Trial in progress: SERANATA, a phase 3 randomized, placebo-controlled trial to evaluate inhaled seralutinib for treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD)

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Presented at:
PVRI 2026 Dublin
28 January–1 February
Dublin, Ireland

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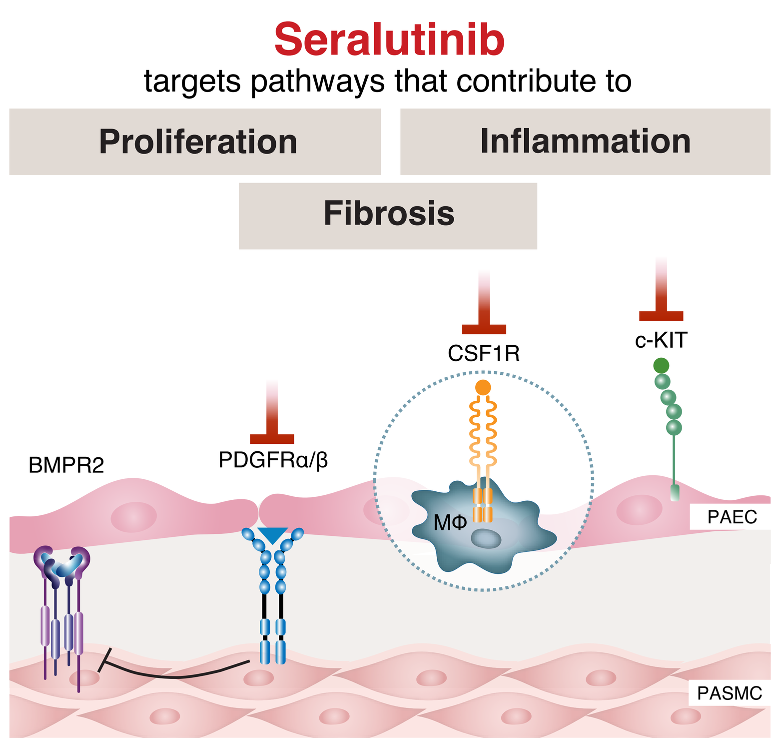
BACKGROUND

- Seralutinib is an inhaled tyrosine kinase inhibitor (TKI) targeting PDGFR, CSF1R, and c-KIT pathways that drive inflammation, proliferation, and fibrosis, key to pulmonary vascular remodeling in pulmonary hypertension (**Figure 1**)[1,2]
- In preclinical models, seralutinib showed significant anti-inflammatory and anti-fibrotic effects[3-6]
- In the phase 2 TORREY study, seralutinib decreased fibrosis-related circulating proteins[7]
- Overlapping pathophysiology between pulmonary arterial hypertension (PAH) and PH-ILD, seralutinib's mechanism of action, and proven efficacy in PAH support its evaluation in PH-ILD

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.

Phase 2 TORREY Study of Inhaled Seralutinib in PAH[8,9]

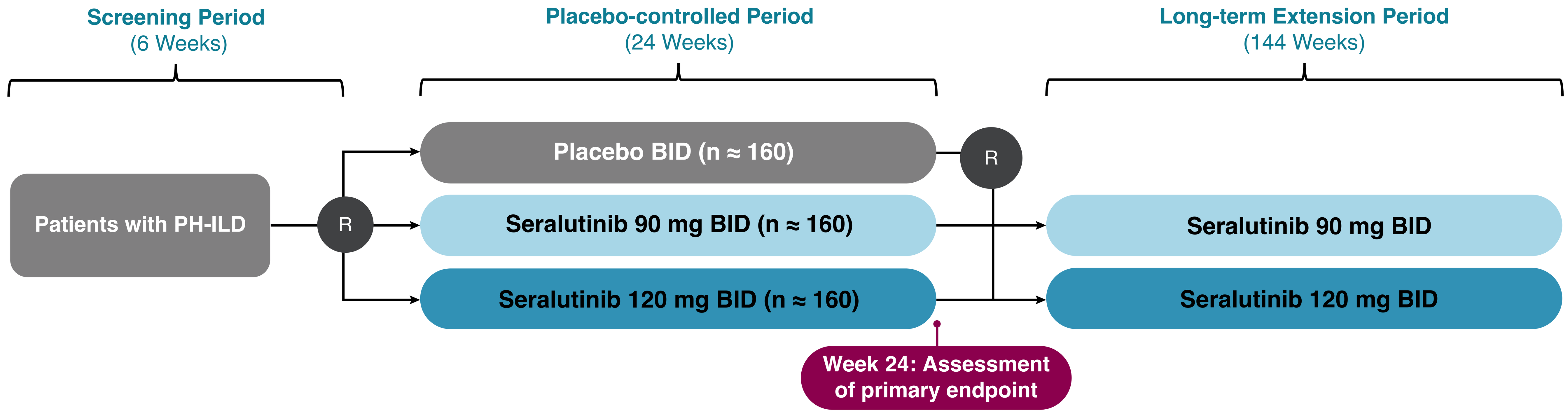
- TORREY was a phase 2, randomized, double-blind, placebo-controlled study evaluating seralutinib in adults with PAH
- TORREY met its primary endpoint of PVR improvement vs. placebo at 24 weeks
- Improvements in echocardiographic parameters and NT-proBNP reductions indicate improved right heart function
- CT imaging substudy findings suggest reverse remodeling of the pulmonary vasculature
- In the 72-week OLE study, seralutinib demonstrated continued improvement in hemodynamics and 6MWD
- Seralutinib showed a favorable tolerability and safety profile
- The phase 3 PROSERA study of seralutinib in PAH is ongoing

