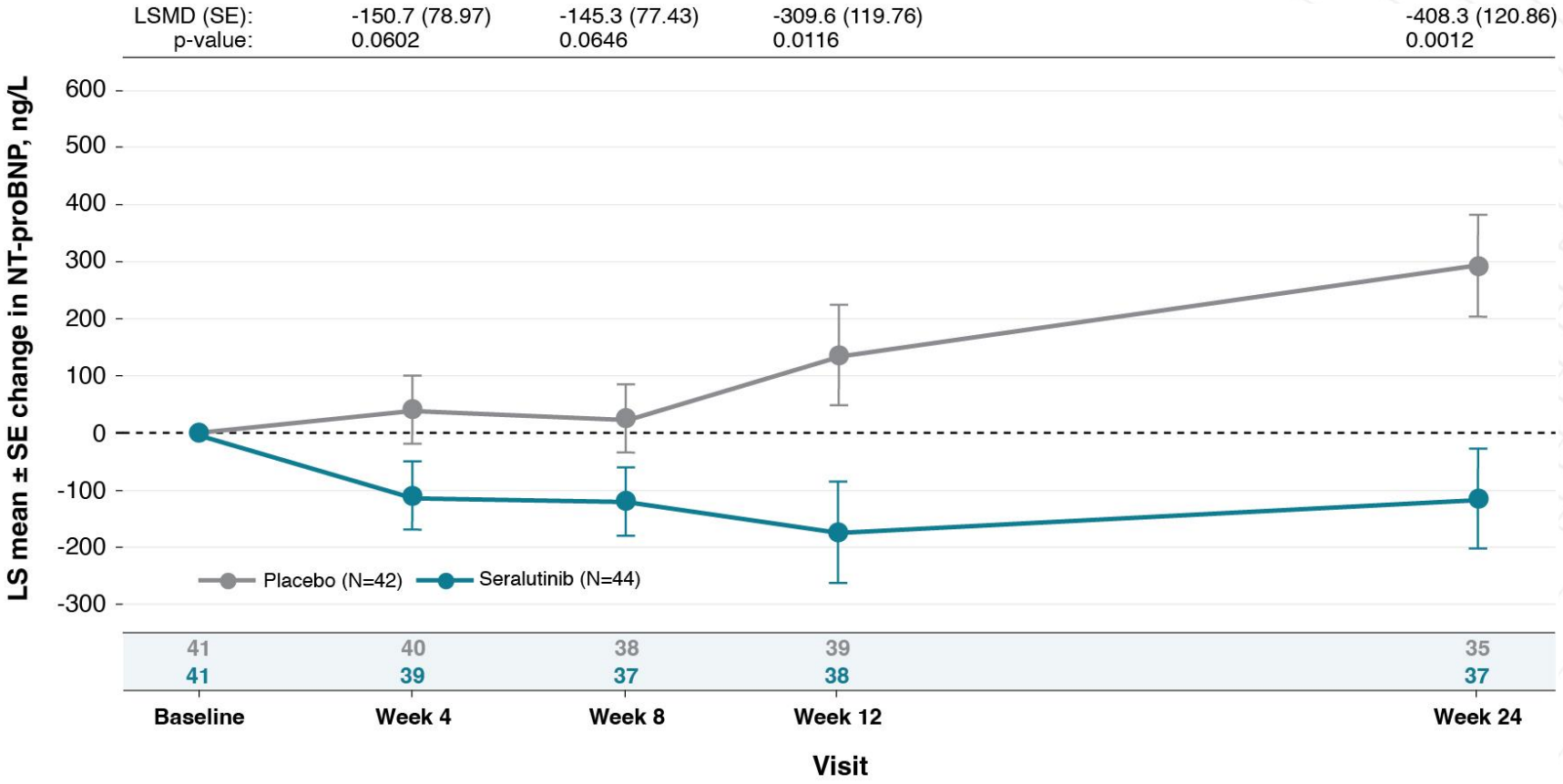
B. Change in 6MWD from BL to each visit for BL FC III patients



- TORREY was not powered for 6MWD
- At Week 24, mean difference in 6MWD was 6.5 m, (p=NS) (**A**)
- Significant improvement in 6MWD in FC III patients (+37.3 m, p=0.0476) (**B**)

ITT Population. Based on a MMRM model.
6MWD, 6-minute walk distance; BL, baseline; FC, functional class; ITT, intention-to-treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model with repeated measures; SE, standard error.

