

Targeted Kinase Inhibition with Seralutinib Attenuates Bleomycin-Induced Fibrosis in Contrast to Imatinib

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BACKGROUND

- Dysregulated kinase signaling drives fibroblast activation, vascular remodeling and extracellular-matrix production in pulmonary fibrosis¹.
- Clinical tyrosine-kinase inhibition has shown inconsistent anti-fibrotic efficacy; Imatinib, a selective inhibitor of BCR-ABL, c-KIT, and PDGFRα/β tyrosine kinases (Fig. 1)², did not benefit patients with IPF³.
- Seralutinib is a potent, inhaled PDGFRα/β, CSF1R, and c-KIT kinase inhibitor (Fig. 1)^{4,5}, able to decrease circulating fibrotic biomarkers, including collagen Iα1^{6,7}.

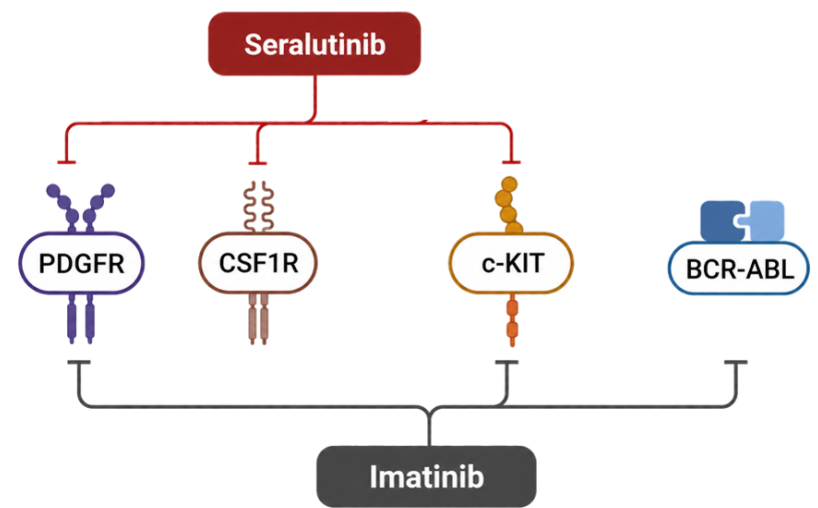


Figure 1. Overview of kinases inhibited by Seralutinib and Imatinib

IMATINIB DOSE SELECTION

- Imatinib doses were selected using PK modelling to compare unbound steady-state plasma exposure in mice and humans, assuming rapid plasma-lung equilibration and comparable exposure-effect relationships across species (Figure 2).
- A two-compartment model simulated mouse exposure at 25, 50 and 100 mpk BID. The predicted average of unbound concentrations were 16, 32 and 64 ng/mL, respectively, compared with 106 ng/mL in humans receiving 600 mg q.d, falling within the range of clinically relevant doses.

