Comparative and Combined Effects of Seralutinib and Nintedanib Reveal Enhanced Anti-Fibrotic and Anti-Inflammatory Activity in Pulmonary Fibrosis Models

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BACKGROUND

- Fibrosis, inflammation and proliferation contribute to pulmonary vascular remodeling and fibrosis in pulmonary hypertension and interstitial lung disease (ILD) [1].
- Seralutinib is an investigational inhaled PDGFRα/β, CSF1R and c-KIT inhibitor[2].
- Nintedanib is approved for multiple fibrosing ILDs and targets overlapping and distinct kinases[3,4].
- Complementary kinase inhibition may provide broader pathway coverage and enhance anti-fibrotic and anti-inflammatory activity relative to either monotherapy.

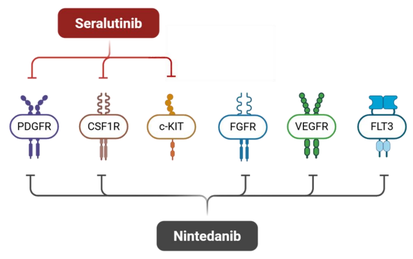


Figure 1. Overview of kinases inhibited by inhaled Seralutinib and Nintedanib

METHODS

BLEOMYCIN MOUSE MODEL

- C57BL/6 mice were challenged with BLM (0.03 UI/mouse) or saline by oropharyngeal route at Days 0 and 4. Seralutinib (30 mpk BID) or Nintedanib (50 mpk BID) or both or vehicle were given by dry powder inhalation or oral solution for 2 weeks starting Day 7 after first BLM challenge **(Table 1)**

Groups	Administration	N
Saline	Placebo (inhalation) + vehicle (oral)	17
BLM	Placebo (inhalation) + vehicle (oral)	25
SERALUTINIB	Seralutinib 30 mpk BID (inhalation) + vehicle (oral)	25
COMBO	Seralutinib 30 mpk BID (inhalation) + Nintedanib 50 mpk BID (oral)	25
NINTEDANIB	Nintedanib 50 mpk BID (oral) + placebo (inhalation)	25

Table 1. Experimental groups

- At Day 21, lung function was assessed by measuring diffusing capacity for carbon monoxide (mDLCO) and forced vital capacity (mFVC)[5], while lung fibrosis was evaluated by histology using Ashcroft scoring and AI-based analysis of Masson's trichrome-stained sections. Biomarker levels in BALF and serum were also quantified by ELISA (**Table 2**).

Functional readouts	Fibrosis evaluation	Biomarkers
mFVC	Histopatological evaluation (Ashcroft score)	Measured in BALF: Collagen-*1α1*, MMP-7, VCAM-I
mDLCO	Automated detection of fibrosis by AI	Measured in serum: SP-D

Table 2. Overview of BLM study assessments[6]

IPF-hPCLS MODEL

- Three independent IPF-hPCLS were cultured and treated with Seralutinib (3μM), Nintedanib (2.5μM), or both.
- Supernatants were collected at 96 h and analyzed for pro-fibrotic and pro-inflammatory markers using a custom Luminex panel

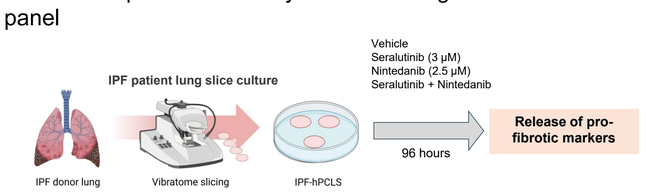
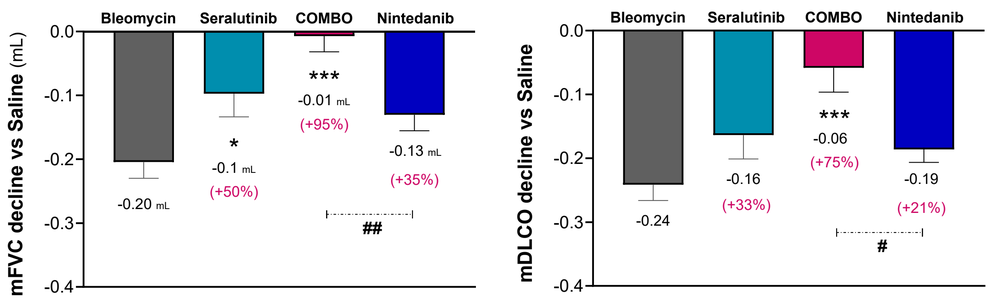


