PHASE 2 TORREY STUDY OF SERALUTINIB IN PULMONARY ARTERIAL HYPERTENSION (PAH): CIRCULATING BIOMARKERS OF PROLIFERATION, INFLAMMATION, AND FIBROSIS IMPROVE WITH TREATMENT

TORREY STUDY

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BACKGROUND

- Abnormal signaling of PDGFRα/β, CSF1R, and c-KIT receptor kinases, as well as BMPR2 deficiency, drive cellular overgrowth in the lung vasculature and play key roles in the development of PAH
- Seralutinib is a novel, potent, inhaled, tyrosine kinase inhibitor that selectively targets these pathways and has the potential to treat pulmonary vascular remodeling in PAH
- The phase 2 TORREY study of seralutinib in adults with WHO Group I pulmonary hypertension (NCT04456998) met its primary endpoint of reduction in pulmonary vascular resistance (PVR) at 24 weeks[1]
- In an exploratory analysis, circulating proteins were measured to characterize the impact of seralutinib on biomarkers and their correlation with hemodynamic response

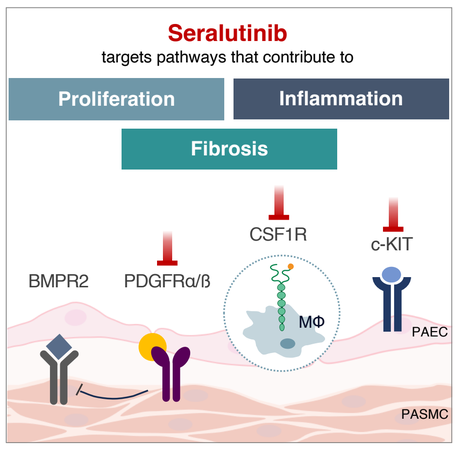

Figure 1. Seralutinib mechanism of action.

Blunt arrows indicate inhibition. BMPR2, bone morphogenetic protein receptor type 2; c-KIT, mast/stem cell growth factor receptor kit; CSF1R, colony stimulating factor 1 receptor; MΦ, macrophage; PAEC, pulmonary artery endothelial cell; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cell; PDGFR, platelet-derived growth factor receptor.

METHODS

- TORREY was a phase 2, multicenter, double-blind, randomized, placebo-controlled study of inhaled seralutinib in PAH. 86 patients (WHO Functional Class [FC] II or III, 2-3 background therapies) were randomized 1:1 to receive inhaled seralutinib 90 mg or placebo twice daily for 24 weeks
- Plasma samples for exploratory biomarker analysis were collected at baseline, Week 12, and Week 24. Proteomics data were generated using the Olink® Explore 3072 assay
- Robust regression with method of moment estimation[2] was applied to identify protein changes from baseline at Weeks 12 and 24 in patients treated with seralutinib vs placebo. As results were hypothesis-generating, a nominal significance criterion of $p < 0.05$ was applied. Functional enrichment analysis of seralutinib-associated proteins was performed using Ingenuity Pathway Analysis (IPA) with the Olink Explore proteins as a background set[3]

RESULTS

Baseline demographics

- The biomarker analysis population comprised 70 patients with paired data at baseline and Week 24 (39 placebo, 31 seralutinib)
- Mean age, years since PAH diagnosis, background PAH medications, and baseline disease activity were similar between groups
- Imbalance between groups included WHO FC and presence of PAH associated with connective tissue disease (CTD)

Table 1. Baseline demographics of TORREY biomarker analysis population.

	Placebo (n=39)	Seralutinib (n=31)
Age, y	49.2 (11.94)	47.9 (13.1)
Years since PAH diagnosis	8.8 (7.39)	7.9 (7.23)
PAH classification, n (%)		
Idiopathic	20 (51.3)	16 (51.6)
Heritable	5 (12.8)	9 (29)
CTD	10 (25.6)	1 (3.2)
Other	4 (10.3)	5 (16.1)
Medications, n (%)		
Prostacyclin use	26 (66.7)	21 (67.7)
Triple therapy	21 (53.8)	19 (61.3)
WHO FC, n (%)		
II	20 (51.3)	19 (61.3)
III	19 (48.7)	12 (38.7)
PVR, dyne*s/cm^5	664.3 (170.83)	678 (253.72)
6MWD, m	415.5 (104.35)	417.3 (77.8)
NT-proBNP, ng/L	584.3 (1070.85)	646 (763.39)

Data presented as mean (SD) unless otherwise noted. 6MWD, 6-minute walk distance; CTD, connective tissue disease; FC, functional class; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization.