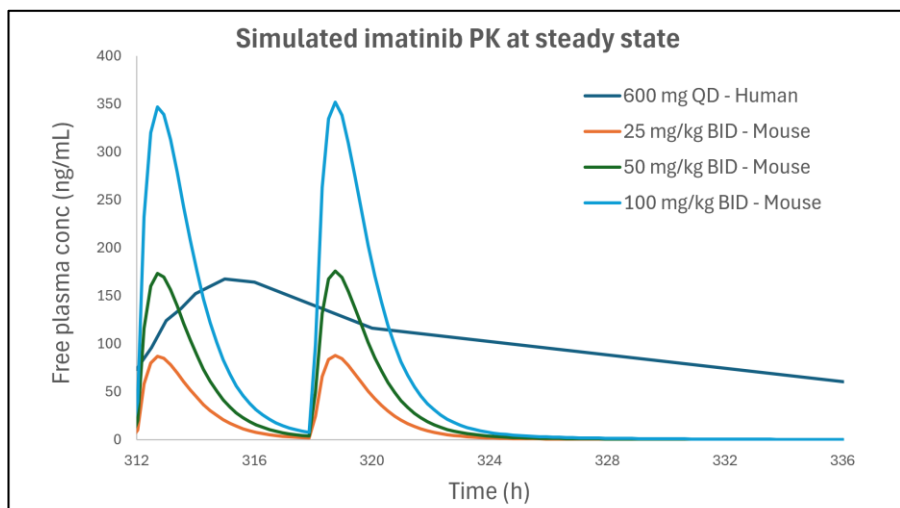


Figure 2. Simulated Imatinib PK steady state Mouse and Human

METHODS

BLEOMYCIN MOUSE MODEL

- C57BL/6 mice were challenged with BLM (0.03 U/mouse) or saline by oropharyngeal route at Days 0 and 4. Two independent studies were carried out with Seralutinib and Imatinib given at different doses (Table 1) respectively by dry powder inhalation and oral solution for 2 weeks starting on Day 7.

Seralutinib study		
Group	Administration	N
Saline/placebo	15 mpk; BID inhalation	7
BLM/placebo	15 mpk; BID inhalation	13
BLM/Seralutinib	5 mpk; BID inhalation	13
BLM/Seralutinib	15 mpk; BID inhalation	13
BLM/Seralutinib	30 mpk; BID inhalation	13

Imatinib study		
Group	Administration	N
Saline/vehicle	1% tween+water; BID oral	7
BLM/vehicle	1% tween+water; BID oral	13
BLM/Imatinib	25 mpk; BID oral	13
BLM/Imatinib	50 mpk; BID oral	13
BLM/Imatinib	100 mpk; BID oral	13

Table 1. Experimental groups

- At Day 21, lung function was assessed by measuring diffusing capacity for carbon monoxide (mDLCO) and forced vital capacity (mFVC)⁸, 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).

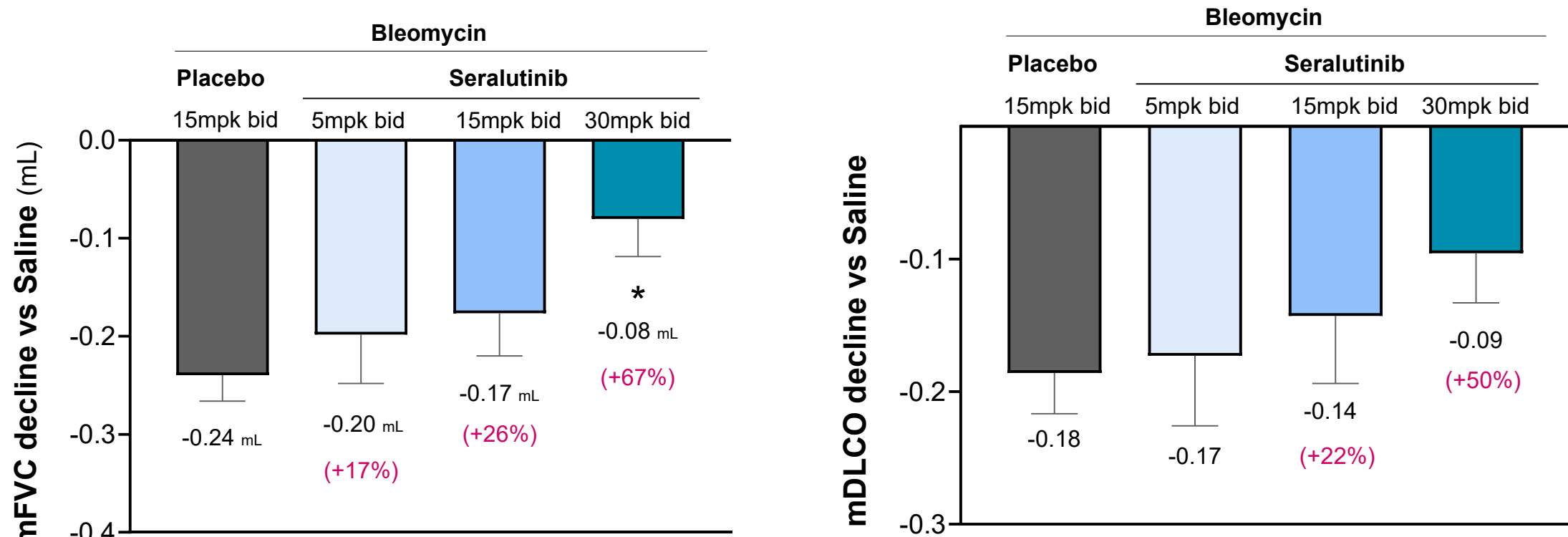
Functional readouts	Fibrosis evaluation	Biomarkers
mFVC	Histopathological evaluation (Ashcroft score)	Measured in BALF: Collagen-1α1, MMP7, VCAM-1
mDLCO	Automated detection of fibrosis by AI	Measured in serum: SP-D

