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SERALUTINIB FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH): RESULTS FROM THE PHASE 2 TORREY TRIAL

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TORREY STUDY

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BACKGROUND

- PDGFR, CSF1R, and c-KIT kinase pathways play key roles in the inflammation, proliferation, and fibrosis that drive pulmonary vascular remodeling in PAH
- Vascular remodeling leads to increased pulmonary vascular resistance (PVR) and decreased pulmonary artery compliance (PAC), resulting in right heart failure
- Seralutinib is a novel tyrosine kinase inhibitor designed for dry powder inhalation that targets these dysfunctional pathways[1] and has the potential to improve PVR and PAC (**Figure 1**)

Figure 1. Seralutinib mechanism of action[1]

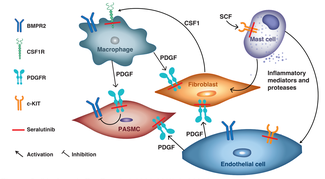


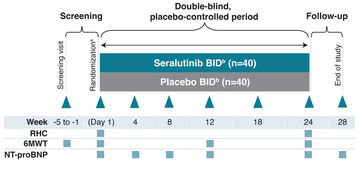
Figure: Galkin A et al. *Eur Respir J.* 2022;60(6):2102356.

METHODS

- Phase 2, randomized, double-blind, placebo-controlled, multicenter study (NCT04456998)[2]
- Inclusion criteria: 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
- Patients randomized 1:1 to seralutinib or placebo twice daily for 24 weeks (**Figure 2**)
- Endpoints
  - Primary: Change in PVR from baseline (BL) to Week 24
  - Secondary: Change in 6MWD from BL to Week 24
  - Exploratory: NT-proBNP
  - Safety assessed during scheduled visits
- RHC analyses: PAC[a] and other cardiopulmonary hemodynamic parameters
- Statistical analyses: Change in PVR from BL to Week 24 based on analysis of covariance (ANCOVA) modelling with multiple imputation. Secondary and exploratory endpoints analyzed used mixed-effects models for repeated measures (MMRM). Analyses based on intention-to-treat (ITT) population.

[a] PAC = stroke volume/(pulmonary artery pulse pressure)

Figure 2. Study schema



[a] Randomization stratified by PVR (< 800 dyne*s/cm^5 vs ≥ 800 dyne*s/cm^5).
[b] Patients started on 60 mg (4 inhalations) BID and after 2 weeks escalated to 90 mg (6 inhalations) BID as tolerated.
6MWT, 6-minute walk test; BID, twice daily; RHC, right heart catheterization.

RESULTS

- 86 patients randomized to treatment at 40 sites worldwide; 80 patients completed the study
- Seralutinib and placebo groups balanced except for WHO FC (seralutinib, 68%/32% FCII/III; placebo, 48%/52% FCII/III)
- 44.2% received parenteral prostacyclin

Table 1. Baseline demographics and disease characteristics. Data presented as mean (SD) unless otherwise noted

Characteristic	Placebo (N=42)	Seralutinib (N=44)
Age, y	49.5 (11.81)	48.3 (12.70)
Female, n (%)	38 (90.5)	40 (90.9)
Race, n (%)		
White	37 (88.1)	37 (84.1)
Other	5 (11.9)	7 (15.9)
Years since PAH diagnosis	8.78 (7.218)	8.07 (7.074)
PAH classification, n (%)		
Idiopathic	22 (52.4)	20 (45.5)
Heritable	5 (11.9)	10 (22.7)
Associated with CTD	11 (26.2)	6 (13.6)
Drug or toxin-induced	4 (9.5)	5 (11.4)
Associated with congenital shunts	0	3 (6.8)
WHO FC, n (%)		
Class II	20 (47.6)	30 (68.2)
Class III	22 (52.4)	14 (31.8)

Characteristic	Placebo (N=42)	Seralutinib (N=44)
mPAP, mmHg	50.0 (9.58)	51.9 (11.71)
PCWP or LVEDP, mmHg	10.8 (2.87)	11.0 (2.82)
Cardiac output, L/min	4.865 (0.985)	5.033 (1.037)
PVR, dyne*s/cm^5	661.3 (164.91)	675.8 (240.35)
6MWD, m	407.1 (107.02)	408.6 (75.11)
NT-proBNP, ng/L	645.6 (1158.75)	611.0 (714.58)
Number of background therapies, n (%)		
< 3	18 (42.9)	19 (43.2)
3	24 (57.1)	25 (56.8)
Prostacyclin/Prostacyclin receptor agonist use, n (%)		
Parenteral	19 (45.2)	19 (43.2)
Oral	10 (23.8)	10 (22.7)

6MWD, 6-minute walk distance; CTD, connective tissue disease; FC, functional class; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WHO, World Health Organization.