Change in NT-proBNP

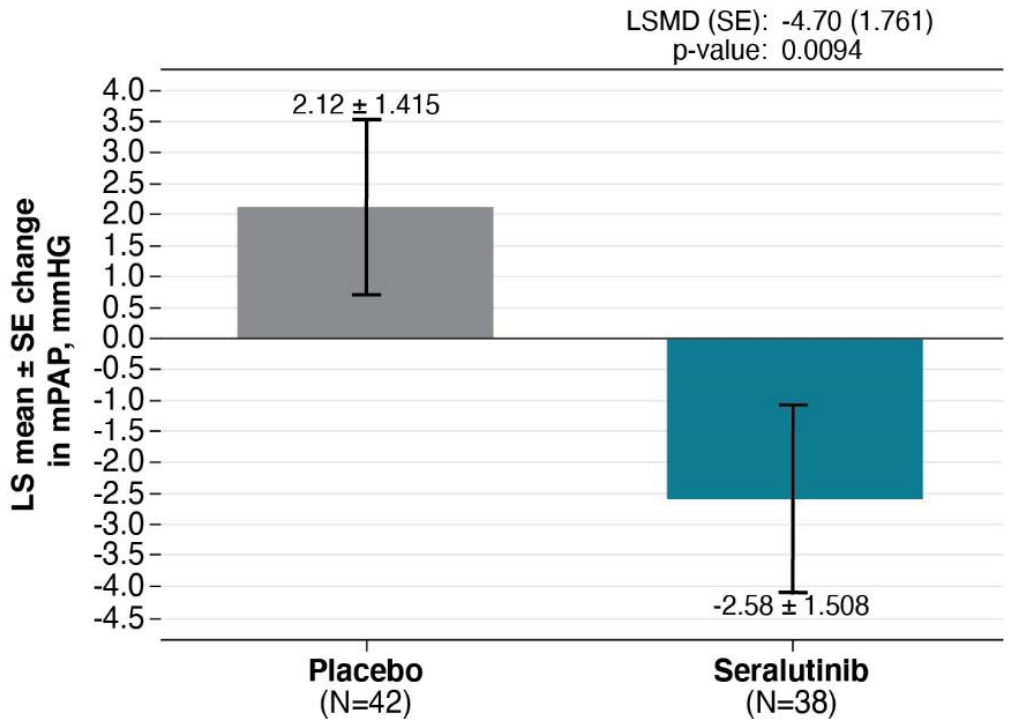


- Seralutinib treatment resulted in significant reduction in NT-proBNP vs placebo at Week 12 (-309.6 ng/L, p=0.0116) and Week 24 (-408.3 ng/L, p=0.0012).

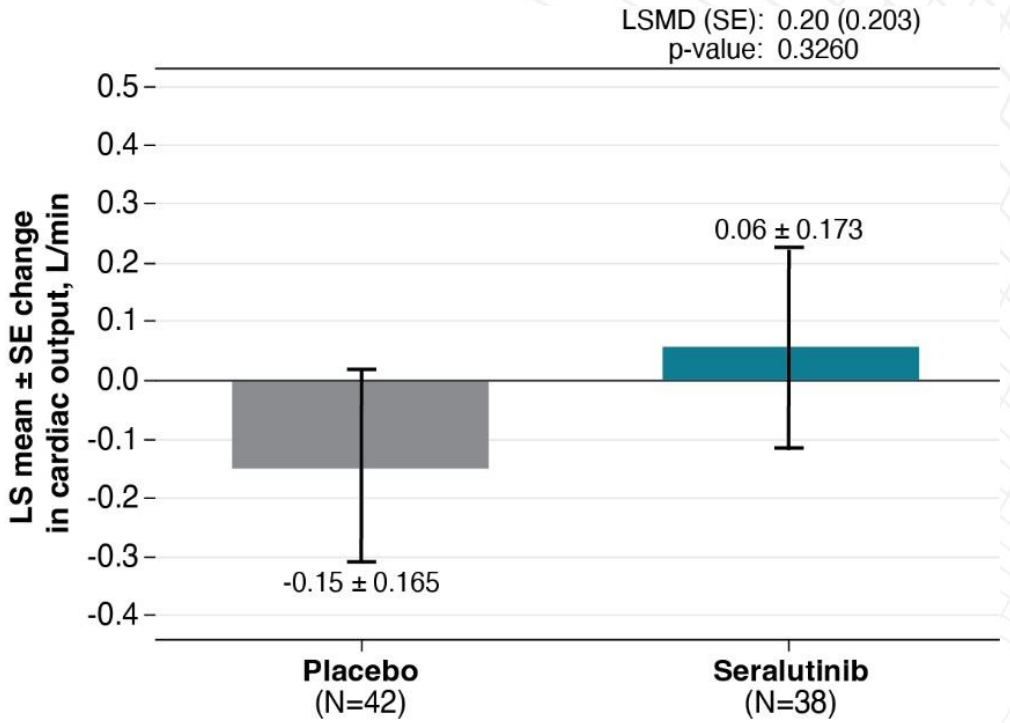
ITT Population. Based on a MMRM model.
ITT, intention-to-treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model with repeated measures; NT-proBNP, N-terminal pro-brain natriuretic peptide; SE, standard error.

