

Phase 2 Clinical Study to Evaluate the Efficacy and Safety of Inhaled GB002 (Seralutinib) for the Treatment of World Health Organization Group 1 Pulmonary Arterial Hypertension

Robert P. Frantz¹, Luke S. Howard², Vallerie V. McLaughlin³, Olivier Sitbon⁴, Roham T. Zamanian⁵, Raymond L. Benza⁶, Kelly Chin⁷, Richard Channick⁸, Matt Cravets⁹, Jean-Marie Bruey⁹, Robert Roscigno⁹, David Mottola⁹, Lawrence S. Zisman⁹, Hossein-Ardeschir Ghofrani¹⁰

¹Mayo Clinic, Rochester, MN, USA; ²Imperial College Healthcare NHS, London, UK; ³University of Michigan, Ann Arbor MI, USA; ⁴Université Paris-Saclay, Le Kremlin-Bicêtre, France; ⁵Stanford University, Menlo Park, CA, USA; ⁶Ohio State University, Columbus, OH, USA; ⁷UT Southwestern Medical Center, Dallas, TX, USA; ⁸UCLA Medical Center, Los Angeles, CA, USA; ⁹Gossamer Bio, Inc., San Diego, CA, USA; ¹⁰Justus-Liebig University Giessen, Giessen, Germany

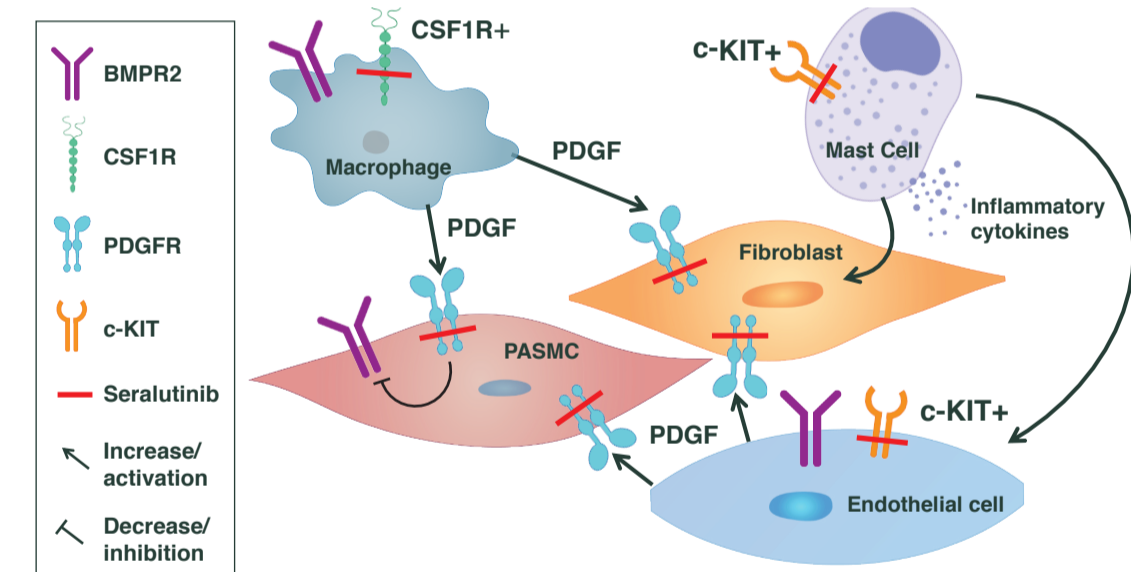
BACKGROUND

- Despite currently available therapies the morbidity and mortality of pulmonary arterial hypertension (PAH) remains high
- PDGF, CSF1R, c-KIT and BMPR2 play a central role in cellular overgrowth in the lung vasculature and are key drivers in the development of PAH^{1,2,3} (Figure 1)
- Seralutinib (formerly GB002) is a novel chemical entity, specifically developed for the treatment of PAH, with an optimized kinase specificity profile (Figure 2)
- Seralutinib has been shown to modulate BMPR2 in preclinical studies
- Seralutinib is delivered via inhalation by dry powder inhaler to potentially maximize the therapeutic index by directly targeting diseased pulmonary arterioles (Figure 3)
- Seralutinib is in clinical development for treatment of WHO Group 1 PAH patients



Dry Powder Inhaler

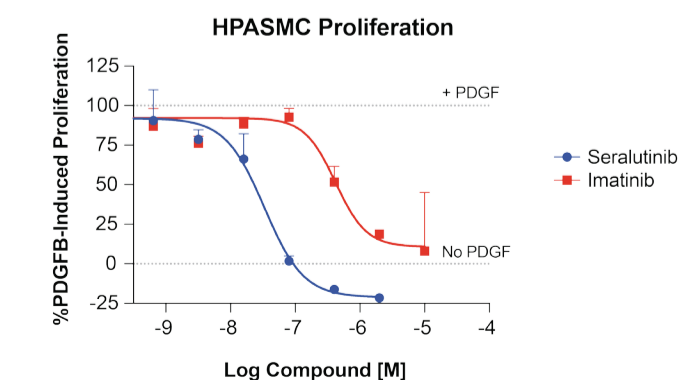
Figure 1. Mode of action of seralutinib in reversing pathologic remodeling in PAH



