Seralutinib Preserved Lung Function and Displayed Broad Anti-Fibrotic Activity in Models of Pulmonary Fibrosis

Annalisa Murgo[1], Ravikumar Sitapara[2], Fabio Bignami[1], Andrew Allen[1], Eduardo Garcia[2], Sidra Hoffman[2], Richard Aranda[2], Simona Spennato[1], Luis Magalhaes[1], Lawrence Ho[2], Giuseppina Federico[1], Bruno Guedes Baldi[3], Vincent Cottin[4], Oksana A. Shlobin[5], Jean-Marie Bruey[2], Daniela Miglietta[1], Ayodeji Adegunsoye[6]

[1]Chiesi Farmaceutici S.p.A., Parma, Italy; [2]Gossamer Bio, Inc., San Diego, CA, USA; [3]Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [4]National Reference Center for Rare Pulmonary Diseases, Louis Pradel Hospital, University of Lyon, Lyon, France; [5]Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, University of Virginia School of Medicine, Falls Church, VA, USA; [6]Interstitial Lung Disease Program, Pulmonary and Critical Care, University of Chicago Medicine, Chicago, IL, USA

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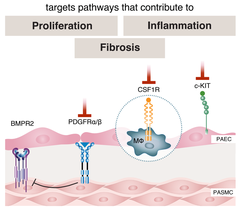
BACKGROUND

- Fibrosis contributes to both pulmonary vascular and parenchymal remodeling in pulmonary hypertension (PH) and interstitial lung disease (ILD)[1] **(Figure 1)**
- Seralutinib is a potent, inhaled PDGFRα/ß, CSF1R, and c-KIT kinase inhibitor in clinical development for PAH and PH-ILD[2,3]
- In the phase 2 TORREY study (NCT04456998) in patients with Group 1 PH, seralutinib decreased circulating fibrotic biomarkers, including collagen Iα1[4,5]
- We investigated whether seralutinib's anti-fibrotic effect on established fibrosis in idiopathic pulmonary fibrosis (IPF) patient-derived precision-cut lung slices (PCLS) translated into functional lung improvement in a bleomycin (BLM) mouse model of lung fibrosis

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.

METHODS

Effect of seralutinib on release of pro-fibrotic markers from IPF human (h) PCLS cultures

- Cryopreserved PCLS from two IPF donors were cultured and treated for 4 d with vehicle and seralutinib (0.1–10 µM) **(Figure 2)**
- Supernatants were collected at 96 h and pro-fibrotic markers were evaluated using a custom Luminex panel

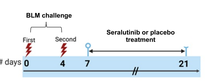
Effect of seralutinib in the bleomycin animal model of lung fibrosis

- C57BL/6 mice were challenged with BLM (0.03 IU/mouse) or saline by oropharyngeal route on days 0 and 4. Seralutinib (20 mpk BID) or vehicle were given by dry powder inhalation for 2 weeks starting on day 7 **(Figure 3)**
- On day 21, the diffusion factor for carbon monoxide (DFCO) was measured with a micro gas chromatograph (Inficom) and forced vital capacity (FVC) was assessed by the FlexiVent system (SCIREQ).[4] Lung fibrosis was assessed by Ashcroft scoring and an artificial intelligence (AI)-based automated image analysis on Masson's trichrome stained lung sections.[5] Biomarker levels were measured by enzyme-linked immunosorbent assays (ELISA) in bronchoalveolar lavage fluid (BALF) and serum samples **(Table 1)**

Figure 2. IPF-hPCLS experimental setup

hPCLS, human precision-cut lung slice; IPF, idiopathic pulmonary fibrosis. Illustration created with BioRender.

Figure 3. Bleomycin experimental protocol and treatment groups



Experimental groups		
Group	**Administration**	**N**
Saline/placebo		4
BLM/placebo	20 mpk; BID inhalation	13
BLM/seralutinib	20 mpk; BID inhalation	13

BID, twice daily; BLM, bleomycin; mpk, milligram per kilogram.

Table 1. Overview of study assessments (bleomycin model)

Functional readouts	Fibrosis evaluation	Biomarkers
FVC	Ashcroft score	Measured in BALF: Collagen-I, MMP-7, CSF1R, VCAM-I
DFCO	Automated detection by AI	Measured in serum: SP-D

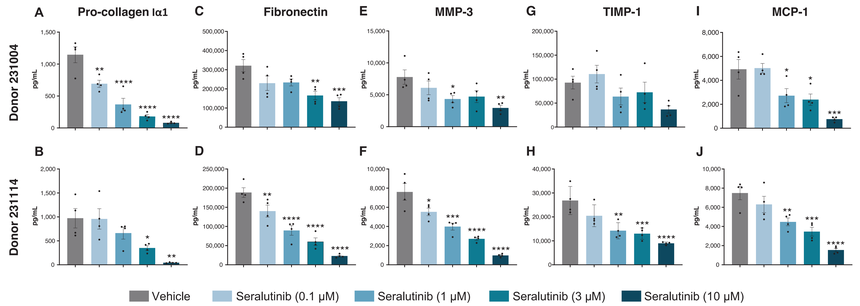
DLCO, or diffusing capacity of the lungs for carbon monoxide (CO), is used to measure how well lungs move gases into the blood.

DFCO, or diffusion factor for CO, is closely related to DLCO, and is a simpler method used in preclinical research to assess how well CO diffuses across the alveolar-capillary membrane in the bloodstream.

