TRIAL IN PROGRESS: PROSERA, A PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF SERALUTINIB IN ADULTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH)

PROSERA STUDY

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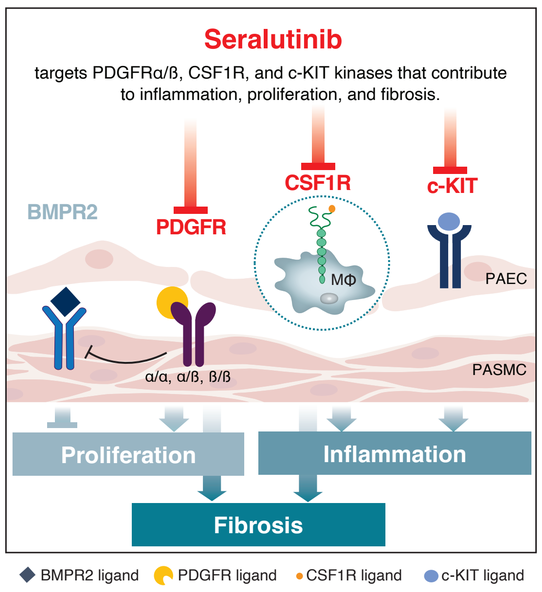
Olivier Sitbon[1], Raymond L. Benza[2], Richard N. Channick[3], Kelly M. Chin[4], Robert P. Frantz[5], Hossein-Ardeschir Ghofrani[6], Anna R. Hemnes[7], Luke S. Howard[8], Vallerie V. McLaughlin[9], Roham T. Zamanian[10], Jean-Marie Bruey[11], Matt Cravets[11], David Mottola[11], Lawrence S. Zisman[11], Ed Parsley[11], Robert F. Roscigno[11], Richard Aranda[11], Jean-Luc Vachiéry[12]

[1]Hôpital Bicêtre (AP-HP), Université Paris-Saclay, Le Kremlin-Bicêtre, France; [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]University of California Los Angeles, UCLA Medical Center, Los Angeles, CA, USA; [4]UT Southwestern Medical Center, Dallas, TX, USA; [5]Mayo Clinic, Rochester, MN, USA; [6]Justus-Liebig-University Giessen and Marburg Lung Center (UGMLC), Institute for Lung Health, Cardio-Pulmonary Institute; Member of the German Center for Lung Research (DZL), Giessen, Germany; [7]Vanderbilt University, Vanderbilt University Medical Center, Nashville, TN, USA; [8]Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK; [9]University of Michigan, Ann Arbor, MI, USA; [10]Stanford University School of Medicine, Stanford Medicine, Stanford, CA, USA; [11]Gossamer Bio, Inc., San Diego, CA, USA; [12]Université Libre de Bruxelles, HUB – Hôpital Erasme, Brussels, Belgium

BACKGROUND

- PDGFRα/β, CSF1R, and c-KIT kinase pathways drive inflammation, proliferation, and fibrosis that contribute to pulmonary vascular remodeling in PAH[1] (**Figure**)
- Seralutinib is a potent tyrosine kinase inhibitor (TKI) targeting these pathways
- Seralutinib is the only inhaled TKI intentionally developed as a treatment for PAH and specifically formulated as a dry powder to reach the site of the disease and limit systemic exposure[2]



Blunted arrows indicate inhibition. BMPR2, bone morphogenetic protein receptor type 2; c-KIT, mast/stem cell growth factor; 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.

The Phase 2 TORREY Study

- Double-blind, randomized, placebo-controlled study of inhaled seralutinib in patients with WHO Group 1 pulmonary hypertension (PAH; NCT04456998)
- TORREY met its primary endpoint, demonstrating a significant reduction in pulmonary vascular resistance (PVR) from baseline to Week 24 (–14.3%; p = 0.0310), with favorable tolerability[3]
- Prespecified subgroup analyses showed greater benefit in Functional Class (FC) III patients and patients with REVEAL 2.0 risk score ≥ 6
- The reduction in PVR and increase in pulmonary arterial compliance in conjunction with a reduction of NT-proBNP indicates that seralutinib is reducing right ventricular afterload and having a beneficial effect on the right heart

PROSERA, A PHASE 3 STUDY OF SERALUTINIB IN PAH

- PROSERA is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of inhaled seralutinib in adults (ages 18–75 y) with WHO Group 1 PH (NCT05934526)
- 350 patients are to be enrolled at ~160 investigational sites globally throughout North America, Europe, Latin America, and Asia Pacific (**Figure 1**)
- Eligible patients will be randomized 1:1 to receive seralutinib 90 mg or placebo twice daily (BID) by dry powder inhalation, in addition to background PAH therapy (**Figure 2**)

Key Inclusion Criteria

- Adults ≥ 18 and ≤ 75 years old
- WHO Group 1 PH
- WHO FC II or III
- PVR ≥ 400 dyne•s/cm^5
- Baseline 6-minute walk distance (6MWD) 150–450 m
- Either REVEAL Lite 2 risk score ≥ 5 or NT-proBNP ≥ 300 ng/L*
- Stable treatment with one to three standard-of-care PAH background therapies

*Key enrichment criteria

Endpoints

Primary

- Change in 6MWD from baseline to Week 24

Key Secondary

- Time from 1st dose to 1st event of clinical worsening
- Proportion of patients who achieve all components of a composite endpoint of clinical improvement at Week 24 in the absence of clinical worsening:
  - Decrease in WHO FC or maintenance of WHO FC II
  - Decrease in NT-proBNP ≥ 30% or maintenance at < 300 ng/L
  - Increase in 6MWD ≥ 10% or ≥ 30 m
- Change vs baseline in NT-proBNP at Week 24
- Proportion of patients with ≥ 1 point decrease in REVEAL Lite 2 risk score vs baseline at Week 24

Safety

- Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs of special interest

Exploratory

- Seralutinib plasma concentrations and pharmacodynamic biomarkers measured in blood and plasma samples

Figure 1. Countries with PROSERA study sites.