PRECLINICAL STUDIES

Figure 2. Seralutinib is a potent PDGFR, CSF1R and c-KIT inhibitor

| Compound | Cell Based IC ₅₀ (nM) | | | | |
|-------------|----------------------------------|--------------|----------------|-------|-------|
| | H1703 PDGFRα | HLF PDGFRβ>α | PASMC PDGFRα=β | CSF1R | c-KIT |
| Seralutinib | 32 | 29 | 33 | 8 | 14 |
| Imatinib | 62 | 579 | 419 | 1032 | 230 |

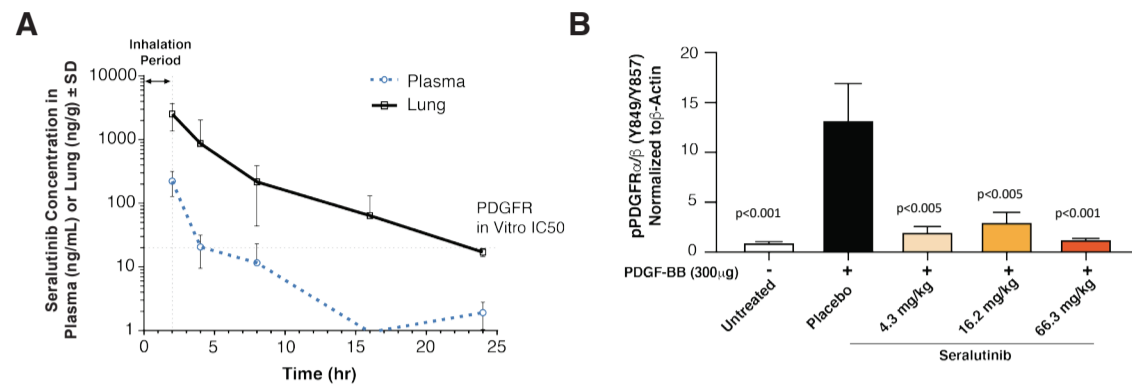


Seralutinib inhibited proliferation of human pulmonary arterial smooth muscle cells (HPASMCs) *in vitro* with an IC₅₀ approximately 10-fold lower than imatinib (data shown as mean ± SEM)

Definition of abbreviations: CSF1R, colony stimulating factor 1 receptor; HLF, human lung fibroblast; HPASMC, human pulmonary arterial smooth muscle cell; PDGFR, Platelet-derived growth factor

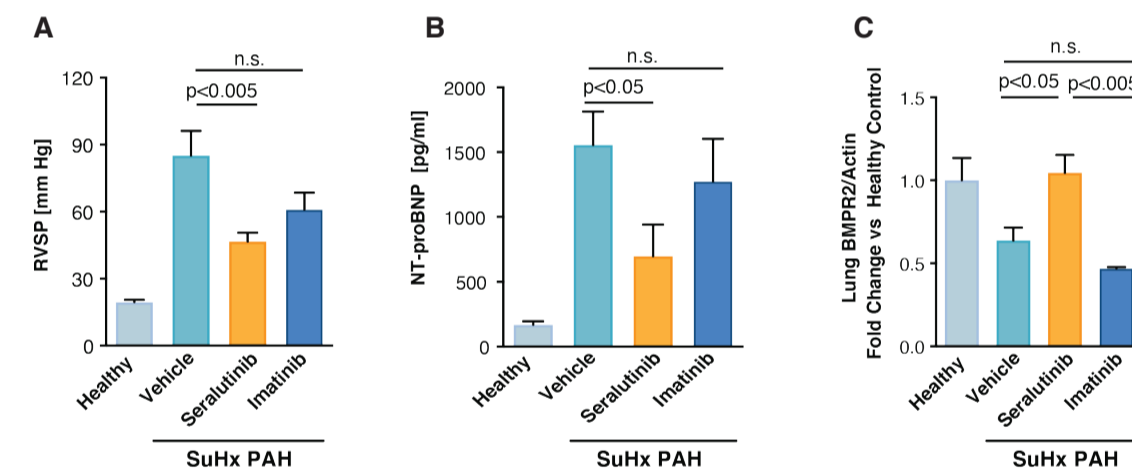
PRECLINICAL STUDIES (CONTINUED)

Figure 3. Seralutinib *in vivo* PK/PD profile



A. Seralutinib (4.3 mg/kg dose, 2 hr passive inhalation) displayed ~30X lung-to-plasma exposure ratio in rat (n=4-8). B. Seralutinib decreased PDGFRβ-stimulated autophosphorylation of PDGFR β in the rat lung by 77-91%. Data shown as mean phosphorylated PDGFR / β-Actin ratio ± SEM (n=4).