Table 2. Overview of BLM study assessment⁹

AIM | In the present study we compare Seralutinib with oral Imatinib in the bleomycin mouse model to evaluate whether differences in target profile and lung-selective delivery translate into improved efficacy.

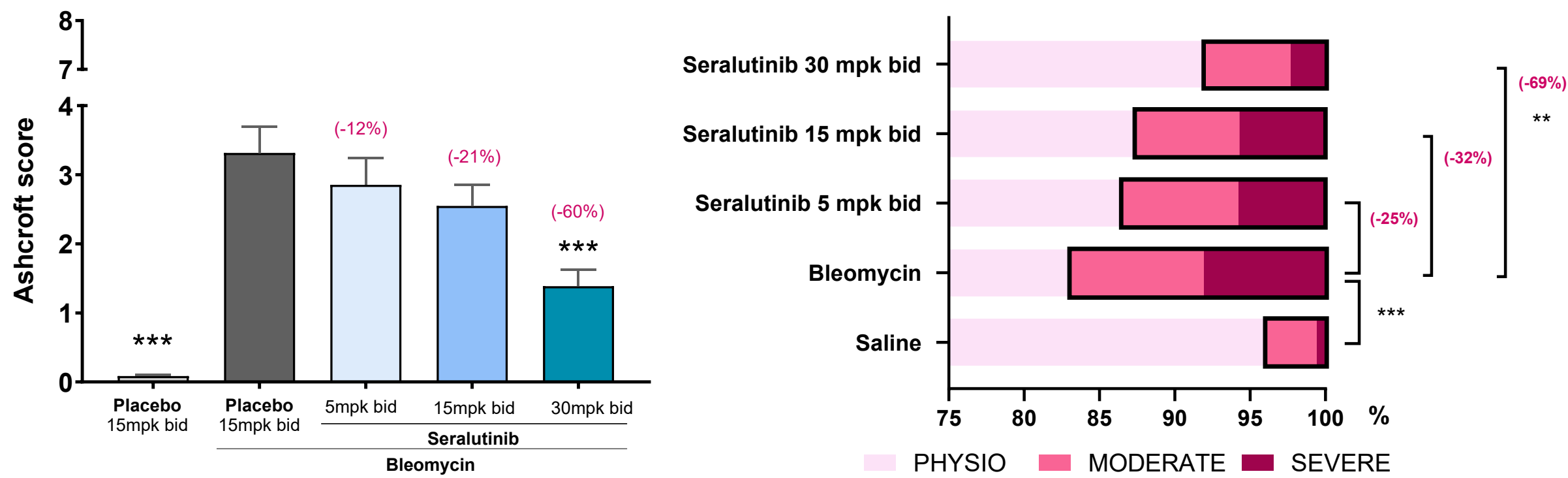
RESULTS

SERALUTINIB IMPROVES LUNG FUNCTION



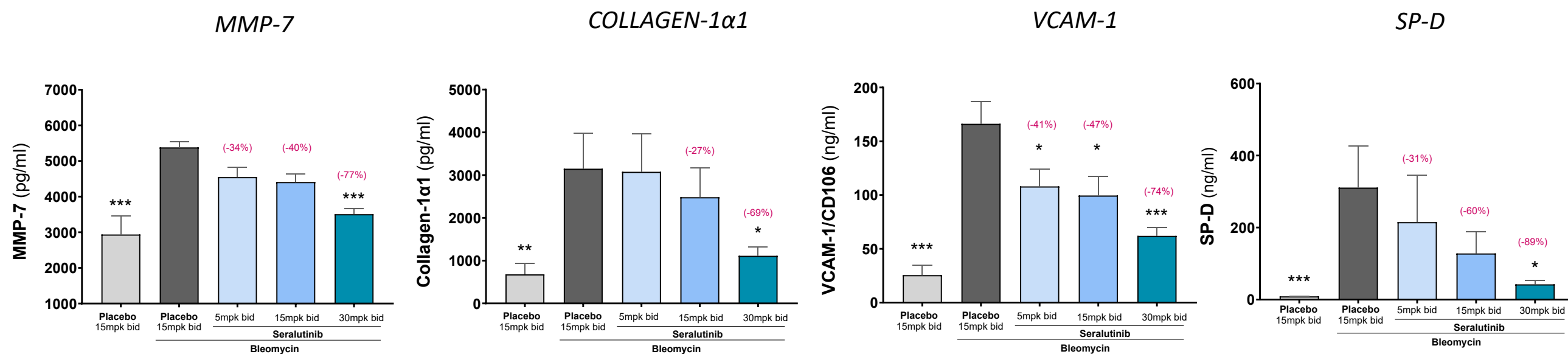