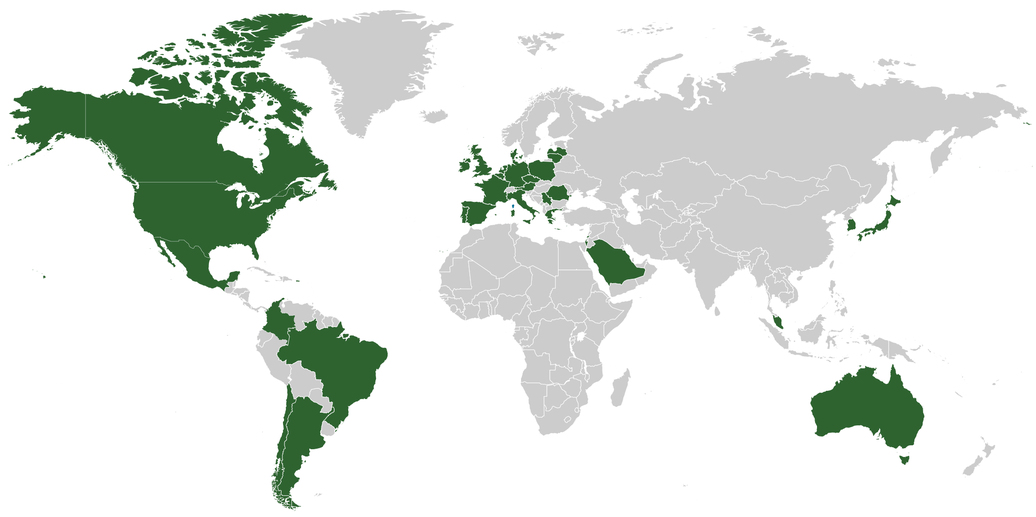
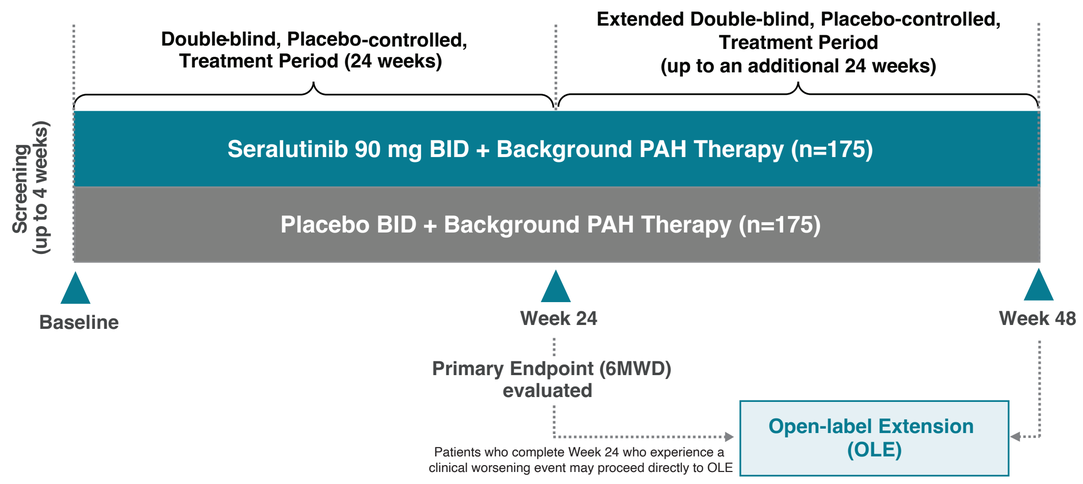


Figure 2. PROSERA study schema.



Functional Respiratory Imaging (FRI) Substudy

Objective:

- To evaluate the effect of seralutinib vs placebo on changes in the pulmonary vasculature as assessed by high-resolution chest computed tomography

Endpoints include changes in:

- Pulmonary vasculature blood volume
- Pulmonary blood volume as % total lung volume
- Fibrosis score
- Image-based ventilation-to-perfusion score from baseline to Week 24

SUMMARY

- Seralutinib is a potent small-molecule TKI that targets PDGFRα/β, CSF1R, and c-KIT, and was specifically designed for inhalation to maximize the therapeutic index and limit systemic exposure
- In the phase 2 TORREY study in patients with PAH, seralutinib demonstrated significant reduction in PVR compared to placebo, and significant improvements in NT-proBNP and right heart function, with favorable tolerability
- The phase 3 PROSERA study in patients with WHO Group 1 PH, FC II/III, is now enrolling (NCT05934526)

References: **1** Pullamsetti SS et al. *Int J Mol Sci* 2023;24(16):12653. **2** Galkin A et al. *Eur Respir J* 2022;60(6):2102356. **3** Frantz RP et al. *Lancet Resp Med* Published online May 2, 2024. doi: 10.1016/S2213-2600(24)00072-9

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