AI, artificial intelligence; BALF, bronchoalveolar lavage fluid; DFCO, diffusion factor for carbon monoxide; FVC, forced vital capacity.

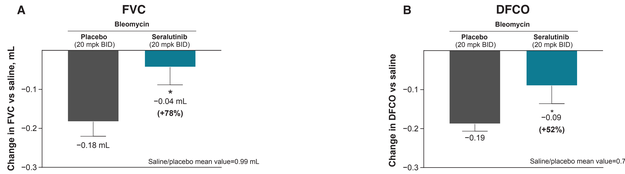
RESULTS

Figure 4. Seralutinib inhibited release of pro-fibrotic markers in IPF-hPCLS



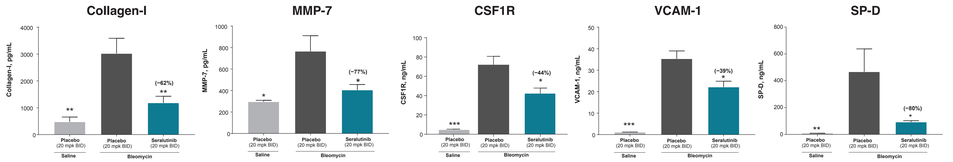
Graphs depict effect of vehicle control and seralutinib on the release of pro-fibrotic markers pro-collagen Iα1 **(A,B)**, fibronectin **(C,D)**, MMP-3 **(E,F)**, TIMP-1 **(G,H)**, and MCP-1 **(I,J)** secreted by IPF-hPCLS at 96 h for both donors tested. Data are expressed as mean ± SEM (n=4). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparisons test. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 versus vehicle. ANOVA, analysis of variance; hPCLS, human precision-cut lung slice; IPF, idiopathic pulmonary fibrosis.

Figure 5. Seralutinib significantly improved lung function relative to placebo in the bleomycin model



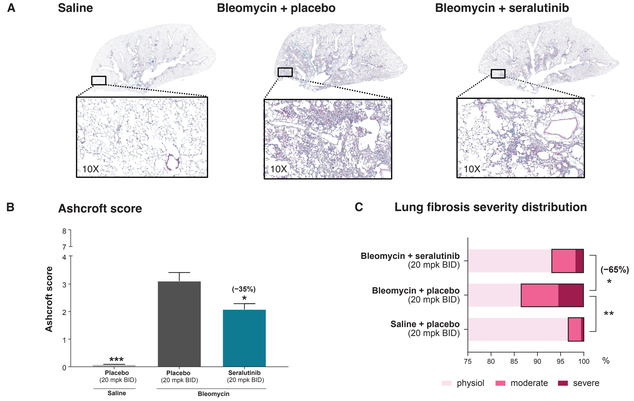
Change in FVC **(A)** and in DFCO **(B)** as measurement of lung function at day 21. Data are expressed as change compared to saline/placebo group and as mean ± SEM. Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparisons test. *p<0.05, **p<0.01, and ***p<0.001 versus BLM/placebo. ANOVA, analysis of variance; BID, twice daily; BLM, bleomycin; DFCO, diffusion factor for carbon monoxide; FVC, forced vital capacity; mpk, milligram per kilogram.

Figure 6. Seralutinib inhibited release of pro-fibrotic and pro-inflammatory biomarkers in the bleomycin animal model of pulmonary fibrosis



Effect of seralutinib on collagen-I, MMP-7, CSF1R, VCAM-1 in BALF, and SP-D in serum. Data represent mean ± SEM values. Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparisons test. *p<0.05, **p<0.01, and ***p<0.001 versus BLM/placebo. ANOVA, analysis of variance; BID, twice daily; BLM, bleomycin; mpk, milligram per kilogram.

Figure 7. Seralutinib significantly reduced lung fibrosis in the bleomycin model



Effect of seralutinib on pulmonary fibrosis. **(A)** Masson's trichrome stained lung slides (representative images), **(B)** Ashcroft score, and **(C)** tissue classification of lung fibrosis severity distribution using AI-based Visiopharm® APPs. Data represent mean ± SEM values. Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparisons test. *p<0.05, **p<0.01, and ***p<0.001 versus BLM/placebo. ANOVA, analysis of variance; BID, twice daily; BLM, bleomycin; moderate, moderate fibrotic tissue; mpk, milligram per kilogram; physiol, physiological tissue; SEM, standard error of the mean; severe, severe fibrotic tissue.

CONCLUSIONS

- Seralutinib dose-dependently decreased pro-collagen Iα1, fibronectin, MMP-3, TIMP-1, and MCP-1 in IPF-hPCLS
- In a mouse model of bleomycin-induced pulmonary fibrosis, seralutinib treatment preserved lung function at a clinically relevant dose
- The relative preservation of lung function was associated with reduced levels of a series of relevant biomarkers in BALF and serum, and with a reduction in pulmonary fibrosis measured by Ashcroft score and AI-based analysis
- These data support the investigation of seralutinib as a potential inhaled treatment option for diseases characterized by interstitial fibrosis

References:
1 Dhont S, et al. *ERJ Open Res.* 2022;8(4):00272-2022. **2** Galkin A, et al. *Eur Respir J.* 2022;60(6):2102356. **3** Pullamsetti SS, et al. *Int J Mol Sci.* 2023;24(16):12653. **4** Ghofrani HA, et al. *Am J Respir Crit Care Med.* 2024;209:A7383. **5** Osterhout R, et al. *Eur Respir J.* 2024;64(suppl 68):OA1872.

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