SUSTAINED EFFECT OF SERALUTINIB ON CIRCULATING BIOMARKERS IN THE TORREY PHASE 2 OPEN-LABEL EXTENSION STUDY

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TORREY STUDY

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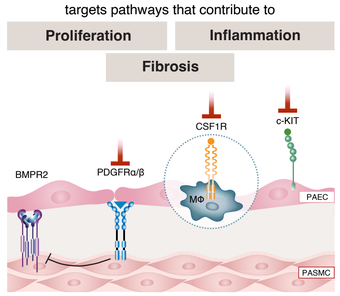
BACKGROUND

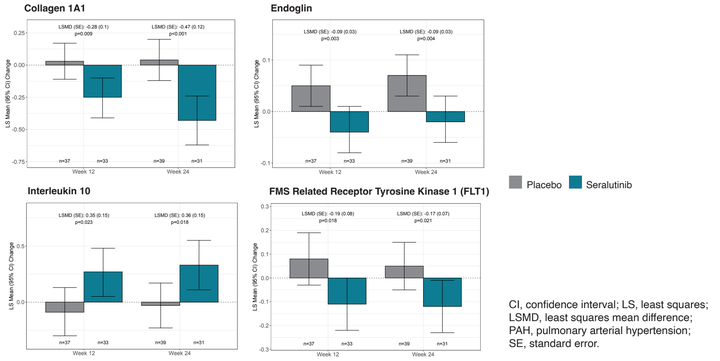
- Seralutinib is a novel, inhaled, tyrosine kinase inhibitor that potently and selectively targets PDGFRα/β, CSF1R, and c-KIT, and has the potential to treat pulmonary vascular remodeling in pulmonary arterial hypertension (PAH) (**Figure 1**)[1,2]
- The phase 2 TORREY study of seralutinib in adults with World Health Organization (WHO) Group I pulmonary hypertension met its primary endpoint of reduction in pulmonary vascular resistance (PVR) at 24 weeks[3]
- The open-label extension (OLE) study of TORREY demonstrates a promising long-term efficacy profile up to 72 weeks, with continued improvement in PVR and exercise capacity[4]
- In an exploratory biomarker analysis of the TORREY study, seralutinib treatment altered 380 circulating proteins following 12 and/or 24 weeks of treatment[5] (**Figure 2**)
- Many of these proteins are relevant to PAH disease biology and the mechanism of action of seralutinib

Figure 1. Seralutinib Mechanism of Action.



Blunted 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; PASMC, pulmonary artery smooth muscle cell; PDGFR, platelet-derived growth factor receptor.

Figure 2. In TORREY, Seralutinib Modulated Circulating Proteins Relevant to Mechanism of Action and PAH Biology.[5]

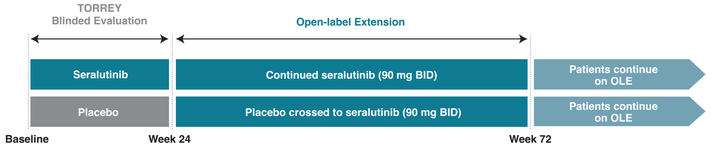


CI, confidence interval; LS, least squares; LSMD, least squares mean difference; PAH, pulmonary arterial hypertension; SE, standard error.

METHODS

- Longitudinal plasma samples were collected prospectively from patients with PAH in the TORREY and OLE studies (**Figure 3**) to characterize circulating biomarkers responsive to seralutinib treatment
- Circulating protein data were generated using Olink® Explore 3072, a multiplexed antibody-based immunoassay
- One-sided Wilcoxon signed-rank tests assessed changes of the 380 seralutinib-associated proteins identified in TORREY following long-term treatment for 48 weeks (placebo-crossed group) or 72 weeks (continued-seralutinib group)
- Results are exploratory and hypothesis-generating

Figure 3. Phase 2 TORREY and Open-label Extension Study Designs.



RESULTS

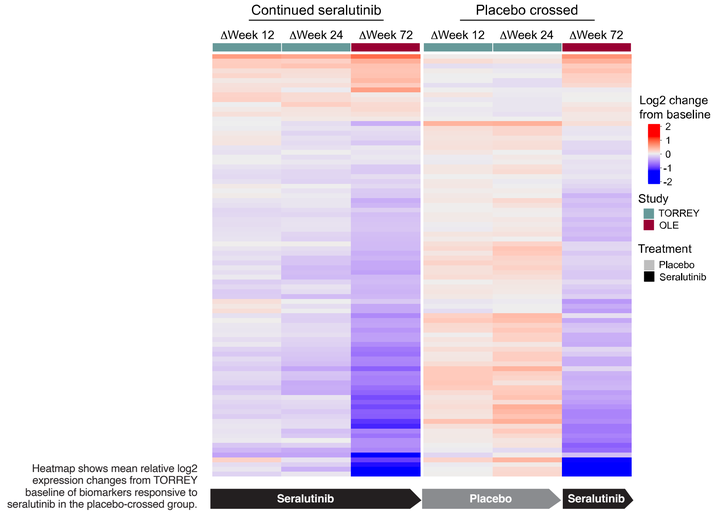
- The OLE biomarker population comprised 45 patients with proteomics data at Week 72
- Baseline characteristics of the OLE population were similar to those in TORREY overall, with similar background PAH medications and baseline disease activity between arms, and imbalances in WHO Functional Class (FC) (**Table 1**)

Table 1. Baseline Characteristics of OLE Biomarker Population. Data presented as mean (SD) unless otherwise noted.