Seralutinib treatment affects circulating proteins

- Robust regression models identified 380 proteins associated with active treatment at 12 weeks (n=216) and/or 24 weeks (n=223)
- Circulating proteins relevant to PAH disease biology were altered by seralutinib treatment relative to placebo, in a direction consistent with disease improvement (**Table 2**), including:
  - Decreased endoglin, a key regulator of endothelial activation, proliferation, and active pulmonary vascular remodeling[4,5]
  - Increased anti-inflammatory factors (IL10, C1QTNF9)
  - Decreased seralutinib target (CSF1R)
  - Decreased fibrotic markers (COL1A1)
- Seralutinib shifted inflammatory, fibrotic, and proliferative markers relevant to the mechanism of action. Several of these changes were also observed in preclinical models[6] (**Figure 2**)
- Functional enrichment analysis of seralutinib-associated protein changes supports inhibition of fibrotic, inflammatory, and proliferative pathways (**Figure 3**)

Table 2. Top 20 PAH disease-associated proteins changing from baseline to Week 24 in seralutinib- vs placebo-treated patients. Proteins are sorted by strength of PAH disease association from OpenTargets.[7] Least squares mean difference (LSMD) units are normalized protein expression (NPX).

Symbol	Protein name	Baseline to Week 12		Baseline to Week 24	
		LSMD (SE)	p value	LSMD (SE)	p value
ENG	Endoglin	–0.09 (0.03)	0.003	–0.09 (0.03)	0.004
PDE5A	cGMP-specific 3',5'-cyclic phosphodiesterase	–0.41 (0.2)	0.044	–0.46 (0.21)	0.029
CSF1R	Macrophage colony-stimulating factor 1 receptor	–0.08 (0.07)	0.303	–0.18 (0.08)	0.035
AGER	Advanced glycosylation end product-specific receptor	0.18 (0.08)	0.031	0.16 (0.08)	0.050
CA2	Carbonic anhydrase 2	–0.18 (0.28)	0.527	–0.37 (0.18)	0.039
VEGFA	Vascular endothelial growth factor A	0.16 (0.08)	0.040	0.12 (0.06)	0.046
CA12	Carbonic anhydrase 12	0.08 (0.06)	0.229	0.13 (0.04)	0.005
MMP10	Stromelysin-2	0.03 (0.12)	0.801	0.27 (0.12)	0.035
DBH	Dopamine beta-hydroxylase	0.04 (0.05)	0.424	–0.14 (0.06)	0.015
EGFR	Epidermal growth factor receptor	–0.06 (0.04)	0.129	–0.08 (0.03)	0.021
C1QTNF9	Complement C1q and TNF-related protein 9A	0.16 (0.08)	0.043	0.19 (0.07)	0.013
COL1A1	Collagen alpha-1(I) chain	–0.28 (0.1)	0.009	–0.47 (0.12)	<0.001
NTF3	Neurotrophin-3	–0.09 (0.14)	0.508	–0.27 (0.13)	0.033
ANPEP	Aminopeptidase N	–0.13 (0.04)	0.003	–0.12 (0.05)	0.032
HEXIM1	Protein HEXIM1	–0.25 (0.16)	0.117	–0.39 (0.17)	0.021
PDCD1	Programmed cell death protein 1	0.24 (0.09)	0.009	0.23 (0.09)	0.011
FLT1	Vascular endothelial growth factor receptor 1	–0.19 (0.08)	0.018	–0.17 (0.07)	0.021
CAT	Catalase	–0.04 (0.16)	0.793	–0.2 (0.08)	0.022
ANGPT2	Angiopoietin-2	–0.06 (0.08)	0.466	–0.17 (0.08)	0.036
IL10	Interleukin 10	0.35 (0.15)	0.023	0.36 (0.15)	0.018

LSMD, least squares mean difference; SE, standard error.