Figure 4. Impact of inhaled seralutinib on hemodynamic parameters and disease biomarkers in the SU5416 hypoxia rat model⁴



Seralutinib treatment led to significant reduction in right ventricular systolic pressure, data shown as mean ± SEM (A), reduced circulating levels of NT-proBNP, data shown as mean ± SEM (B), and increased lung BMPR2 protein expression, data shown as fold change ± SEM (C).

PHASE 1 STUDIES

- Phase 1a – Randomized, placebo-controlled, double-blind, two-part single ascending (3.75 to 90 mg) and multiple ascending (18 to 90 mg, BID, 7 d) dose studies in healthy volunteers (N=62)⁵
- Summary of results
 - Seralutinib was rapidly absorbed into and cleared from systemic circulation
 - Exposure increased in a dose-proportional manner; minimal accumulation in plasma was observed
 - Seralutinib was well tolerated at doses up to 90 mg BID
- Phase 1b - a study of seralutinib administered for 14 days in PAH subjects has been completed, inclusive of target engagement and biomarker assessments; an OLE study is ongoing

Phase 2 Study of Seralutinib in PAH



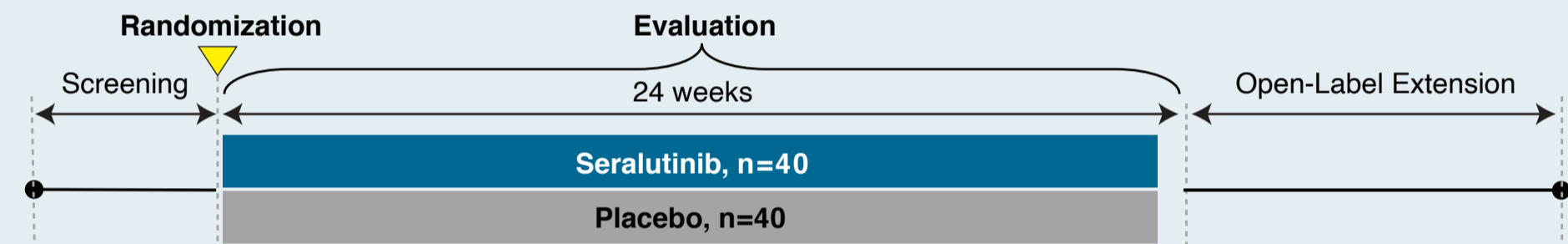
Selected Inclusion Criteria

- Current diagnosis of symptomatic PAH classified by one of the following:
 - IPAH, HPAH, PAH-CTD
 - PAH associated with anorexigen or methamphetamine use
 - Congenital heart disease with simple systemic to pulmonary shunt at least 1 year after surgical repair
- 6MWD ≥ 150 m and ≤ 550 m at screening
- WHO FC II or III
- Treatment with standard of care PAH background therapies, including PGIs
- RHC data consistent with the diagnosis of PAH and PVR ≥ 400 dyne-s/cm⁵

Selected Exclusion Criteria

- Evidence of chronic thromboembolic disease or acute pulmonary embolism
- WHO Pulmonary Hypertension Group 2–5
- HIV-associated PAH
- History of left-sided heart disease and/or clinically significant cardiac disease
- Inhaled prostanoids
- Use of anticoagulants
- History of intracranial hemorrhage

TORREY Study Schema



Endpoints

- Primary:** Change in pulmonary vascular resistance from baseline to week 24
- Safety:** Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and treatment-emergent adverse events of special interest (AESIs)
- Exploratory:** Change in WHO FC & Risk Score, right ventricular function by echocardiography, QoL, NT-proBNP, biomarkers, disease modification sub-studies
- Secondary:** Change in six-minute walk distance from baseline to week 24 (Δ6MWD)

TORREY – SUBSTUDIES

Functional Respiratory Imaging

Evaluate effect of seralutinib on pulmonary vascular remodeling by quantifying changes in pulmonary arterial blood volume based on image reconstruction from high resolution CT scans

Heart Rate Expenditure during 6MWT

Assessment of HR parameters during/after 6MWT to provide insight into prognosis or treatment effect beyond standard 6MWT (seralutinib vs placebo).

- Determine if heart rate expenditure per unit distance (HRE/D) is a more sensitive measure of response to therapy vs 6MWD alone
- Assess HRE on beat-by-beat basis to determine absolute beat decrement and rate of HR decline

SUMMARY

- Seralutinib is a unique, inhaled, small-molecule kinase inhibitor that targets PDGFR α/β, CSF1R, and c-KIT, and modulates BMPR2
- The inhaled route of administration for seralutinib targets the diseased pulmonary arterioles at doses predicted to be locally effective while limiting systemic exposure which may reduce the risk of adverse events
- A phase 2 trial (TORREY; NCT04456998) in subjects with WHO Group 1 PAH is currently recruiting

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https://goss.bio/3czQKIF