Cardiopulmonary Hemodynamics

A. **Change in mPAP**



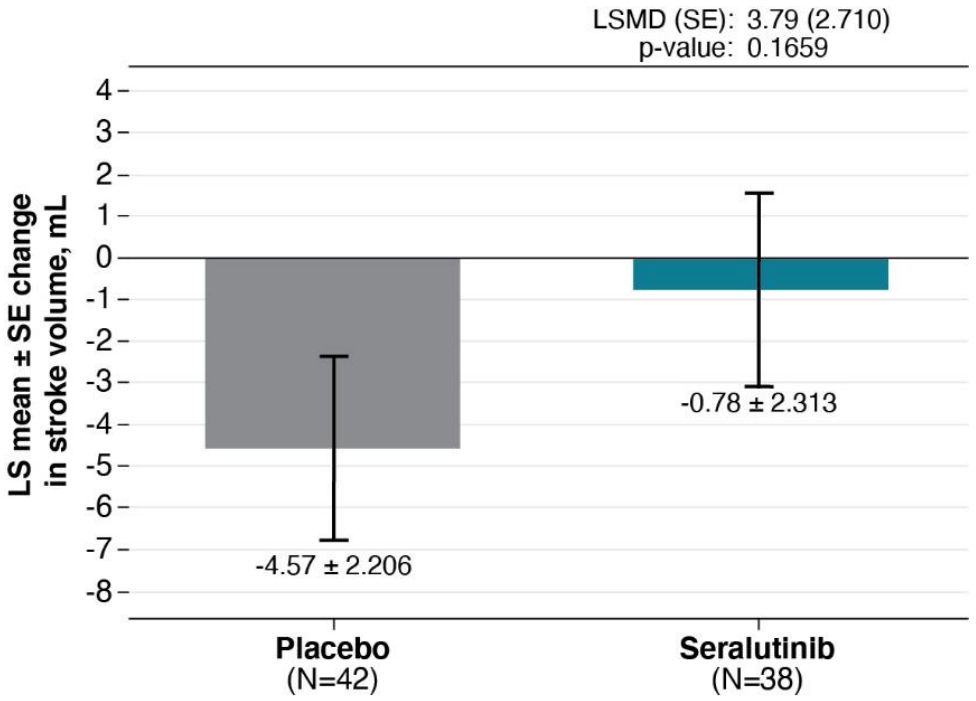
B. **Change in cardiac output**



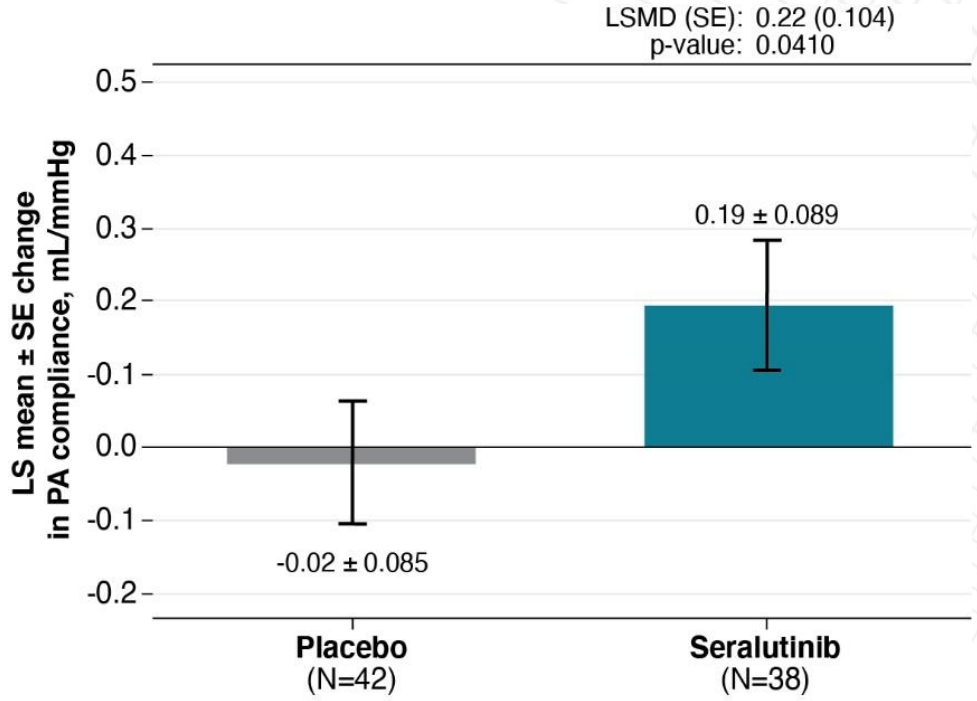
Assessed by right heart catheterization from BL to Week 24; ANCOVA – Observed Cases.
ANCOVA, analysis of covariance; BL, baseline; LS, least squares; LSMD, least squares mean difference; mPAP, mean pulmonary artery pressure; SE, standard error.

Cardiopulmonary Hemodynamics (cont.)