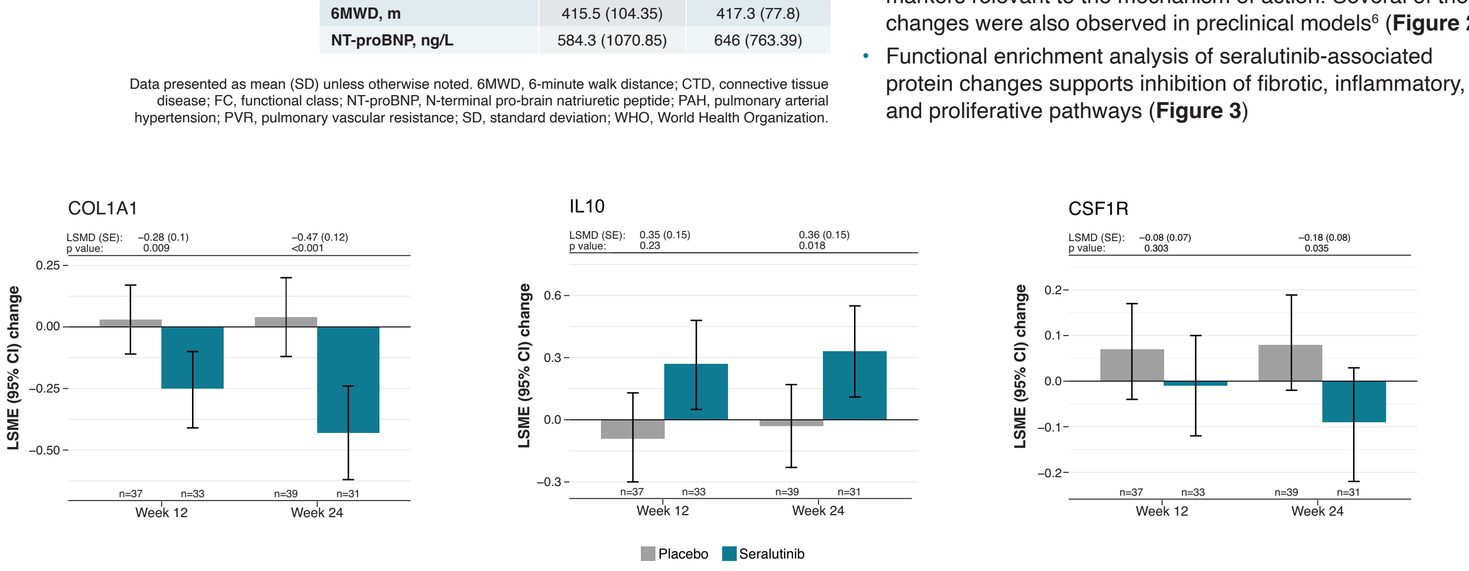

Figure 2. Least squares mean estimates (LSME) of expression changes from baseline in selected proteins in patients with PAH treated with placebo or seralutinib. CI, confidence interval; LSMD, least squares mean difference; SE, standard error.

Seralutinib decreases vascular remodeling biomarkers that correlate with pulmonary hemodynamics and right heart function

Vascular endothelial growth factor receptor 1 (FLT1)

- FLT1 is a marker of endothelial activation expressed in pulmonary artery smooth muscle cells. Circulating FLT1 has been shown to predict WHO FC, disease severity, and progression[4,8]
- Circulating FLT1 is downregulated in patients treated with seralutinib vs placebo and correlates with PVR in TORREY (**Figure 4A**)

Angiopoietin-2 (ANGPT2)

- ANGPT2 is an angiogenic factor upregulated in PAH circulation and plexiform lesions associated with disease progression and vascular remodeling[9]
- Circulating ANGPT2 is downregulated in patients treated with seralutinib vs placebo, and correlates with PVR, PAC, NT-proBNP, and RVFWS in TORREY (**Figure 4B**)

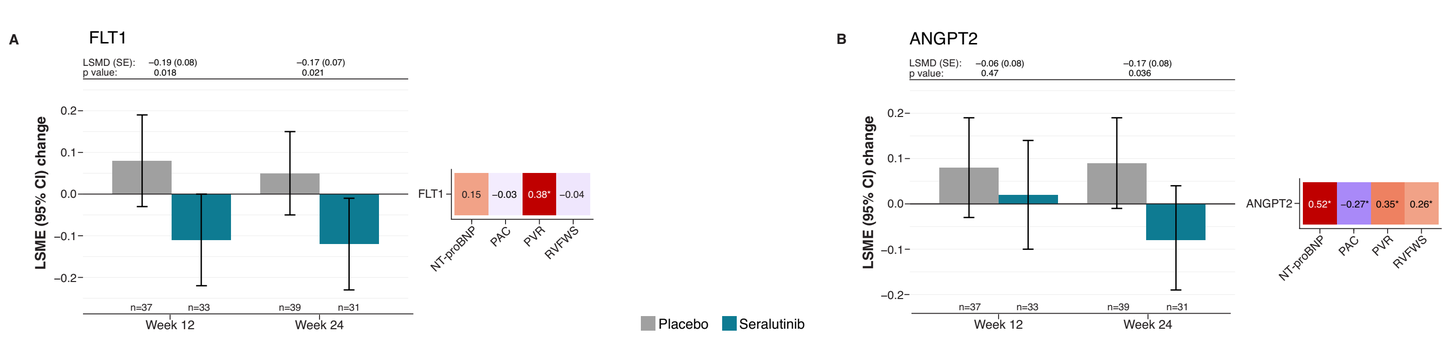

Figure 4. Vascular remodeling proteins downregulated by seralutinib and correlated with PVR. Least squares mean estimates (LSME) of expression changes from baseline in seralutinib- or placebo-treated patients. Heatmaps show Pearson correlations coefficients between baseline protein expression values with N-terminal pro-brain natriuretic peptide (NT-proBNP), pulmonary arterial compliance (PAC), pulmonary vascular resistance (PVR), and right ventricular free wall strain (RVFWS) values at baseline. Color corresponds to magnitude of correlation (red = positive, blue = negative); asterisks indicate correlations with $p < 0.05$. CI, confidence interval; LSMD, least squares mean difference; SE, standard error.