At 30 mpk BID, lung function improves by +67% (p≤0.05) and +50% as measured by decline in mFVC and mDLCO versus bleomycin placebo, respectively

SERALUTINIB DOSE-DEPENDENTLY REDUCES LUNG FIBROSIS



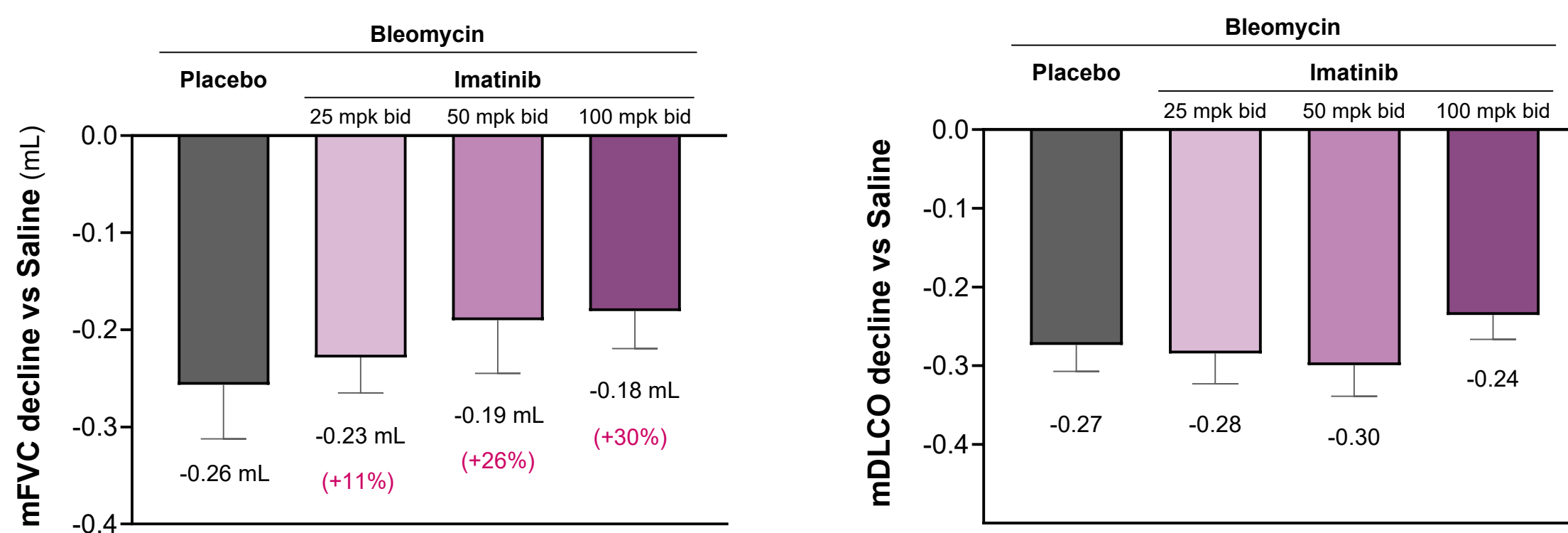
At 30 mpk BID, lung fibrosis was reduced by 60% based on the Ashcroft score and 69% using AI-based histopathological analysis