A. Change in stroke volume



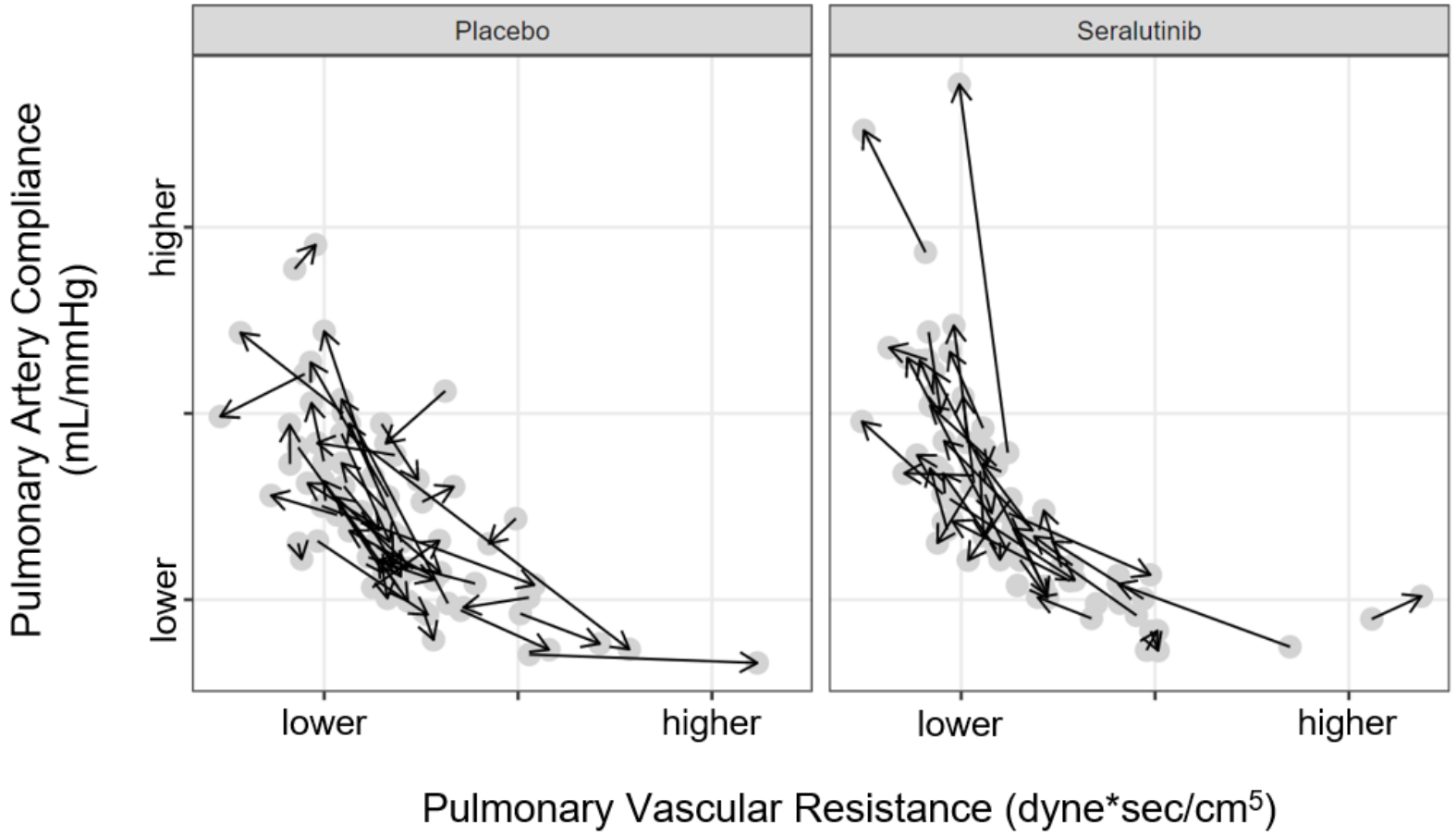
B. Change in PA compliance



Assessed by right heart catheterization from BL to Week 24; ANCOVA – Observed Cases.
ANCOVA, analysis of covariance; BL, baseline; LS, least squares; LSMD, least squares mean difference; mPAP, mean pulmonary artery pressure; SE, standard error.

Seralutinib Effect on RV Afterload: Relationship Between PVR and PAC

- Improvements in PVR and PAC suggest that seralutinib is decreasing both fixed and pulsatile components of RV afterload



Scale is the same for both placebo and seralutinib graphs.
PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance; RV, right ventricular.

Summary of Adverse Events

Frequency of adverse events	Placebo (N=42)	Seralutinib (N=44)
Number of subjects with at least one (%):		
TEAE	36 (85.7)	41 (93.2)
Severe TEAE	2 (4.8)	6 (13.6)
Related TEAE	22 (52.4)	28 (63.6)
TEAE leading to discontinuation of study drug[a]	1 (2.4)	6 (13.6)
TEAE leading to withdrawal from study	0	4 (9.1)
SAE	6 (14.3)	10 (22.7)

[a] TEAEs leading to discontinuation of study drug (by preferred term): Placebo: Liver function test abnormal (1); seralutinib: cough (1), AST increased / ALT increased (1), hemoptysis (1), dry mouth (1), abdominal pain lower (1), transaminases increased (1)

Incidence of TEAEs by preferred term[b]: ≥ 5% higher in seralutinib group, n (%)

Cough	16 (38.1)	19 (43.2)
Diarrhea	3 (7.1)	6 (13.6)