RESULTS

Figure 3. A. Seralutinib significantly reduced PVR at Week 24 vs placebo (14.3%, p=0.0310). **B.** Reduction of PVR in FC III patients (20.8%, p=0.0427). **C.** Reduction of PVR in patients with a baseline REVEAL 2.0 risk score of ≥ 6 (22.7%, p=0.0134)

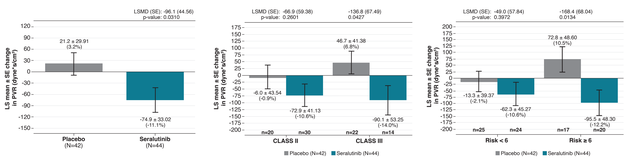
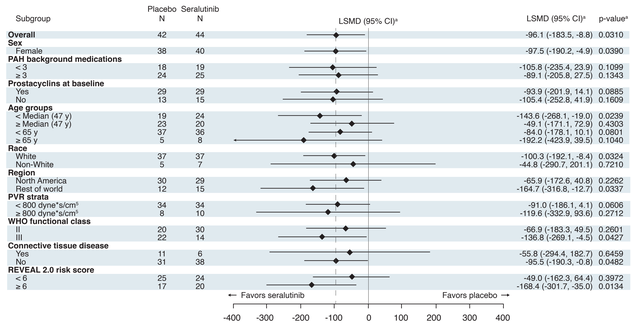


Figure 4. Consistent reduction of PVR across pre-specified subgroups with seralutinib treatment



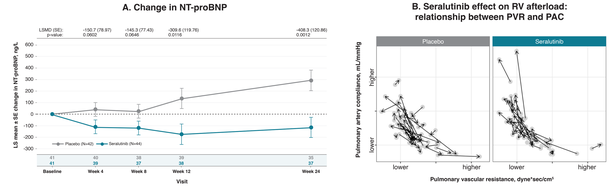
[a] Based on an ANCOVA model with multiple imputation.

Table 2. Change from baseline to Week 24 in pulmonary hemodynamic parameters. A significant reduction in mPAP (p=0.0094) was the main driver of the observed reduction in PVR. Treatment with seralutinib was associated with a significant improvement in PAC (p=0.0410)

Parameter	Placebo (N=42)	Seralutinib (N=38)	
	LS mean change ± SE	LS mean change ± SE	LS mean difference (95% CI)
mRAP, mmHg	0.85 ± 0.532	-0.14 ± 0.576	-0.99 (-2.350, 0.367)
PASP, mmHg	1.74 ± 2.321	-5.24 ± 2.469	-6.98 (-12.77, -1.19)*
PADP, mmHg	1.95 ± 1.127	-1.47 ± 1.197	-3.43 (-6.21, -0.64)*
mPAP, mmHg	2.12 ± 1.415	-2.58 ± 1.508	-4.70 (-8.203, -1.188)*
Cardiac output, L/min	-0.15 ± 0.165	0.06 ± 0.173	0.20 (-0.204, 0.605)
Cardiac index, L/min/m^2	-0.02 ± 0.092	0.11 ± 0.097	0.13 (-0.100, 0.359)
PCWP or LVEDP, mmHg	1.04 ± 0.574	0.54 ± 0.608	-0.50 (-1.963, 0.963)
PVR, dyne*s/cm^5	21.2 ± 29.91	-74.9 ± 33.02	-96.1 (-183.5, -8.8)*
PA compliance, mL/mmHg[a]	-0.02 ± 0.085	0.19 ± 0.089	0.22 (0.009, 0.423)*
Stroke volume, mL	-4.57 ± 2.206	-0.78 ± 2.313	3.79 (-1.606, 9.190)
Stroke volume index, mL/m^2	-1.81 ± 1.263	0.38 ± 1.313	2.19 (-0.917, 5.299)

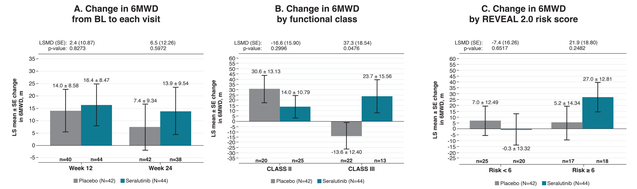
* p<0.05. [a] PA compliance = stroke volume/PA pulse pressure; PA pulse pressure = PASP-PADP. Observed cases, except for PVR, which used multiple imputation.
LS, least squares; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PA, pulmonary artery; PAC, pulmonary artery compliance; PASP/PADP, pulmonary artery systolic/diastolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SE, standard error.

Figure 5. A. Seralutinib treatment resulted in significant reduction in NT-proBNP vs placebo at Week 12 (-309.6 ng/L, p=0.0116) and at Week 24 (-408.3 ng/L, p=0.0012). **B.** Directional improvement in PAC-PVR relationship in seralutinib-treated patients vs placebo from BL to Week 24



Scale is the same for both placebo and seralutinib graphs.

Figure 6. A. At Week 24, the least-square mean difference in 6MWD between seralutinib and placebo groups was 6.5 m (p=NS). **B.** Significant improvement in 6MWD in FC III patients (+37.3 m, p=0.0476). **C.** Numerical trend favoring seralutinib in patients with a REVEAL 2.0 risk score of ≥ 6 (+21.9m, p=NS)



- Types of adverse events (AEs) observed were consistent with an inhalation therapy, i.e., mild-to-moderate cough
- Most treatment-emergent AEs reported were mild-to-moderate in severity
- No fatal AE was reported
- No adverse effect on pulmonary function or hematologic parameters
- Liver enzyme elevations > 3x upper limit of normal (3 seralutinib patients, 2 placebo patients)

Table 3. Overall summary of adverse events

	Placebo (N=42)	Seralutinib (N=44)
Frequency of adverse events		
Number of patients 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	1 (2.4)	6 (13.6)
TEAE leading to withdrawal from study	0	4 (9.1)
SAE	6 (14.3)	10 (22.7)
Incidence of TEAEs by preferred term[a]: ≥ 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.
[a] Coded using MedDRA v 24.0.
MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Seralutinib, an inhaled PDGFR, CSF1R, and Kit tyrosine kinase inhibitor, 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 patients 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

References: 1 Galkin A et al. *Eur Respir J.* 2022;60(6):2102356. **2** Frantz RP et al. *Pulm Circ.* 2021;11(4):20458940211057071.

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