Figure 3. IPF-hPCLS experimental setup

AIM | Evaluate whether dual targeting with inhaled Seralutinib and Nintedanib provides greater anti-fibrotic and anti-inflammatory activity than either monotherapy in bleomycin-treated mice and IPF-derived precision-cut lung slices.

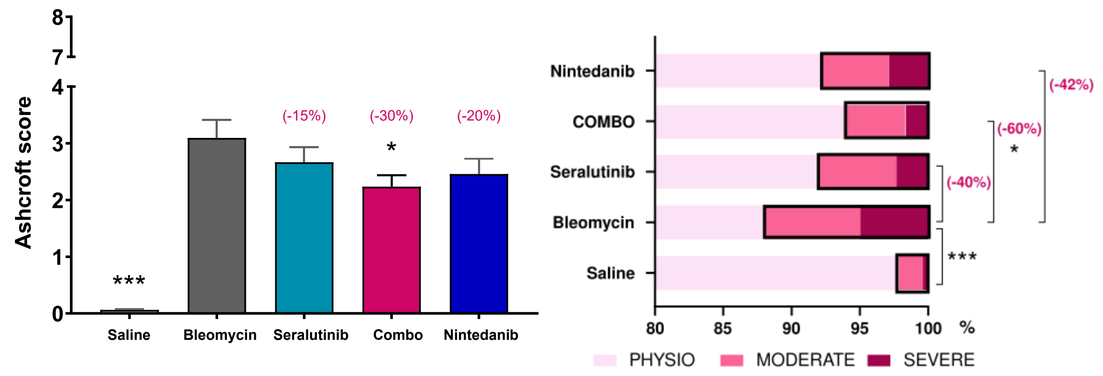
RESULTS

LUNG FUNCTION IN BLEOMYCIN MODEL



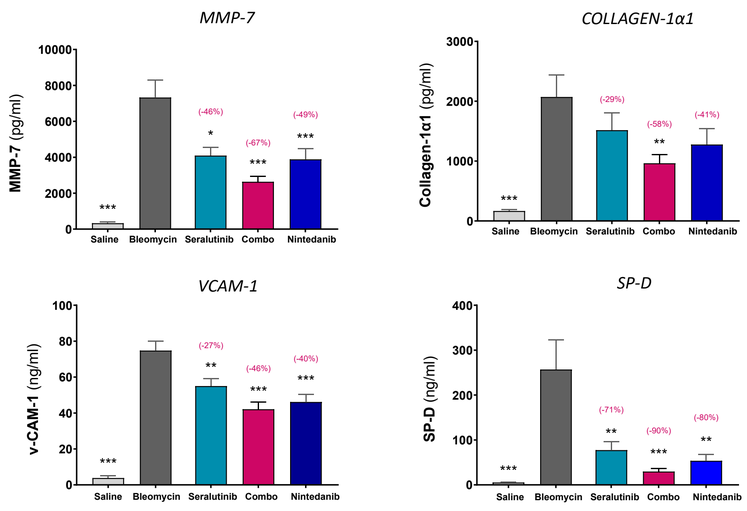
Combination treatment produced the greatest preservation of mFVC and mDLCO compared with either monotherapy