Dizziness	2 (4.8)	5 (11.4)
Nightmare	1 (2.4)	4 (9.1)
Abdominal pain lower	0	3 (6.8)
Nasopharyngitis	0	3 (6.8)
Throat irritation	0	3 (6.8)

Safety Population.
ALT, alanine transaminase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event. [b] Coded using MedDRA v 24.0.

Conclusions

- Seralutinib, a PDGFR, CSF1R, and c-KIT tyrosine kinase inhibitor administered by dry powder inhaler, demonstrated clinical activity and safety in the Phase 2 TORREY trial
- TORREY met the primary endpoint of reduction in PVR in a heavily treated, prevalent study population on standard of care background medications
- Prespecified subgroup analyses showed greater benefit in FC III and subjects with REVEAL 2.0 risk score ≥ 6
- The reduction in PVR and increase in PAC in conjunction with a reduction of NT-proBNP indicates that seralutinib is reducing RV afterload and having a beneficial effect on the right heart
- Proof of concept has been demonstrated and a global registrational Phase 3 program in PAH is planned

CSF1R, colony stimulating factor 1 receptor; FC, functional class; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PDGFR, platelet-derived growth factor receptor; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RV, right ventricular.

Acknowledgements

- 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 personnel: R. Aranda, M. Cravets, E. Elman, D. Mottola, E. Parsley, R.F. Roscigno, L.S. Zisman