TORREY: NCT04456998; OLE: NCT04816604; PROSERA: NCT05934526. 6MWD, 6-minute walk distance; CT, computed tomography; NT-proBNP, N-terminal pro b-type natriuretic peptide; OLE, open-label extension; PVR, pulmonary vascular resistance.

SERANATA, A PHASE 3 STUDY OF SERALUTINIB IN PH-ILD

- SERANATA is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of two doses of inhaled seralutinib in adults with PH-ILD (NCT07181382)
- The study will enroll ~480 participants across sites in North America, Europe, Latin America, and Asia-Pacific
- Patients will be randomized 1:1:1 to twice daily seralutinib 90 mg, 120 mg, or placebo administered by a dry powder inhaler during a 24-week double-blind period (**Figure 2**)
- Patients continuing into the long-term extension remain on their respective seralutinib dose or switch from placebo to seralutinib 90 mg or 120 mg in 1:1 randomized fashion for continued dose-blinded evaluation of safety and efficacy

Figure 2. Study schema



Key Inclusion Criteria

- Adults aged ≥18 and ≤80 years[a]
- WHO Group 3 PH associated with:
  - Idiopathic interstitial pneumonia[b]
  - SARD-ILD[b]
  - Fibrosing hypersensitivity pneumonitis
  - Occupational ILD
- RHC meeting all three of the following criteria[c]:
  - PVR ≥4 Wood Units
  - PCWP or LVEDP ≤15 mmHg
  - mPAP ≥25 mmHg
- FVC ≥45% predicted at screening
- 6MWD ≥100 m and ≤475 m at screening
- Stable treatment regimen prior to screening[d]

[a]19-year minimum age in South Korea; [b]Patients meeting the criteria for idiopathic interstitial pneumonia with autoimmune features will be classified as SARD-ILD; [c]Historic RHC up to 12 weeks prior to screening may be acceptable for eligibility; [d]Applies to background medications for PH, fibrosis, and SARD-ILD.

Endpoints*

Primary

- Change in 6MWD from baseline to week 24

Key secondary

- Time to first clinical worsening event[a]
- Change in NT-proBNP levels from baseline to week 24
- Change in absolute FVC from baseline to week 24

Selected safety

- Incidence of TEAEs, serious TEAEs, and TEAEs of special interest
- Changes to vital signs, clinical laboratory parameters
- Changes in pulmonary function test, including FEV_1, FEV_1/FVC ratio, DLCO

[a]Defined as any of the following Adjudication Committee-confirmed events: death (all causes); hospitalization (≥24 hours) due to a worsening cardiopulmonary indication; ≥15% 6MWD decline from baseline.
*Placebo-controlled period.

Exploratory Substudies*

Evaluate the effects of seralutinib vs. placebo over 24 weeks.

RHC Substudy

Changes in hemodynamic parameters, including mPAP, PVR, cardiac output, and cardiac index

ECHO Substudy

Changes in ECHO parameters, including RAA, RVFWS, LVEF, and TAPSE

HRCT Substudy

Changes in HRCT parameters, including pulmonary vascular blood volume and fibrosis score

*Substudies are optional and will be conducted at participating sites only.

6MWD, six-minute walk distance; BID, twice daily; DLCO, carbon monoxide diffusing capacity; ECHO, echocardiography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LVEDP, left ventricular-end diastolic pressure; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with ILD; PVR, pulmonary vascular resistance; R, randomization; RAA, right atrial area; RHC, right heart catheterization; RVFWS, right ventricular free wall strain; SARD-ILD, systemic autoimmune rheumatic disease-associated ILD; TAPSE, tricuspid annular plane systolic excursion; TEAE, treatment-emergent adverse event; WHO, World Health Organization.

SUMMARY

- Seralutinib is an inhaled TKI designed to target key drivers of vascular remodeling—PDGFR, CSF1R, and c-KIT—central to inflammation, proliferation, and fibrosis in PH
- The overlapping pathophysiology between PAH and PH-ILD, and supporting preclinical, clinical, and biomarker evidence provide a strong rationale for evaluating seralutinib in PH-ILD
- SERANATA, a global phase 3 trial (NCT07181382), is underway to evaluate seralutinib's efficacy and safety in PH-ILD

Acknowledgements: We gratefully acknowledge the contributions of Dr. Lucilla Piccari, who passed away on December 18, 2025, to this work.

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Research supported by: Gossamer Bio, Inc.