SERALUTINIB MODULATES DISEASE-RELEVANT BIOMARKERS



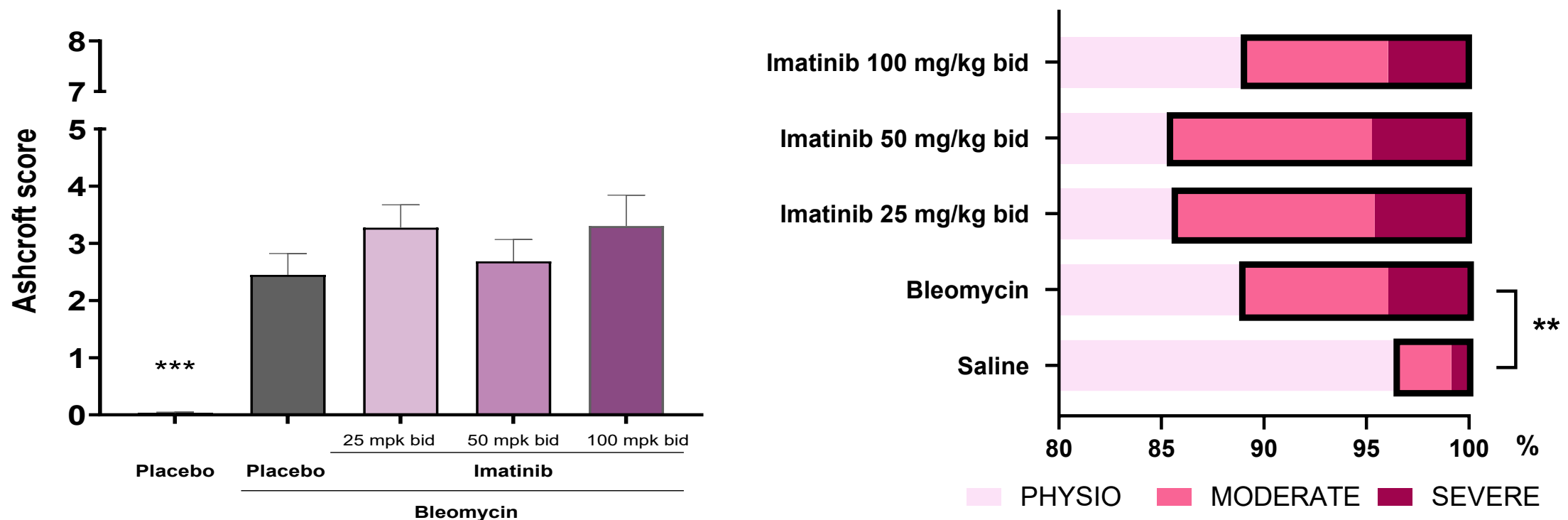
Maximal reductions at 30 mpk BID: MMP-7 -77%, Collagen-1α1 -69%, VCAM-1 -74%, SP-D -89% (all p≤0.05)