HISTOLOGICAL FEATURES IN BLEOMYCIN MODEL



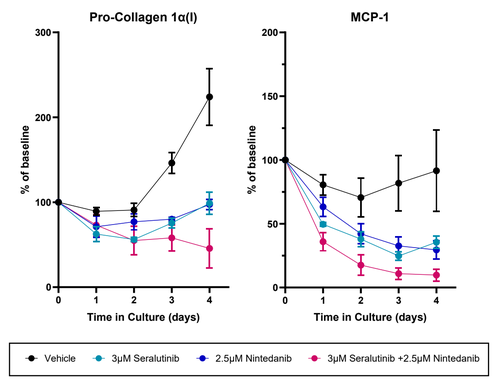
Combination treatment produced the greatest reduction in histopathologic fibrosis across both Ashcroft scoring and AI-based fibrosis quantification

DISEASE-RELEVANT FIBROTIC BIOMARKERS IN BLEOMYCIN MODEL



Combination treatment produced the greatest biomarker reductions across BALF and serum biomarkers associated with fibrosis and tissue injury

EFFECT ON PRO-FIBROTIC MARKERS IN IPF-hPCLS



Loewe Synergy Score				
Biomarker	Seralutinib dose (μM)	Nintedanib dose (μM)	Day 3	Day 4
proCOL1A1	3	2.5	6.1	9.3
MCP-1	3	2.5	4.6	3.8

Table 3. Synergistic Effects of Seralutinib and Nintedanib Confirmed by Loewe Synergy Scoring

- **Combination of Seralutinib and Nintedanib potentiates inhibitory effects on pro-fibrotic protein secretion in IPF-hPCLS (N=3 donors)**
- **The positive Loewe synergy score indicates synergism at selected dose/timepoints (Table 3)**

CONCLUSIONS

- While Seralutinib efficacy was comparable to Nintedanib as a single agent, combining both therapies resulted in superior improvements across multiple disease-relevant endpoints in the bleomycin model, including lung function parameters, histopathological readouts, and translational biomarkers in BALF and serum.
- The superior efficacy of the Seralutinib-Nintedanib combination was reproduced in IPF-hPCLS, reinforcing the translational potential of the findings from the bleomycin model, demonstrating synergistically suppression of proCOL1A1 and MCP-1.
- The broader magnitude of response observed with the combination suggests that the two compounds may act together, leading to a more effective attenuation of fibrotic progression.

Statistics: *p<0.05, **p<0.01, ***p<0.001 vs bleomycin; #p<0.05, ##p<0.01 between indicated groups. Analyses used one-way ANOVA with Dunnett's, Šídák's or Tukey's multiple comparisons test.

Abbreviations: AI, artificial intelligence; BID, twice daily; BLM, bleomycin; mDLCO, mouse diffusing lung capacity for carbon monoxide; mFVC, mouse forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; hPCLS, human precision-cut lung slices; PHYSIO, physiological lung tissue; MMP–7, metalloproteinases–7; VCAM–1, Vascular Cell Adhesion Molecule–1; SP–D, Surfactant Protein–D; proCOL1A1, pro–collagen1A1; MCP–1, Monocyte Chemoattractant Protein – 1

Figure 1 was created by BioRender

TAKE-HOME

- Seralutinib plus Nintedanib produced the most consistent benefit across functional, histopathologic, and biomarker endpoints in complementary translational models.
- **These data support clinical evaluation of inhaled Seralutinib as an add-on therapy to existing anti-fibrotic treatments.**

References: **1** Bhatt J et al *Front Immunol.* 2025;6:1549277; **2** Galkin A et al *Eur Respir J.* 2022;60(6):2102356;**3** Flaherty KR et al *N Engl J Med.* 2019;381(18):1718-1727; **4** Grimminger F et al *Eur Respir J*. 2015;45(5):1426-1433; **5** Chang A et al *Eur Respir J.* 2025; 65: 2402317; **6** Murgo A et al *Front Immunol.* 2023;14:1303646.

Research supported by: Chiesi Farmaceutici S.p.A. and Gossamer Bio USA, Inc.

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