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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]

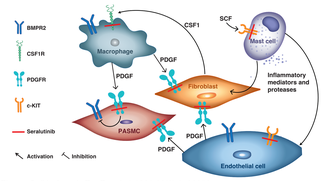


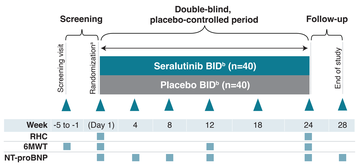

Figure: Galkin A et al. *Eur Respir J.* 2022;60(6):2102356.

## 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)

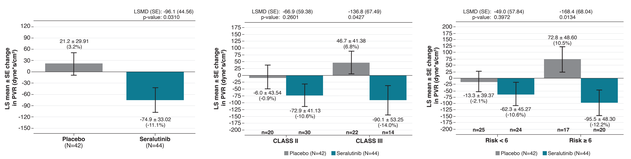
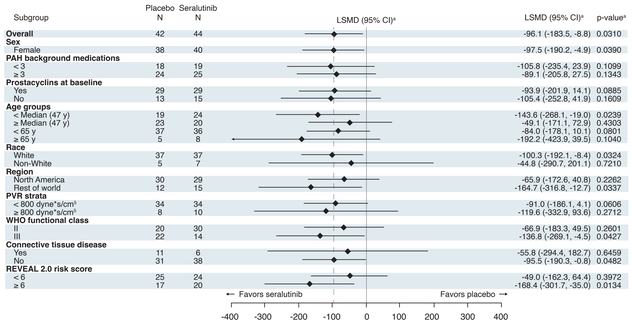



**Figure 4.** Consistent reduction of PVR across pre-specified subgroups with seralutinib treatment



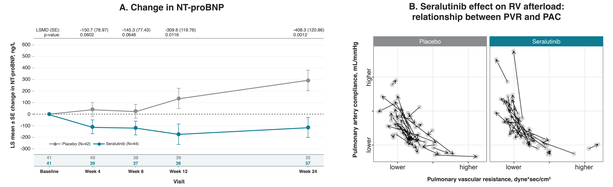

[a] Based on an ANCOVA model with multiple imputation.

**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) |

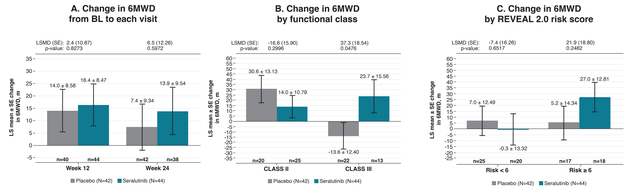
* p<0.05. [a] PA compliance = stroke volume/PA pulse pressure; PA pulse pressure = PASP-PADP. Observed cases, except for PVR, which used multiple imputation.
LS, least squares; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PA,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