Characteristic	Placebo crossed (n=22)	Continued seralutinib (n=23)	Overall (n=45)
Age at PAH diagnosis, y	42.5 (11.26)	45.3 (13.54)	43.9 (12.41)
Years since PAH diagnosis	7.8 (6.94)	7.3 (6.41)	7.5 (6.60)
PAH classification, n (%)			
Idiopathic/Heritable	11 (50)/3 (13.6)	12 (52.2)/7 (30.4)	23 (51.1)/10 (22.2)
CTD/Other	6 (27.3)/2 (9.1)	1 (4.3)/3 (13)	7 (15.6)/5 (11.1)
Medications, n (%)			
Prostacyclin use	16 (72.7)	16 (69.6)	32 (71.1)
Triple therapy	14 (63.6)	15 (65.2)	29 (64.4)
WHO FC II, n (%)	9 (40.9)	15 (65.2)	24 (53.3)
WHO FC III, n (%)	13 (59.1)	8 (34.8)	21 (46.7)
REVEAL 2.0 risk score ≥6, n (%)	9 (40.9)	10 (43.5)	19 (42.2)
PVR, dyne*s/cm^5	660.4 (164.33)	620.4 (149.2)	639.9 (156.29)
6MWD, m	403.9 (116.52)	410.9 (76.48)	407.4 (97.04)
NT-proBNP, ng/L	569.5 (877.68)	539.7 (708.36)	554.3 (786.62)

6MWD, six-minute walk distance; CTD, connective tissue disease; FC, Functional Class; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open-label extension; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SD, standard deviation; WHO, World Health Organization.

Figure 4. Change From Baseline to Weeks 12, 24, and 72 in Seralutinib-associated Biomarkers.

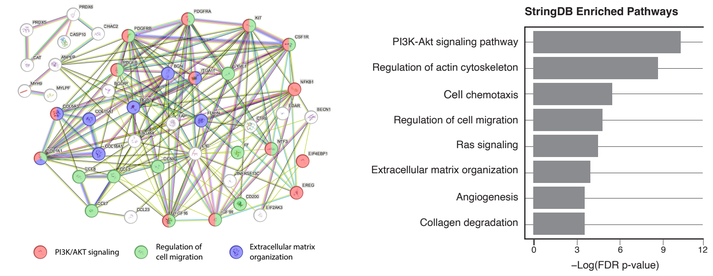


Heatmap shows mean relative log2 expression changes from TORREY baseline of biomarkers responsive to seralutinib in the placebo-crossed group.

- In the continued-seralutinib arm, 169/380 (45%) of protein changes at 24 weeks were maintained or deepened through 72 weeks
- In the placebo-crossed arm, 152/380 (40%) of the previously identified seralutinib-associated protein changes were recapitulated at nominal significance (P<0.05) following 48 weeks of treatment in the OLE

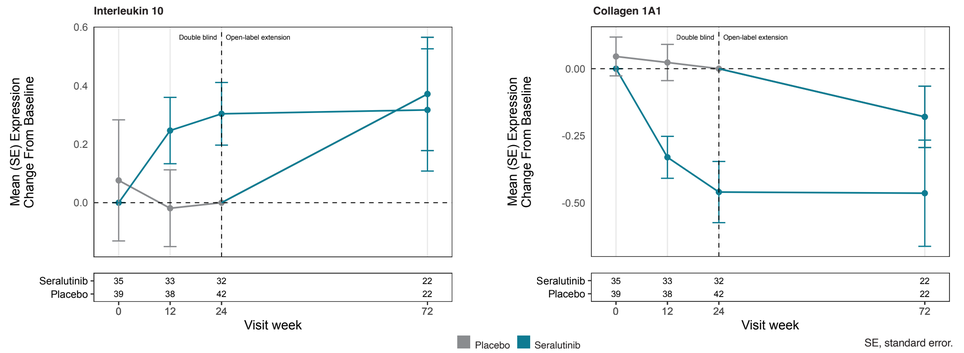
Figure 5. StringDB Network Analysis of Protein Changes Following Long-term Seralutinib Treatment.

- A StringDB network analysis was performed to identify proteins highly interconnected with each other and with the seralutinib targets
- Functional enrichment analysis of this network supports that pathways relevant to PDGFR signaling, proliferation, migration, and remodeling are downregulated by treatment (**Figure 5**)



StringDB network analysis of seralutinib-associated proteins changing over long-term treatment. Network includes seralutinib targets and highly interconnected seralutinib-associated proteins changing in TORREY and OLE. Enrichment p-values are calculated using the background set of Olink Explore proteins. Pathways are downregulated (z-score <0).

Figure 6. Biomarker Changes Relevant to the Mechanism of Action of Seralutinib Were Maintained Over 72 Weeks of Treatment. Representative proteins shown.



SE, standard error.

- Interleukin 10 is a pleiotropic anti-inflammatory cytokine with vasculoprotective properties that was increased by seralutinib in Sugen Hypoxia lung tissue and is also increased in PAH patient plasma
- Collagen 1A1 is elevated in PAH fibrotic tissue and is decreased by seralutinib at the protein level in human lung fibroblasts, and is decreased in this study
- These proteins highlight the consistency of seralutinib's effects in preclinical models and patients with PAH

CONCLUSIONS

- 40% of proteins responsive to seralutinib treatment during the placebo-controlled treatment period (TORREY) were recapitulated in the placebo-crossed population of the OLE
- The observed long-term biomarker changes support a sustained effect of seralutinib on proteins and pathways relevant to PAH pathogenesis
- Protein changes relate to proliferation, inflammation, and matrix remodeling, and support the mechanism of action of seralutinib observed in preclinical studies
- Results will be prospectively validated in the currently enrolling phase 3 PROSERA study (NCT05934526)

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