IMATINIB SHOWED LIMITED FUNCTIONAL BENEFIT



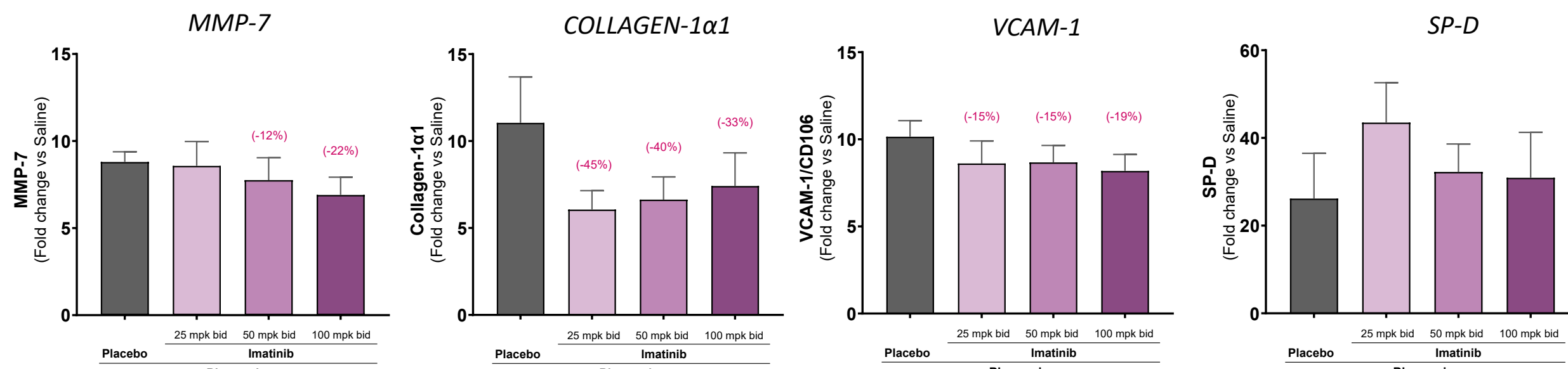
Limited and no improvement in mFVC and mDLCO respectively across 25–100 mpk BID

IMATINIB SHOWS NO HISTOLOGICAL RESCUE



Ashcroft score and AI-based fibrosis analysis remained unchanged

BIOMARKERS REMAIN LARGELY UNCHANGED WITH IMATINIB TREATMENT



No consistent biomarker response was observed across clinically relevant exposure-matched dose

CONCLUSIONS

- Seralutinib showed dose-dependent antifibrotic activity, evidenced by improved function, reduced lung fibrosis, and modulation of key biomarkers.
- Imatinib showed no efficacy, in line with its clinical profile in IPF.
- These findings support further evaluation of whether lung-selective delivery and target profile contribute to antifibrotic effects.

TAKE-HOME

- Seralutinib produced concordant functional, histologic, and biomarker evidence of antifibrotic activity in the bleomycin mouse.
- In contrast to Seralutinib, Imatinib did not show a consistent response under exposure-relevant dosing conditions in line with lack of clinical benefit in IPF.
- These preclinical data support further evaluation of inhaled Seralutinib as an anti-fibrotic strategy for fibrotic ILDs.

Statistics: *p<0.05, **p<0.01, ***p<0.001 vs bleomycin. Analyses used one-way ANOVA with Dunnett's test or Kruskal-Wallis with Dunn's multiple-comparison test

Abbreviations: AI, artificial intelligence; BALF, bronchoalveolar lavage fluid; BID, twice daily; BLM, bleomycin; mDLCO, mouse diffusing capacity for carbon monoxide; mFVC, mouse forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PHYSIO, physiological lung tissue; MMP-7, metalloproteinase-7; VCAM-1, Vascular Cell Adhesion Molecule-1; SP-D, Surfactant Protein-D.

Figure 1 was created by BioRender

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