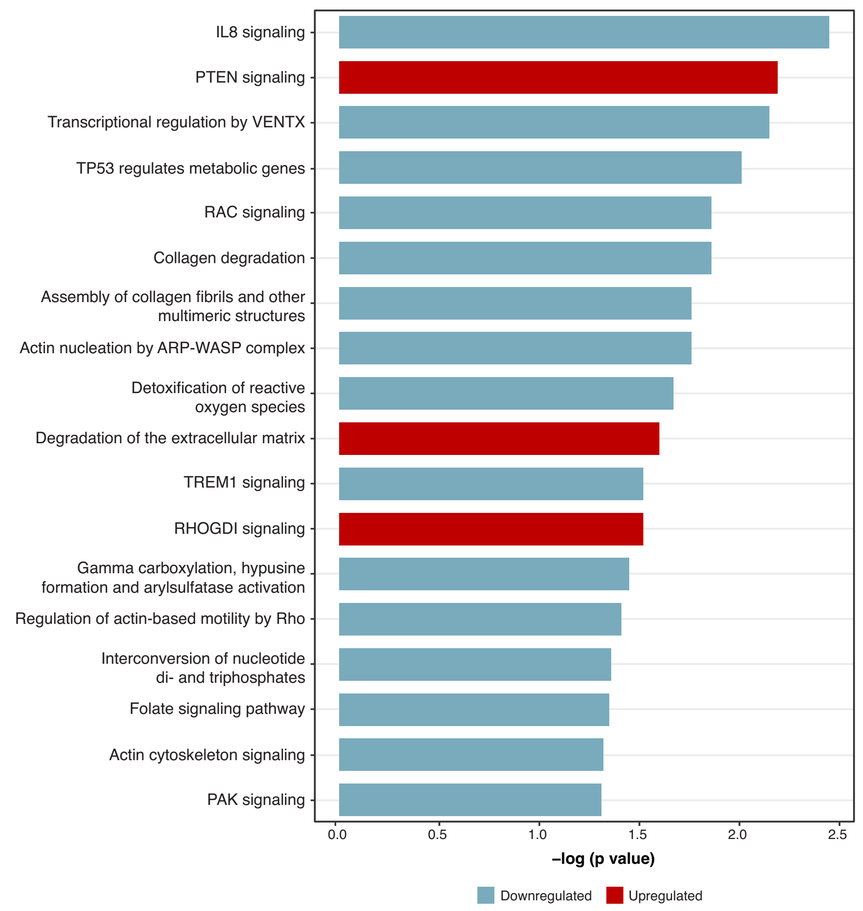

Figure 3. Top enriched directional canonical Ingenuity Pathway Analysis (IPA) pathways in differentially expressed circulating proteins between seralutinib- and placebo-treated patients. Disease-specific pathways are excluded.

CONCLUSIONS

- The observed protein biomarker changes in the phase 2 TORREY study suggest that seralutinib favorably changes inflammatory, proliferative, and fibrotic proteins in patients with PAH
- Seralutinib decreases biomarkers associated with vascular remodeling in a direction consistent with clinical improvement
- PROSERA, a randomized, double-blind, placebo-controlled, multicenter, phase 3 study to evaluate the efficacy and safety of seralutinib for the treatment of WHO Group 1 PH is enrolling (NCT05934526)

References: **1** Frantz RP, et al. *Lancet Resp Med* Published online May 2, 2024. doi: https://doi.org/10.1016/S2213-2600(24)00072-9 **2** Maronna RA, Martin D, Yohai VJ. *Robust Statistics: Theory and Methods (with R)* John Wiley & Sons; 2019. **3** Krämer A, et al. *Bioinformatics* 2014; 30(4):523-530. **4** Malhotra R, et al. *Pulm Circ* 2013; 3(2):369-380. **5** Welch CL, et al. *Genet Med* 2023; 25(11)100925. **6** Galkin A, et al. *Eur Respir J* 2022; 60(6):2102356.**7** Ochoa D, et al. *Nucleic Acids Res* 2023; 51(D1):D1353-D1359. **8** Hirsch K, et al. *J Heart Lung Transplant* 2023; 42(2):173-182. **9** Enomoto N, et al. *Sci Rep* 2021; 11(1):15502.

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